Polski Merkuriusz Lekarski

POLISH MEDICAL JOURNAL

ISSN 1426-9686

VOLUME LI, 2023, ISSUE 5, SEP– OCT

EDITORIAL BOARD

Polski Merkuriusz Lekarski cited by PUBMED/MEDLINE, SCOPUS, INDEX COPERNICUS, EBSCO, POLISH MEDICAL BIBLIOGRAPHY, Ministry of Education and Science.

© **ALUNA PUBLISHING**
Z.M. Przesmyckiego 29
05-510 Konstancin-Jeziorna, Poland
tel. +48 604 776 311
a.luczynska@wydawnictwo-aluna.pl

www.polskimerkuriuszlekarski.pl

Distribution and subscription
Bartosz Guterman
tel. +48 22 245 10 55
prenumerata@wydawnictwo-aluna.pl

CONTENTS

ORIGINAL ARTICLE

Pol Merkur Lek, 2023; LI, 5: 441-447

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305101

PREGNANT WOMEN WITH COVID-19 AND PLACENTA ANGIOGENESIS

Alla V. Boychuk[1], Yuliia B. Yakymchuk[1], Oksana O. Shevchuk[1], Sandor G. Vari[2], Iryna M. Nikitina[3]

[1]I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE
[2]INTERNATIONAL RESEARCH AND INNOVATION IN MEDICINE PROGRAM, CEDARS-SINAI MEDICAL CENTER, LOS ANGELES, CA, USA
[3]SUMY STATE UNIVERSITY, SUMY, UKRAINE

ABSTRACT

Aim of our research was to conduct a clinical and laboratory analysis of the impact of COVID-19 on pregnancy and the condition of the fetus.

Materials and Methods: At the first stage, we conducted a retrospective examination of 50 pregnant women treated at Ternopil Municipal Hospital No.2 (Ukraine) between November 2020 and January 2022 with the history of COVID-19, confirmed by PCR test, and 25 pregnant COVID-19 negative pregnant women (control group). At the second stage, we performed prospective cohort study and involved 40 pregnant women treated with the history of COVID-19, confirmed by PCR, and 10 pregnant COVID-19 negative women with a physiological course of pregnancy as a control group.Women were divided into the following groups: group I -10 women diagnosed with COVID-19 during the first trimester of pregnancy: group II-15 women diagnosed during the second trimester; group III-15 women diagnosed during the third trimester. Ultrasound examination and cardiotocograms were performed to assess fetus status. Blood samples were collected at delivery. To determine whether COVID-19 could alter placental angiogenesis, vascular endothelial growth factor A (VEGFA), PlGF and interleuin-32-α were assessed.

Results: We identified that concentration of VEGFA was 95.30±5.65 pg/ml in control group. In women who had COVID-19 in first trimester, this index was 1.3 times higher, in second trimester 1.63 times higher and in third trimester by 2 times compared to control group. PlGF concentration was only 27,4 percent in group I, 16 percent in group II and 30 percent in group III,compared to control group. Concentration of interleuin-32-α was 67.27±5.63 pg/ml in control group and increased to 167 percent in group I, by 2.8 times in group II and by 6.3 times in group III compared to control group.

Conclusions: COVID-19 has a negative impact on placental angiogenesis, including VEGFA and PlGF. Fetal post-COVID-19 syndrome requires timely diagnosis of disorders and further study. Post-COVID-19 syndrome is an immune-dependent pathology in which the processes of protracted cytokine activation occur in the body of a pregnant woman.

KEY WORDS: COVID-19, SARS-CoV-2, pregnancy, VEGFA, PlGF, IL-32-α, fetus, fetal growth retardation

INTRODUCTION

COVID-19 in pregnancy was associated with consistent and substantial increases in severe maternal morbidity and mortality and neonatal complications when pregnant women with COVID-19 diagnosis were compared to pregnant women without [1-3]. COVID-19 affected all population, including the vulnerable category of pregnant women. Uncertainty exists about the potential for vertical transmission from mothers infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to the fetus in utero [1, 3, 4]. SARS-CoV-2 in pregnancy causes fetal SARS-CoV-2 syndrome. The virus causes inflammatory changes in the endothelium, which upsets the balance of the coagulation system [2, 4, 5].

Currently, information on the course of COVID-19 during pregnancy is limited. Several studies have shown that SARS-CoV-2 infection during pregnancy increases the risk of pregnancy complications with increased rates of hospitalization to intensive care units, need for mechanical ventilation and mortality [5, 6]. Other studies found the course of COVID-19 in pregnant women is similar to other categories of population and could not affect the pregnancy [6, 7, 8]. Therefore, the assessment of pregnancy, fetal status, diagnosis of placental insufficiency in pregnant women with SARS-CoV-2 is a topical issue in obstetric practice and is important for the birth of future healthy generations [3, 6, 9].

The development of placental tissue during pregnancy is under the influence of a number of growth factors and disturbances in the condition, growth and development of the fetus are accompanied by morphological and functional changes in the placenta and disturbances in the metabolic and endocrine function of the placenta [6, 9, 10].

According to the literature [11, 12] the development of placental dysfunction depends on the vascular and hormonal homeostasis, which directly affect the activity of markers of endothelial dysfunction and angiogenesis.

Initially, endothelial vascular growth factor, a signaling protein, was called a vascular permeability factor because its leading feature was a stimulating effect on the formation of new vessels [5, 10, 13, 14].

After the formation of new vessels, vascular endothelial growth factor (VEGF) acts as an inhibitory agent for apoptosis, which contributes to the prolongation of the life of endothelial cells, causes vascular inflammation and produces damage to endothelial cells [4]. VEGF is a factor that ensures the release of fibrinogen, fibronectin and other coagulation factors from blood vessels. Vascular endothelial growth factor A (VEGFA), one of the isomers, increases vascular permeability 1000 times stronger than histamine [2, 15, 16].

VEGFA, a cytokine released under the influence of hypoxia, exerts a powerful mitogenic effect on endothelial cells in the process of angiogenesis [15, 17]. Pathological activation of VEGF, disruption of the state of the endothelium, growth of reactive oxygen species and suppression of nitrogen oxides [2, 15, 18, 19] is characterized by damage to arterioles and arteries. VEGFA plays a key role in the pathogenesis of microangiopathy, regulating the proliferation of vascular endothelial cells. As a result, there is increased proliferation and migration of cells as well as reduced apoptosis. The content of VEGFA in blood serum can play an important prognostic value as a negative marker. Thus, blood VEGFA in pregnant women can be an integral marker of endothelial dysfunction and pathological angiogenesis [15, 20, 21, 22, 23].

Studies of placental growth factors, including VEGFA, and their receptors in uncomplicated pregnancy rise with increasing gestational age. A decrease in the level of VEGFA in the blood of pregnant women correlates with an improvement in the functional state of fetoplacental insufficiency and the intrauterine state of the fetus [10, 20-22, 24].

AIM

The aim of our research was to conduct a clinical and laboratory analysis of the impact of COVID-19 on pregnancy and the condition of the fetus.

MATERIALS AND METHODS

The research consisted of two stages at Ternopil Municipal Hospital No.2 (Ukraine) between November 2020 and January 2022.

At the first stage, we conducted a retrospective examination of 50 pregnant women with COVID-19 (main group) during pregnancy and 25 pregnant women (control group) with a physiological course of pregnancy, who gave birth to live, full-term infants with mass-growth characteristics according to gestational age. The condition of the fetus was assessed according to ultrasound examination of the pregnant woman, determination of biophysical profile and Doppler, performed on Samsung SonoAce R3 device and cardiotocography. Criteria for inclusion in the study were laboratory confirmed COVID-19 by polymerase chain reaction test (PCR).

At the second stage, we performed prospective cohort study and involved 40 pregnant women treated with the history of COVID-19, confirmed by PCR, and 10 pregnant COVID-19 negative women with a physiological course of pregnancy as a control group. According to the history of COVID-19, women were divided into the following groups: group I – 10 women (25 percent), who were diagnosed with COVID-19 during the first trimester of pregnancy, group II – 15 (37.5 percent) during the second trimester and group III – 15 women (37.5 percent) during the third trimester. Blood samples were collected during the delivery. To determine whether SARS-CoV-2 infection could alter placental angiogenesis, a panel of biomarkers was assessed, including VEGFA, placental growth factor and interleukin-32-α (IL-32-α) (ELISA kits from Abcam).

The condition of the fetus was assessed by ultrasound examination of the pregnant woman. Determination of biophysical profile and Doppler examination were performed on Samsung SonoAce R3 device and cardiotocography. Anthropometric parameters were determined: biparietal size , thigh length, fronto-occipital size, average diameters of the thorax and abdomen, the ratio of head circumference to fetal abdomen circumference and the ratio of femur length to abdominal circumference. Placetography evaluated the location of the placenta, its thickness and degree of maturity [7, 17, 18, 20-22, 24].

A Cadence basic mother and baby monitor and a Qiston bT-350 LCD fetal monitor were used to record cardiotocograms (CTG). The recording was performed for 30 minutes. The scale of W. Fisher et al. (1976) was used to analyze CTGs. The score of 8-10 points correspond to normal CTG, 5-7 points indicate initial fetal disorders, 4 points and less may indicate severe fetal disorders [10, 11, 13, 16, 20]. Statistical processing of the results was performed with STATISTICA 10.0 software.

All participants were informed about the aims, organization, methods of the study and signed an informed consent to participate in it, and all measures were taken to ensure the anonymity of the patients. Approved by I. Horbachevsky Ternopil National Medical University Ethical Committee (protocol number 61 on November 13, 2020), the research was conducted in compliance with the main provisions of the Rules of Ethical Principles of Conducting Scientific Medical Research with Human Participation approved by the Declaration of Helsinki (1964-2013).

RESULTS AND DISCUSSION

The following results were obtained because of the research in the examined groups. It was found that the average age of pregnant women was 27.4±0.3 in the main group, and 26.8±0.2 years in the control group ($P>0.05$).

Coronavirus disease was diagnosed in 21 pregnant women (42.0%) in mild form (HQM-Home Quarantined with Mild symptoms), 8 (16.0%) had pneumonia and were hospitalized (HMO – Hospitalized with Moderate course) and 21 (42,0 %) had pneumonia and needed oxygen support (HSV – Hospitalized oxygen-dependent patients with Severe symptoms) (Table 1).

Table 1. Distribution of pregnant women by the severity of the course of SARS-Cov-2

	Group I	Group II	Group III	Total
HQM	10	6	5	21
HMO	-	2	6	8
HSV		7	14	21
Total	10	15	25	50

HQM – Home Quarantined with Mild disease course, HMO – Hospitalized with Moderate course.
– Hospitalized oxygen-dependent patients with Severe symptoms. First trimesters (Group I), Second trimesters (Group II), Third trimesters (Group III)

The main complaints of patients were fever in 82.0 percent (41 pregnant women), cough in 84.0 percent (42 pregnant women), myalgia in 70.0 percent (35 pregnant women), headache in 86.0 percent (43 pregnant women), sore throat in 48.0 percent (24 pregnant women) and general weakness in 74.0 percent (37 pregnant women). Six pregnant women (12.0 percent) had a mild, asymptomatic course of the disease.

Among pregnant women with a history of SARS-CoV-2 (compared to control group), 15 (30 percent) (OR=7.1; 95 percent CI: 1.21-13.2; *P*<0.01) had severe disorders of placenta blood flow and umbilical cord of the fetus. In 26 pregnant women (52 percent) (OR=20.4; 95 percent CI: 2.56-16,3; *P*<0.01) intrauterine growth retardation was diagnosed. In six pregnant women (12 percent) (OR=1.5; 95 percent CI: 1.01-3.12; *P*<0.01) there was highly resistant blood flow with no diastolic part, which indicates a threatening condition and fetal distress syndrome that was found with Doppler in the umbilical artery of the fetus.

The condition of the fetus was assessed by ultrasound and CTG of the fetus. Decrease in amplitude of oscillations of less than 3 beats/min, absence of accelerations and emergence of decelerations testify to the expressed signs of a fetal hypoxia and demand timely treatment and making the decision of urgent delivery.

Partial umbilical vein thrombosis with reverse blood flow was observed in three (6 percent) patients. Antenatal fetal death occurred in three (6 percent) women 24±5 days after the disease. In 88 percent of the examined women, the pregnancy ended with the labor in term, 2.0 percent of pregnancies ended at 26-27 weeks and 10 percent of pregnant women at 33-34 weeks.

The presence of pathological processes in the fetoplacental complex negatively affected the condition of the fetus, and led to delayed growth, leading to an increased risk of perinatal mortality. Based on ultrasound, fetal growth retardation was diagnosed in 26 pregnant women, which amounted to 52.0 percent among all examined in the basic group and 43 pregnant women (86.0 percent) were diagnosed with certain pathological changes in the placenta.

CTG is a simultaneous recording of uterine contractions and fetal heart rate. This method allows researchers to comprehensively assess the reactivity (ability to change heart rate under the influence of various factors) of the fetal heart rate. Based on the analysis of CTGs, it was found that the basal rhythm in pregnant women of the main group was 121.7±2.23 beats/min compared to healthy pregnant women that were 145.6±3.12) beats/min.

The frequency variability for one minute in pregnant women of the main group before treatment was 3.09±0.12, which is significantly lower compared to the control group at 6.58±0.13. Analyzing the CTGs, we also noticed that accelerations were found in 31 (70.5 percent) pregnant women with coronavirus disease and 100 percent in healthy pregnant women. The number of accelerations in the main group was 2.03±0.09 and in the control group was 5.14±0.19, (*P*<0.05). The results of the analysis of CTGs are presented in Table 2.

The analysis of CTG parameters revealed a significant difference in pregnant women with coronavirus disease compared with women in the control group. A significant decrease in the length of the stable rhythm and significant disturbances of acceleration reactions were diagnosed. The increase in the number, duration and depth of deceleration is noteworthy. All this indicates a decrease in the reactivity of the cardiovascular system of the fetus and is a characteristic feature of hypoxia.

In diagnosing the fetal condition in pregnant women with coronavirus disease, criteria were identified that indicate the initial signs of fetal distress including a decrease in the amplitude of oscillations less than 5 beats/min, a decrease in the number of accelerations to 3 or less and the appearance of spontaneous decelerations. Signs such as a decrease in the amplitude of oscillations less than 3 beats/min, no acceleration and the appearance of decelerations indicate severe signs of fetal hypoxia and require timely treatment and resolution of timely delivery.

During ultrasound investigation of pregnant women with a history of SARS-CoV-2, it was found that 15 pregnant women (30 percent) (OR=7.1; 95 percent S CI: 1.21-13.2; *P*<0.01) revealed severe disorders of blood flow in the placenta and umbilical cord of the fetus. In 26 pregnant women (52 percent) (OR=20.4; 95 percent CI: 2.56-16.3; *P*<0.01) fetal growth retardation syndrome was observed and in six pregnant women (12 percent) (OR=1.5) 95 percent CI: 1.01-3.12, *P*<0.01) Dopplerography in the umbilical artery of the fetus diagnosed highly resistant blood flow without diastolic part, which indicated a threatening condition and distress of the fetus.

We studied the peculiarities of changes in the activity of angiogenesis factors VEGFA and placental growth factor (PlGF) in pregnant women with postpartum syndrome. The

Table 2. Evaluation of cardiotocograms in pregnant women with coronavirus disease (M ± m)

Indicator		Main group (n = 44)	Control group (n = 25)
Basal rhythm beats/min		121.7±2.23*	145.6±3.12
Variability	amplitude beats/min	6.11±0.13*	19.10±0.18
	frequency for 1 min	3.09±0.12*	6.58±0.13
Acceleration in 30 minutes		2.03±0.09*	5.14±0.19
Deceleration in 30 minutes		spontaneous, early	missing

** P < 0.05 reliability compared with the control group*

Table 3. Effect of SARS-CoV-2 on placental vascular growth factors (M ± m)

Indexes	Healthy pregnant women in 3 trimesters	Pregnant with positive SARS-CoV-2		
		1st trimester	2nd trimester	3rd trimester
	Control group	I group	II group	III group
	n = 10	n = 10	n = 15	n = 15
PIGF, pg/ml	144.53±15.55	39.57±9.71 P_1<0.001	23.35±1.41 P_1<0.001 P_2>0.05	43.92±4.81 P_1<0.001 P_2>0.05 P_3<0.001
VEGFA, pg/ml	95.30±5.65	122.84±2.66 P_1<0.001$_1$	155.42±8.57 P_1<0.001 P_2<0.001	192.20±10.02 P_1<0.001 P_2<0.001 P_3<0.01
IL-32-α pg/ml	67.27±5.63	113.0±5.79 P_1<0.001	191.5±13.11 P_1<0.001 P_2<0.001	425.5±17.25 P_1<0.01 P_2<0.001 P_3<0.001
P_1	Reliability between indicators in pregnant women with a physiological course and I, II, III groups of patients with SARS-CoV-2			
P_2	Reliability between indicators of group I and groups II and III of patients with SARS-CoV-2			
P_3	Reliability between indicators 2 and 3 groups of patients with SARS-CoV-2			

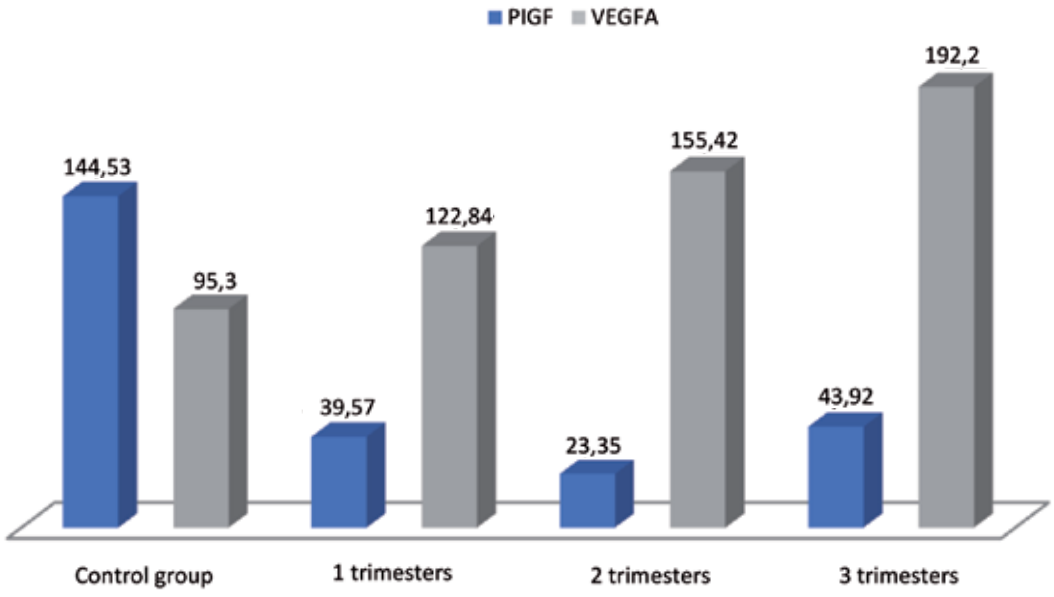


Fig. 1. The content of the placental growth factor and vascular endothial growth factor in pregnant women of the control group and pregnant women with SARS-CoV-2 is different at different periods of gestation.

average level of VEGFA during the physiological course of pregnancy in the third trimester according to our research corresponded to the value of 95.30±5.65 pg/ml (Table 3).

In patients who contracted SARS-CoV-2 in the first trimester of pregnancy and the pregnancy continued to develop (group I), at the time of delivery, the VEGFA indicator was 122.84±2.66 pg/ml, which was significantly different (*P1*<0.001) from the VEGFA indicators of the control group and was 129 percent (Fig. 1).

At the same time, SARS-CoV-2 disease in the second trimester led to an increase in the VEGFA index in the third trimester compared to the first group (*P2*<0.001) and its average value was 155.42±8.57 pg/ml, which is 1.6 times higher than in the control group.

In the third trimester with the disease, the concentration of VEGFA reaches its maximum values at 192.20±10.02 pg/ml, which is two times higher than in the control group at the same time during an uncomplicated pregnancy (95.30±5, 65 pg/ml) and is significantly different from indicators of the I (122.84±2.66 pg/ml) and II groups (155.42±8.57 pg/ml, *P*<0.001).

In our opinion, the dynamics of the growth of the VEGFA level is justified by the increased growth of the vascular-epithelial system of the placental bed of the uterus, which is compensated by the greater increase in the volume of blood flowing through the vessels of the uterus, which were negatively affected by the SARS-CoV-2 virus on the fetal-placental complex, restraining the adequate growth and development of the fetus and its adaptation to the pathological course of pregnancy.

Immune disorders are significant in the development of post-COVID-19 syndrome in pregnant women. One of the mechanisms of the development of an extreme violation of the functional state of the fetoplacental complex is the syndrome of delayed fetal development, a change in the immune response of the maternal organism, which is accompanied by a violation of the immune response of the maternal organism, a violation of the processes of activation of immunocompetent cells [10].

Cytokines are informative molecules that adapt protective mechanisms to maintain the homeostasis of a pregnant woman's body [10, 20-22, 24]. We investigated the state of cytokine IL-32-α in peripheral and umbilical cord blood in healthy pregnant women and in pregnant women with positive SARS-CoV-2 in the first, second and third trimesters of pregnancy.

During the physiological course of pregnancy, the level of IL-32-α reached 67.27±5.63 pkg/ml. In pregnant women with positive SARS-CoV-2 in the first trimester of pregnancy, in comparison with healthy pregnant women, there is an increase in the concentration of IL-32-α in the peripheral blood of pregnant women by 67 percent (up to 113.0±5.79, *P*<0.001). Therefore, even in the third trimester, after more than 16-20 weeks of SARS-CoV-2 disease, post-COVID-19 syndrome is accompanied by a violation of the activation of cytokine activity in the blood of pregnant women.

In the second group of pregnant women, the content of IL-32-α in the blood increased more than 2.8 times and reached the level of 191.5±13.11 pg/ml, compared to the group of healthy pregnant women (*P*<0.001).

In the third group of pregnant women, IL-32-α increased 6.3 times and amounted to 425.5±17.25 pkg/ml, compared to the control group of pregnant women (*P*<0.001).

From the data presented in Table 2, we can see that post-COVID-19 syndrome is accompanied by prolonged activation of cytokine activity. The content of the cytokine progressively increases, in accordance with the shortening of the period of development of the post-COVID-19 syndrome.

Data on the content of the placental growth factor PlGF in pregnant women of the control group and pregnant women with SARS-CoV-2 at different stages of gestation are presented in Table 2 and Figure 1.

Under the conditions of the physiological course of pregnancy, the level of PlGF at full-term pregnancy was 144.53±15.55 pg/ml. According to the literature, its level fluctuates during the entire physiological pregnancy with a rapid increase in concentration until the end of the second trimester and a gradual decrease in the third trimester [4, 15, 23, 25].

According to the results of our study, the average level of PlGF in the first group of pregnant women was 39.57±9.71 pg/ml, which was 1.3 times higher than the control indicators (*P*<0.001).

In the second group, the level of PlGF reached its maximum decrease, and its value reached the level of 23.35±1.41 pg/ml, which is only 16 percent of the indicator in pregnant women with a physiological course of pregnancy in the third trimester (*P*<0.001).

In the third group, its value was 43.92±4.81 pg/ml, which indicates a certain increase in the level of PlGF, and this indicator did not differ significantly (*P*>0.05) from the indicators of the first group (39.57±9.71 pg/ml) and was 30 percent of the PlGF level in women with an uncomplicated pregnancy (144.53±15.55 pg/ml, (*P*<0.001)).

Finally, in women who had COVID-19 in the first trimester, the PlGF level was lower by 3.6 times (*P*<0.001); in second trimester lower by 6.2 times and in third trimester by 3.3 times compared to the control group. As for the PlGF concentration, it was lower and consist 27.4 percent in group I (*P*<0.001); 16.1 percent in group II (*P*<0.001) and 30.4 percent in group III (*P*<0.001) compared to COVID-19 negative women with a physiological course of pregnancy.

The concentration of IL-32-α was 67.27±5.63 pg/ml in women of control group. It increased by 67 percent (*P*<0.001) in group I, by 2.8 times (191.5±13.11 pg/ml) in group II and by 6.3 times (425.5±17.25 pg/ml) in group III (*P*<0.001) compared to the control group.

The condition of the fetus with post COVID-19 syndrome in 3 trimesters assessed by ultrasound and CTG of the fetus was associated with decreasing of amplitude of oscillations, absence of accelerations, emergence of decelerations, signs of a fetal hypoxia and urgent delivery.

As an organ unique to pregnancy, the placenta is pivotal to pregnancy outcomes. SARS-CoV-2 infection has a negative impact on vascular-endothelial system of the placenta during different times of gestation,

which is confirmed by increased level of VEGFA along the gestation period. VEGFA represents a growth factor with important pro-angiogenic activity, increasing the vascular permeability, promoting cell migration and actively contributes to regulating the normal and pathological angiogenic processes [26, 27].

So, the SARS-CoV-2 virus has different effects at different periods of gestation. The virus causes abnormal development of the vessels of the placenta, disruption of their growth, differentiation and functioning, and causes placental stress, which leads to various disorders of the state of the fetus and delay in its development. These disorders are associated with inadequate production of VEGFA, as well as a violation of the coagulation and anticoagulation system of the blood and the development of chronic disseminated intravascular coagulation syndrome. Violation of the processes of cellular regulation is based on the function of the endothelium to produce several biologically active substances that affect the tone and angiogenesis of blood vessels, regulate hemostasis, adhesion and aggregation of platelets as well as immune and anti-inflammatory responses [4, 14, 17, 18, 28]. The processes of angiogenesis in the placenta are closely related to the functional capacity of the endothelium under the pathological effect of SARS-CoV-2, which ensures the development of the placenta and the formation of its vascular system [15, 21, 29].

On the one hand, increasing of the level of VEGFA leads to stimulating of angiogenesis, but on the other hand, decreasing of the level of the PlGF caused loss of trophoblast metabolic activity [4], placental insufficiency via autocrine mechanism. It finalized clinically as the post-COVID-19 fetus distress syndrome.

CONCLUSIONS

COVID-19 in pregnancy was associated with consistent and substantial increases in severe maternal morbidity and mortality and neonatal complications when pregnant women with and without COVID-19 diagnosis were compared. Fetal post-COVID-19 syndrome accompanied by growth retardation syndrome, distress, antenatal fetal death and increased thrombosis in the vessels of the placenta and umbilical cord were observed.

Thus, based on anamnestic data, ultrasound examination and cardiotocography revealed differences in the course of pregnancy in women who contracted coronary heart disease during pregnancy compared with healthy pregnant women, indicating a violation of fetal-placental circulation and placental dysfunction.

SARS-CoV-2 has a negative impact on placental angiogenesis, including VEGFA, and PlGF. Fetal post-COVID-19 syndrome requires timely diagnosis of disorders, long-term anticoagulant therapy and further study. Post-COVID-19 syndrome is an immune-dependent pathology in which the processes of protracted cytokine activation occur in the body of a pregnant woman. The presence of COVID-19 in a pregnant woman is of concern requiring an objective assessment of the condition of the pregnant woman and the fetus, as well as the need to predict the development of complications during pregnancy, at childbirth and perinatal risks.

REFERENCES

1. Blitz MJ, Gerber RP, et al. Preterm birth among women with and without severe acute respiratory syndrome coronavirus 2 infection. Acta Obstetricia et Gynecologica Scandinavica, 2021; 100(12):2253-2259.
2. Di Toro F, Gjoka M, Di Lorenzo G, et al. Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. Clin Microbiol Infect. 2021;27(1):36-46.
3. Einarsdóttir K, Swift EM, Zoega H. Changes in obstetric interventions and preterm birth during COVID-19: A nationwide study from Iceland . Acta Obstetricia et Gynecologica Scandinavica, 2021;100(10):1924-1930.
4. Facciolà A, Micali C, Visalli G, et al. COVID-19 and pregnancy: clinical outcomes and scientific evidence about vaccination. Eur Rev Med Pharmacol Sci. 2022;26(7):2610-2626.
5. Boychuk AV, Budnyk TA, Boyarchuk OR. Provision of pregnant women with vitamin D and its influence on anthropometric indicators of the newborn. Voprosu pitania. 2020;89(5):80-88.
6. Castro P, Matos AP, Werner H, Lopes FP, Tonni G, Júnior AJJ. Covid-19 and pregnancy: an overview. Rev Bras Ginecol Obstet. 2020;42(7):420-426.
7. Mirbeyk M, Saghazadeh A, Rezaei N. A systematic review of pregnant women with COVID-19 and their neonates. Arch Gynecol Obstet. 2021;304(1):5-38.
8. Mulvey JJ, Magro CM, Ma LX, Nuovo GJ, Baergen RN. Analysis of complement deposition and viral RNA in placentas of COVID-19 patients. Ann Diagn Pathol. 2020;46:151530.
9. Aabakke AJM, Petersen TG, et al. Risk factors for and pregnancy outcomes after SARS-CoV-2 in pregnancy according to disease severity: A nationwide cohort study with validation of the SARS-CoV-2 diagnosis. Acta Obstetricia et Gynecologica Scandinavica, 2023;102 (3):282-293.
10. Aimes RT, Zijlstra A, Hooper JD, et al. Endothelial cell serine proteases expressed during vascular morphogenesis and angiogenesis. Thromb Haemost. 2003;89(3):561-572.
11. Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M. Severe COVID-19 during pregnancy and possible vertical transmission. Am J Perinatol. 2020;37(8):861-865.
12. Bikdeli B, Madhavan MV, Gupta A, et al. Pharmacological agents targeting thromboinflammation in COVID-19: review and implications for future research. Thromb Haemost. 2020;120(7):1004-1024.
13. Dashraath P, Wong JLJ, Lim MXK, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020;222(6):521-531.

14. GUO D, Lv Y, Qi Y, Pan S. Increased circulating microparticles and inflammatory factors aggravate coronavirus disease 2019 (COVID-19). Res Square. 2020. https://doi.org/10.21203/rs.3.rs-19182/v1.
15. Kant Sahu K, Lal A, Kumar Mishra A. COVID-2019 and pregnancy: A plea for transparent reporting of all cases. Acta Obstetricia et Gynecologica Scandinavica, 2020; 99(7):951.
16. León-Juárez M, Martínez-Castillo M, González-Garcia LD, et al. Cellular and molecular mechanisms of viral infection in the human placenta. Pathogl Dis. 2017;75(7):93.
17. Melincovici CS, Boşca AB, Şuşman S, et al. Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis. Rom J Morphol Embryol. 2018;59(2):455-467.
18. Schwartz DA. An analysis of 38 pregnant women with COVID-19, their newborn infants, and maternal-fetal transmission of SARS-CoV-2: maternal coronavirus infections and pregnancy outcomes. Arch Pathol Lab Med. 2020;144(7):799-805.
19. Zaigham M, Andersson O. Maternal and perinatal outcomes with COVID-19: A systematic review of 108 pregnancies. Acta Obstet Gynecol Scand. 2020;99(7):823-829.
20. Serrano B, Mendoza M, et al. Shared risk factors for COVID-19 and preeclampsia in the first trimester: An observational study .Acta Obstetricia et Gynecologica Scandinavica. 2022;101(7):803-808.
21. Muyayalo KP, Huang DH, Zhao SJ, Xie T, Mor G, Liao AH. COVID-19 and Treg/Th17 imbalance: Potential relationship to pregnancy outcomes. Am J Reprod Immunol. 2020;84(5):e13304.
22. Narang K, Enninga EAL, Gunaratne MDSK, et al. SARS-CoV-2 infection and COVID-19 during pregnancy: a multidisciplinary review. Mayo Clin Proc. 2020;95(8):1750-1765.
23. Rizzo G, Mappa I, et al. Effect of SARS-CoV-2 infection during the second half of pregnancy on fetal growth and hemodynamics: a prospective study. Acta Obstetricia et Gynecologica Scandinavica. 2021; 100(6):1034-1039.
24. Severinsen ER, Kähler LKA, et al. Mental health indicators in pregnant women compared with women in the general population during the coronavirus disease 2019 pandemic in Denmark. Acta Obstetricia et Gynecologica Scandinavica. 2021;100(11):2009-2018.
25. Vergara-Merino L, Meza N, et al. Maternal and perinatal outcomes related to COVID-19 and pregnancy: An overview of systematic reviews. Acta Obstetricia et Gynecologica Scandinavica. 2021; 100(7):1200-1218.
26. Wastnedge EAN, Reynolds RM, van Boeckel SR. Pregnancy and COVID-19. Physiol Rev. 2021;101(1):303-318.
27. Rasmussen SA, Kelley CF, Horton JP, Jamieson DJ. Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. Obstet Gynecol. 2021;137(3):408-414.
28. Yang J, D'Souza R, Kharrat A, Fell DB, Snelgrove JW, Shah PS. COVID-19 pandemic and population-level pregnancy and neonatal outcomes in general population: A living systematic review and meta-analysis. Acta Obstetricia et Gynecologica Scandinavica. 2021;101(3):273-292.
29. Wenling Y, Junchao Q, Xiao Z, Ouyang S. Pregnancy and COVID-19: management and challenges. Rev Inst Med Trop Sao Paulo. 2020;62:62.

ACKNOWLEDGEMENTS

We thank Cedars-Sinai Medical Center's International Research and Innovation in Medicine Program and the Association for Regional Cooperation in the Fields of Health, Science and Technology (RECOOP HST Association) for their support of our study and our organization as a participating Cedars-Sinai Medical Center — RECOOP Research Center (CRRC).

FUNDING

This research was supported by the Regional Cooperation for Health, Science and Technology Association (RECOOP HST Association) RECOOP Grant # 028 COVID-19 disease and comorbidities during pregnancy.

ORCID AND CONTRIBUTIONSHIP
Alla V. Boychuk: 0000-0002-2191-0383[A,B,D,E,F]
Yuliia B. Yakymchuk: 0000-0002-3905-1310[A,D,E]
Oksana O. Shevchuk: 0000-0003-2473-6381[C,F]
Sandor G. Vari: 0000-0003-2962-2017[A,B,D,E,F]
Iryna M. Nikitina: 0000-0001-6595-2502[F]

ADDRESS FOR CORRESPONDENCE
Alla V. Boychuk
Obstetrics and Gynaecology Department,
I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine
e-mail: boychuk_alla@tdmu.edu.ua

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 02.04.2023
ACCEPTED: 07.09.2023

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 448-455

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305102

COMPARING THE EFFECTIVENESS OF CONCENTRATE OF ALL PROTHROMBIN COMPLEX FACTORS WITH RECOMBINANT HUMAN COAGULATION FACTOR VIIa IN THE TREATMENT OF BLEEDING AFTER CARDIAC SURGERY

Maciej Zagórski[1], Justyna Sejboth[2]

[1]CARDIAC SURGERY, INTENSIVE CARE UNIT, CENTRAL CLINICAL HOSPITAL OF THE MEDICAL UNIVERSITY OF LODZ, LODZ, POLAND
[2]DEPARTMENT OF ANAESTHESIA AND INTENSIVE THERAPY, SCHOOL OF HEALTH SCIENCES IN KATOWICE, MEDICAL UNIVERSITY OF SILESIA IN KATOWICE, KATOWICE, POLAND

ABSTRACT

Aim: The authors evaluated the effectiveness of treatment with recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors in patients with massive postoperative bleeding that could not be controlled with traditional therapy.
Materials and Methods: In the period from 2020 to 2021, recombinant human coagulation factor VIIa was administered to 18 patients after cardiac surgery (group I), while the concentrate of all prothrombin complex factors was administered to 16 patients postoperatively (group II). During this period, 647 patients were operated on. The patients had normal coagulation screening tests (APTT, INR, TT, fibrinogen level, and PLT level) before surgery. Mean blood loss before and after administration of eptacog alfa and the total prothrombin complex concentrate was assessed. The mean dose of eptacog alfa was 30.95 mcg/kg b.w., and the total prothrombin complex factor concentrate dose was 14.17 mcg/kg b.w. After transfusion with red blood cell concentrate, fresh frozen plasma, and platelet concentrate, in the absence of improvement in the dynamics of postoperative drainage, it was decided to include recombinant human coagulation factor VIIa or a concentrate of all prothrombin complex factors in the treatment.
Results: After administration of recombinant human coagulation factor VIIa at a dose of 30.95 mcg/kg b.w., bleeding stopped in 12 patients, but the remaining 6 patients required reoperation due to persistently high drainage. The decision to perform a rethoracotomy was made by a team of cardiothoracic surgeons and anesthesiologists, taking into account the dynamics of drainage (bleeding) and the hemodynamic stability of the patient. After the administration of concentrate of all prothrombin complex factors at a dose of 14.17 U/kg b.w., bleeding stopped in 12 patients. Four patients required reoperation due to persistent bleeding.
Conclusions: Treatment with recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors is effective and safe for cardiac surgery patients.

KEY WORDS: bleeding, cardiac surgery, hemorrhagic shock, eptacog alfa, concentrate of all prothrombin complex factors

INTRODUCTION

Patients operated on in cardiac surgery wards often receive antiplatelet drugs that block blood coagulation (VKA - vitamin K antagonists and NOAC - novel oral anticoagulants). These are patients with stable angina or unstable angina/recent myocardial infarction, often after implantation of a drug-eluting stent, with persistent atrial fibrillation. For this reason, they are at risk of increased bleeding during and immediately after surgery. Achieving proper hemostasis requires more attention than in other surgical specialties [1-5]. Appropriate anesthetic management plays a key role in preventing complications and reducing mortality in this group of patients.

If sudden bleeding occurs during or immediately after the procedure, and it does not stop after using traditional methods of treatment (transfusions of fresh frozen plasma (FFP), red blood cell concentrate (RBCc), and platelet concentrate), activated human recombinant coagulation factor VII [6, 7] or a concentrate of human prothrombin complex factors, which contains factors II, VII, IX, X [8, 9], can be administered.

Prolonged bleeding may cause hemorrhagic shock. Coagulopathy, acidosis, and hypothermia are the "lethal triad". Deepening hemorrhagic shock can turn into irreversible shock and lead to the death of the patient [4, 5].

Recombinant human coagulation factor VIIa has been introduced for the treatment of hemophilia A and B [10, 11]. Currently, it is used in various clinical specialties, including to control bleeding after multi-organ injuries [1, 3, 7-9, 12, 14]. A national consultant in the field of anesthesiology and intensive care has developed guidelines for treatment with eptacog alfa [21].

Concentrate of all prothrombin complex factors has been introduced for the treatment of patients with hepatic

insufficiency accompanied by disorders in the hemostasis system. It is used for the treatment of patients who are taking VKAs who have experienced complications due to this or are being prepared for urgent surgery [8].

AIM

The aim of this study was to assess the effectiveness of treatment of postoperative bleeding in patients undergoing cardiac surgery with activated factor VII and a concentrate of all human prothrombin complex factors.

MATERIALS AND METHODS

A retrospective analysis was conducted on 34 patients treated in the period from 2020 to 2021 in our clinic due to ischemic heart disease, valve replacements, and thoracic aortic aneurysms in whom postoperative bleeding occurred. During this period, 647 patients underwent cardiac surgery in our clinic. Study limitations: especially a very small sample size due to, among other things, technical problems and drug availability problems (Covid-19 period). All patients underwent coagulation system screening (APTT, INR, fibrinogen, and platelet levels) before the procedure. The values were within normal limits.

The operated patients received fentanyl, rocuronium, and etomidate for induction of anesthesia. Anesthesia was maintained with an infusion of propofol with fentanyl and fractionated doses of rocuronium at regular intervals. After the procedure, the patients were intubated under the influence of analgosedation and transported to the intensive care unit. The circulatory system was monitored with ECG, blood pressure measurement (direct) from the radial artery, and central venous pressure (CVP) measurement (Table 1).

Eighteen patients (14 men and 4 women) aged 34–79 years with a mean age of 56±22.5 received recombinant human coagulation factor VIIa (group 1), while 16 patients (12 men and 4 women) aged 61–81 years with a mean age of 71 ± 10 received concentrate of all prothrombin complex factors (group 2).

In the 18 patients in the recombinant human coagulation factor VIIa group, increased postoperative drainage was observed after surgery in the postoperative ward. In the concentrate of all prothrombin complex factors group, 16 patients had bleeding after surgery in the postoperative ward.

Treatment of bleeding included volume control with crystalloids. At the same time, according to the recommendations of the national consultant in the field of anesthesiology and intensive care, hypothermia and acidosis were treated; electrolyte disturbances were compensated; and RBCc, FFP, and Platelet Concentrate were transfused. According to the latest transfusion guidelines, RBCc was transfused in relation to FFP as 1:1 [3-5]. In addition, antihemorrhagic drugs, including tranexamic acid, calcium ions, and protamine sulphate, were administered. Despite the administration of drugs and blood products, life-threatening bleeding persisted. Recombinant human coagulation factor VIIa was administered 55–182 minutes (average 117.78±44.95) after surgery. It was administered once intravenously for 15 minutes at a dose of 30.95 ± 16.65 mcg/kg. The effect of the administration of recombinant human coagulation factor VIIa was assessed on the basis of the following: complete blood count, coagulation parameters, amount of blood in the chest drainage tube, bleeding dynamics, and number of resternotomies.

In group II, concentrate of all prothrombin complex factors was administered 51–193 minutes (average 122.56± 45.14) after surgery. It was administered once intravenously for 15 minutes at a dose of 17.46 ± 8.85 U/kg b.w. (body weight).

The average time of administration of the preparations from the end of the operation was not statistically significantly different ($p>0.05$). The effect of administering concentrate of all prothrombin complex factors was assessed on the basis of the following: complete blood count, coagulation parameters, amount of blood in safety drains, bleeding dynamics, and number of resternotomies.

Bleeding decreased significantly within 15±3 minutes after the administration of recombinant human coagulation

Table 1. Type of cardiac surgery performed in patients

Type of cardiac surgery	Group 1 Number of patients	Group 2 Number of patients
Procedures in CPB	10	7
Procedures without CPB	8	9
Valve replacement	3	2
Aortic aneurysms	1	2
CABG	5	3
Others	1	0
OPCAB	8	9
Total	18 (2.78%)	16 (2.47%)
Total operations	647	

CPB – Cardiopulmonary Bypass, CABG – Coronary Artery Bypass Grafting, OPCAB – „Off Pump" Coronary Artery Bypass

factor VIIa and 18 ± 2 minutes after using concentrate of all prothrombin complex factors. This difference was not statistically significant (p> 0.05).

In order to develop statistical data, comparisons of quantitative variables in the two groups were performed using the Mann-Whitney test. The analysis adopted a significance level of 0.05. Thus, all p-values below 0.05 were interpreted as statistically significant associations. A Microsoft Excel spreadsheet from the Microsoft Office 2018 package (Microsoft Corporation, Redmond, Washington, USA) was used to collect the data and perform the initial calculations, and the statistical analysis was performed using the R program (version 4.1.3).

RESULTS

After the first dose of recombinant human coagulation factor VIIa, bleeding stopped in 12 patients. Six patients required chest revision due to persistent bleeding, despite administration of the preparation. After the first dose of concentrate of all prothrombin complex factors, bleeding stopped in 12 patients. Four patients required chest revision due to persistent bleeding, despite concentrate of all prothrombin complex factors administration. The differences here were not statistically significant.

The average blood loss before recombinant human coagulation factor VIIa administration was 690 ml. Twelve hours after recombinant human coagulation factor VIIa administration, it was 396 ml (p=0.009) (Table 2, Fig. 1). The mean rate of bleeding through chest tubes before recombinant human coagulation factor VIIa administration was 171.8 ml/h; after recombinant human coagulation factor VIIa administration, it was 47.5 ml/h (p=0.001) (Table 2). There was a significant reduction in the abovementioned parameters (Table 2).

The mean blood loss before concentrate of all prothrombin complex factors administration was 635.6 ml. Twelve hours after concentrate of all prothrombin complex factors administration, it was 541.7 ml (p=0.04) (Fig. 1). The average rate of bleeding through chest drains before concentrate of all prothrombin complex factors administration was 117.8 ml/h; after concentrate of all prothrombin complex factors administration, it decreased to 33.6 ml/h. (p=0.001) (Fig. 2). There was a significant reduction in the abovementioned parameters.

After the administration of recombinant human coagulation factor VIIa, the mean INR decreased from 1.58 to 1.07. APTT decreased from 63.5 seconds to 37.5 seconds (Table 2). The administration of recombinant human coagulation factor VIIa clearly reduced the need for blood products, including RBCc, FFP, and platelet concentrate.

After the administration of concentrate of all prothrombin complex factors, the mean INR decreased from 1.48 to 1.02. APTT decreased from 60.5 seconds to 33.5 seconds (Table 2). The administration of concentrate of all prothrombin complex factors, significantly reduced the need for blood products, including RBCc, FFP, platelet concentrate, and cryoprecipitate (Table 3).

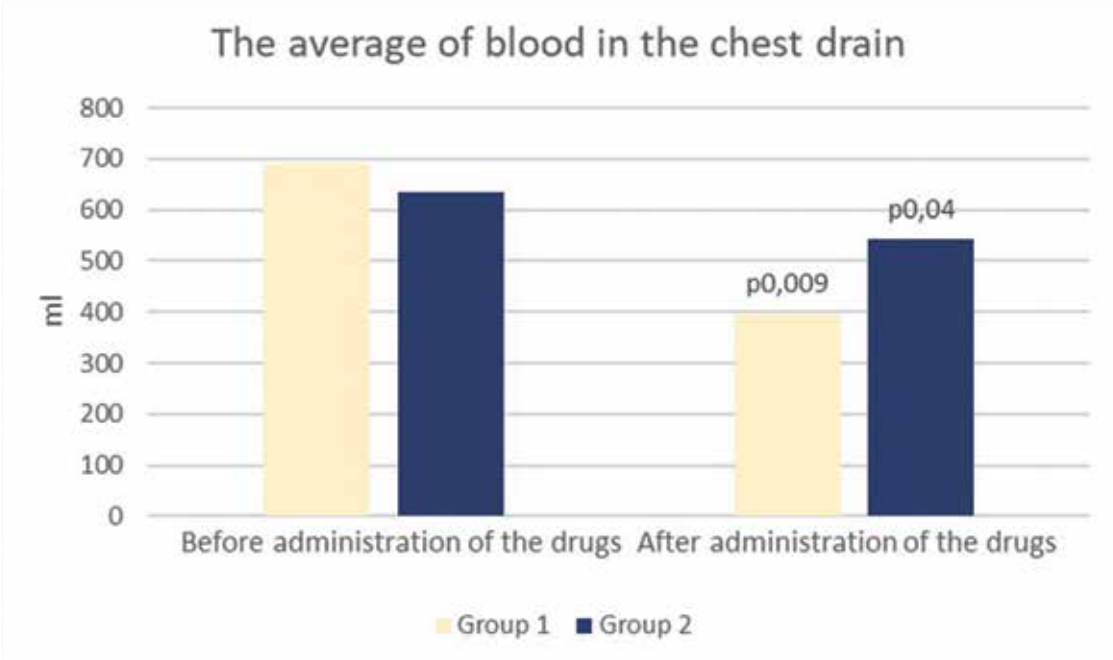
On average, before the administration of recombinant human coagulation factor VIIa, 559.6 ml of RBCc, 717.7 ml of FFP, and 328.5 ml of PC were transfused. After the administration of recombinant human coagulation factor VIIa, the amount of transfused blood preparations decreased significantly, amounting to 418.1 ml of RBCc, 438.5 ml of FFP, and 57.9 ml of platelet concentrate (Fig. 3-5). These differences were statistically significant. No side effects or thrombotic complications were noted after the administration of recombinant human coagulation factor VIIa.

On average, 673.2 ml of RBCc, 876.9 ml of FFP, and 467.75 ml of platelet concentrate were transfused before concentrate of all prothrombin complex factors administration. After the administration of concentrate of all prothrombin complex factors, the number of transfused preparations decreased, amounting to 637.4 ml of RBCc, 723.6 ml of FFP, and 294 ml of platelet concentrate (p = 0.006) (Fig. 3-5). None of the patients experienced side effects or thrombotic complications after the administration of concentrate of all prothrombin complex factors.

Table 2. Selected laboratory parameters (before and after administration of recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors)

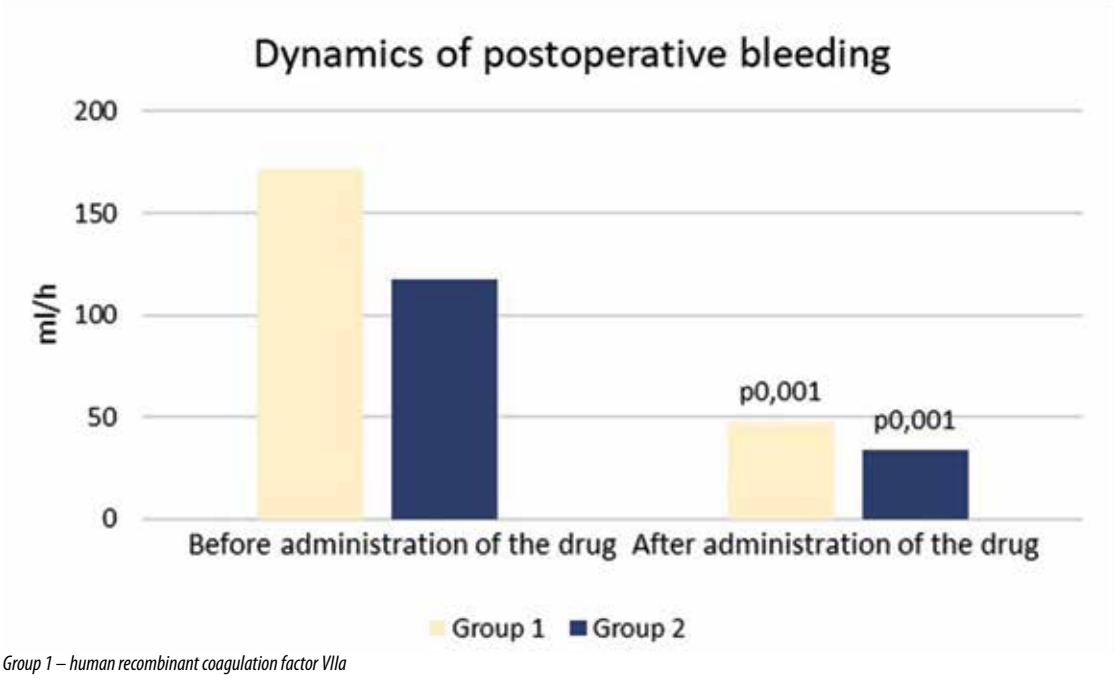
Parameter	Before administration			12 hours after administration		
	Group 1	Group 2	p	Group 1	Group 2	p
Hgb g/l	9.5±3.9	9.2±3.6	0.3	10.9±1.5	10.5±1.7	0.31
RBC mln/mm^3	3.48±0.88	3.38±0.78	0.4	3.68±0.61	3.58±0.41	0.36
Hct %	30.5±8.5	28.5±8.5	0.43	31.5±4.5	31.2±4.0	0.33
PLT tys./mm^3	190±97.5	180±9.5	0.41	216±161	202±111	0.36
APTT s	63.5±31.5	60.5±32.5	0.14	37.5±9.5	33.5±7.5	0.14
INR	1.58±0.68	1.48±0.48	0.2	1.07±0.31	1.02±0.33	0.13
D-dimery mcg/ml	3646±3354	3594±3254	0.24	1908±1558	1856±1428	0.23
Fibrynogen g/l	3.1±1.39	3.2±1.29	0.22	4.42±2.28	4.32±2.08	0.24
AT %	71.5±24.5	70.5±14.5	0.15	95±25	90±21	0.13

Hgb – Hemoglobin, RBC – Red Blood Cell, Hct – Haematocrit, PLT – Platelet, APTT – Activated Partial Thromboplastin Time, INR – International Normalized Ratio, AT – Antithrombin



Group 1 – human recombinant coagulation factor VIIa
Group 2 – concentrate of human prothrombin complex factors

Fig. 1. The average amount of blood in the chest drain (ml) before and after administration of recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors.



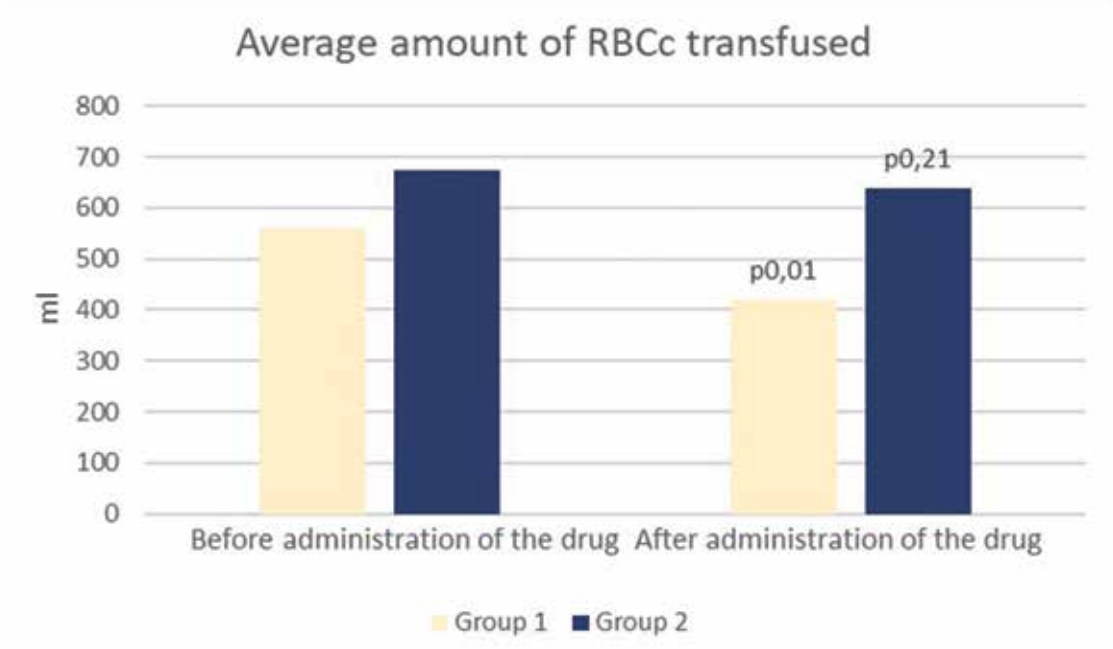
Group 1 – human recombinant coagulation factor VIIa
Group 2 – concentrate of human prothrombin complex factors

Fig. 2. Dynamics of postoperative bleeding in patients (ml/h) before and after administration of recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors.

Table 3. Blood loss, bleeding dynamics, amount of transfused blood and funds in both groups before and after drug administration

	Group 1			Group 2		
	Before	After	p	Before	After	p
Blood loss	690	396	0.009	635.6	541.7	0.04
Bleeding dynamics	171.8	47.5	0.001	117.8	33.6	0.001
RBCc	559.6	418.1	0.01	673.2	637.4	0.21
FFP	717.7	438.5	0.001	876.9	723.6	0.06
PC	328.5	57.9	0.001	467.7	294	0.006

RBCc – Red Blood Cell concentrate, FFP – Fresh Frozen Plasma, PC – Platelet Concentrate



Group 1 – human recombinant coagulation factor VIIa
Group 2 - concentrate of human prothrombin complex factors

Fig. 3. Average amount of RBCc transfused (ml) before and after administration recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors.

DISCUSSION

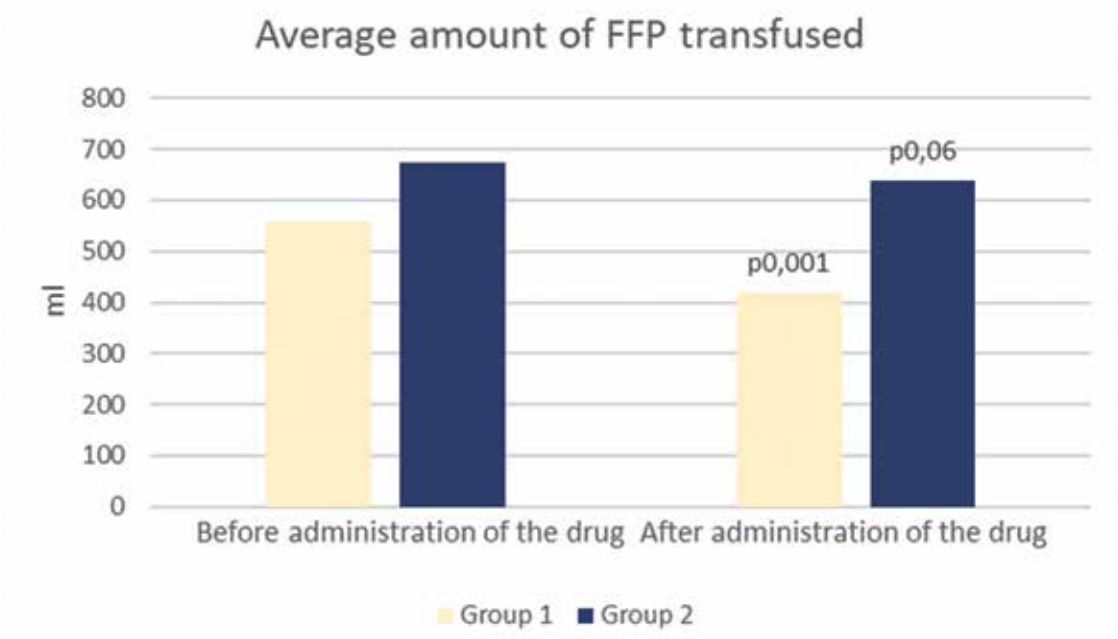
Patients treated for various cardiac diseases require chronic use of antiplatelet drugs and/or anticoagulants. Cardiac surgery in these patients is associated with an elevated risk of intraoperative and postoperative bleeding [1].

The standard drugs and blood products administered in these cases often do not accomplish the desired effect. Massive bleeding in a very short time can lead to hypovolemic shock, myocardial ischemia, and deterioration of the patient's condition, including death. In this case, the administration of recombinant human coagulation factor VIIa or concentrate of all prothrombin complex factors can be a life-saving procedure. Bleeding was stopped quickly and decisively [1-5, 7].

Concentrate of all prothrombin complex factors contains factors II, VII, IX, and X. It supplies coagulation factors to the tenase/prothrombinase complex, activating the hemostasis system on "two floors" [15].

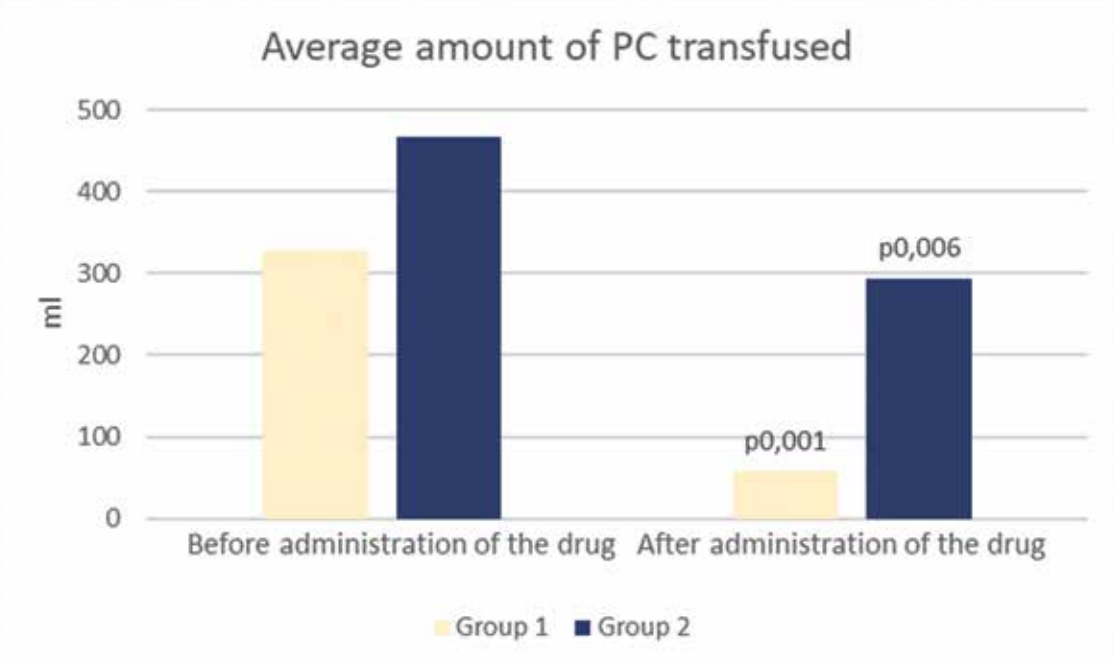
The timing of administration of recombinant human coagulation factor VIIa or concentrate of all prothrombin complex factors is very important. Administration before the patient "bleeds out" increases the chances of survival. Massive postoperative drainage (bleeding) disturbs the homeostasis of the circulatory system. Avoiding massive transfusions of blood and blood products prevents complications related to this.

According to the recommendations of the national consultant in the field of anesthesiology and intensive care, it is recommended to administer recombinant human coagulation factor VIIa in an initial dose of 80 mcg/kg b.w. We use this preparation after the exhaustion of standard therapeutic agents and after surgical hemostasis. If bleeding recurs after the administered dose, an additional dose



Group 1 – human recombinant coagulation factor VIIa
Group 2 - concentrate of human prothrombin complex factors

Fig. 4. Average amount of FFP transfused (ml) before and after administration recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors.



Group 1 – human recombinant coagulation factor VIIa
Group 2 - concentrate of human prothrombin complex factors

Fig. 5. Average amount of platelet concentrate transfused (ml) before and after administration of recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors.

of 80 mcg/kg b.w. should be administered [21]. Other authors claim similar protocols [9, 11, 17, 18].

In our clinic, we administered doses of 35 mcg/kg b.w., which had a good effect. Treatment with recombinant human coagulation factor VIIa reduced the amount of blood and blood products transfused, and the amount of blood in drains was significantly reduced [19, 20].

In our clinic, we administer two – four packages in an average dose with very good results. After the administration of concentrate of all prothrombin complex factors, the amount of blood transfused, and blood products decreased, but to a lesser extent than after recombinant human coagulation factor VIIa, while the amount of blood in drains decreased significantly. This reduces the risk of immunological and infectious complications after the transfusion of blood products.

Despite their high price, both preparations should be available in every cardiac surgery department. They are beneficial for the treatment of severe hemorrhage after cardiac surgery. These drugs are safe, and they do not cause embolic complications (in contrast to the first-generation human prothrombin complex coagulation factors) [1, 2, 19, 20]. Concentrate of all prothrombin complex factors is a second-generation preparation. First-generation prothrombin and proteins C and S were added to the composition. To date, there have been few reports in the literature about the occurrence of thromboembolic complications [19]. We have not observed such complications. Concentrate of all prothrombin complex factors is cheaper than recombinant human coagulation factor VIIa and equally effective in the treatment of hemorrhage in cardiac surgery.

CONCLUSIONS

Recombinant human coagulation factor VIIa and concentrate of all prothrombin complex factors reduce bleeding in patients undergoing cardiac surgery and reduce the amount of transfused blood products required.

After the administration of recombinant human coagulation factor VIIa, patients received a smaller amount of blood products (RBCc and FFP).

After receiving recombinant human coagulation factor VIIa, patients had less blood loss.

Clinical efficacy (number of patients who required rethoracotomy) was comparable between the two groups.

REFERENCES

1. Al Douri MA, Shafi T, Al Khdairi DA. Effect of the administration of recombinant activated factor VIIa in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. Blood Coagul Fibrinolysis, 2000;11,(Suppl 1):121-127.
2. Baral P, Cotter E, Gao G. Characteristics Associated with mortality in 372 patients receiving low-dose recombinant factor VIIa (rVIIa) for cardiac surgical bleeding. J Cardiothorac Vasc Anesth. 2019;33,(8):2133-2140.
3. Korsak J. Ostra utrata krwi i jej leczenie. In: Łętowska M, Korsak J, eds. Transfuzjologia Kliniczna. Bielsko-Biała: Alfa-medica Press; 2009, p.71-81. (Polish)
4. Szurlej D. Przetaczanie krwi i jej składników w kardiochirurgii. In: Łętowska M, Korsak J, eds. Transfuzjologia Kliniczna. Bielsko-Biała: Alfa-medica Press; 2009, p.151-154. (Polish)
5. Kietaibl S, Ahmed A, Afshari A et al. Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care. Second update 2022. Eur J Anaesthesiol. 2023;40:254-260.
6. Hoffmann T, Assmann A, Dierksen A. A role for low-dose recombinant activated factor VII in refractory bleeding after cardiac surgery: Lessons from an observational study. J Thorac Cardiovasc Surg. 2018;156,(4):1564-1573.
7. Abdel-Meguid ME. Prophylactic administration of recombinant activated factor VII in coronary revascularization surgery. Saudi J Anaesth. 2013;7:301-304.
8. Hayes K, Fernando MC, Young L. Prothrombin complex concentrate in cardiac surgery for treatment of non-surgical bleeding. Cochrane database of Systemic Reviews 2020, Issue 3. Art.: CD 0113551.
9. Roman M, Biancari F, Ahmed AB. Prothrombin complex concentrate in cardiac surgery: a systematic review and meta-analysis. Ann Thorac Surg. 2019;107: 1275-1283.
10. Singh SP, Chauhan S, Choudhury M. Recombinant activated factor VII in cardiac surgery: single-center experience. Asian Cardiovasc Thorac Ann. 2014;22:148-154.
11. Feih JT, Juul JJ, G Rinka JR. Adequacy of hemostatic resuscitation improves therapeutic efficacy of recombinant activated factor VII and reduces reexploration rate for bleeding in postoperative cardiac surgery patients with refractory hemorrhage. Ann Card Anaesth. 2019;22(4):388-393.
12. Kurkluoglu M, Engle AM, Costello JP. Single center experience on dosing and adverse events of recombinant factor seven use for bleeding after congenital surgery. J Saudi Heart Assoc. 2015;27:18-22.
13. Cappabianca G, Mariscalco G, Biancari F. Safety and efficiacy of prothrombin complex concentrate as first-line treatment in bleeding after cardiac surgery. Critical Care. 2016;20:61-69.
14. Michalska-Krzanowska G, Stanek R, Gżegżółka R. Doświadczenia własne z zastosowaniem rekombinowanego aktywowanego czynnika VIIa w leczeniu ciężkich krwotoków w kardiochirurgii. Kardiochirurgia i Torakochirurgia Polska.2008;5:158-162. (Polish)
15. Golański A J. Struktura i funkcje układu hemostazy. In: Jastrzębska M, ed. Diagnostyka laboratoryjna w hemostazie. Warszawa: Oinpharma; 2009, p. 31-56. (Polish)
16. Fitzgerald J, Lenihan M, Callum J. Use of prothrombin complex concentrate for management of coagulopathy after cardiac surgery: a propensity score matched comparison to plasma. BJA. 2018;120(5):928-934.
17. Green L, Roberts N, Cooper J. A pragmatic pilot phase II randomized controlled trial of prothrombin complex concentrates (PCC) versus fresh frozen plasma (FFP) in adult patients who are undergoinog heart surgery (PROPHESY). Trials 2019;20(1): 684.
18. Harper PC, Smith MM, Brinkman NJ. Outcomes following three-factor inactive prothrombin complex concentrate versus recombinant activated factor VII administration during cardiac surgery. J Cardiothorac Vasc Anesth. 2018;32(1):151-157.

19. Roman M, Biancari F, Ahmed AB et al. Prothrombin complex concentrate in cardiac surgery: a systematic review and meta-analysis. Ann Thorac Surg. 2019; 107(4):1275-1283.
20. Warren L. Intensywna terapia pacjentów z obrażeniami pourazowymi. In: Hurford, E. ed. Intensywna Terapia. Kraków: Wydawnictwo Medycyna Praktyczna; 2003,p.587-588. (Polish)
21. Wordliczek J, Wujtewicz M, Dąbrowska- Parafinowicz D. Zastosowanie rekombinowanego czynnika VII u chorych z zagrażającym życiu krwawieniem. In: Mayzner-Zawadzka, E ed. Wybrane zalecenia postępowania w anestezjologii. Warszawa: Wydawnictwo Lekarskie PZWL;2006,p.61-66. (Polish)

ORCID AND CONRTIBUTIONSHIP
Maciej Zagórski: 0000-0003-4999-4491[A-D]
Justyna Sejboth: 0000-0002-5215-1877[D-F]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 15.06.2023
ACCEPTED: 08.09.2023

ADDRESS FOR CORRESPONDENCE
Maciej Zagórski
Cardiac Surgery. Intensive Care Unit,
Central Clinical Hospital of the Medical University of Lodz,
Lodz, Poland
e-mail: maciejzag@poczta.fm

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 456-463

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305103

PREVALENCE OF AEROBIC VAGINITIS AFTER GYNECOLOGICAL SURGERIES AND ASSOCIATED ADVERSE PREGNANCY OUTCOME IN UKRAINE

Aidyn G. Salmanov[1,2], Iryna P. Netskar[1], Valerii V. Kostikov[3], Volodymyr Artyomenko[4], Svitlana M. Korniyenko[4], Victor O. Rud[5], Orusia A. Kovalyshyn[6]

[1]SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE
[2]INSTITUTE OF PEDIATRICS, OBSTETRICS AND GYNECOLOGY OF THE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE, KYIV, UKRAINE
[3]NATIONAL CANCER INSTITUTE, KYIV, UKRAINE
[4]ODESA NATIONAL MEDICAL UNIVERSITY, ODESA, UKRAINE
[5]NATIONAL PIROGOV MEMORIAL MEDICAL UNIVERSITY, VINNYTSIA, UKRAINE
[6]LVIV MEDICAL INSTITUTE, LVIV, UKRAINE

ABSTRACT

Aim: To determine prevalence of Aerobic Vaginitis (AV) after gynecologic surgery, risk factors and antimicrobial resistance of responsible pathogens, and adverse pregnancy outcomes in Ukraine.

Materials and Methods: Multicenter retrospective cohort study was conducted from January 2020 to December 2022 in fifteen medical clinics from eight regions of Ukraine. Smears were analyzed using Donders' classification method and Dong's modified AV diagnosis for Gram stains. Definitions of HAIs were adapted from the CDC/NHSN. Antibiotic susceptibility testing of bacteria was determined by Kirby-Bauer disc diffusion test according to the protocol of the EUCAST.

Results: Prevalence of AV among women's undergoing gynecologic surgery in Ukraine was 68.7%. Of the total AV cases, 70.3% were in non-pregnant and 29,7% in pregnant women. The most common pathogen of AV was *Escherichia coli*, followed by *Enterococcus faecalis*, *Streptococcus agalactiae, Staphylococcus aureus, Enterococcus faecium, Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Among the *S. aureus* strains, 11,6% of MRSA (Methicillin resistant *S.aureus*) were isolated whereas none of the CoNS were cefoxitin resistant. History of vaginal infection, history of post-operative infection and antibiotic use acted as an important risk factor of AV incidence rate. The presence of AV worsened pregnancy outcomes, by increasing the incidence of preterm birth, the premature rupture of membranes, miscarriage, neonatal jaundice, and neonatal infection.

Conclusions: Aerobic Vaginitis after gynecological surgeries in Ukraine is a common medical problem in women that is associated with significant morbidity, adverse pregnancy outcome, and hence frequent medical visits.

KEY WORDS: Prevalence, aerobic vaginitis, gynecological surgery, antibiotic use, risk factors, pregnancy outcomes, Ukraine

INTRODUCTION

Female genital tract infections have a high incidence among different age groups and represent an important impact on public health. Vaginitis is one of the most common gynecological diseases in women and may severely affect the quality of life in patients. According to literature, most pathogens may cause the disease, and may take the form of bacterial vaginitis, mixed vaginitis, *Candida vaginitis*, *Mycoplasma vaginitis*, and *Trichomonas vaginitis* [1], the latter having been the most common type in past decades [2]. However, the incidence of *Trichomonas vaginitis* has been decreasing in recent years, while that of bacterial vaginitis has remained stable [3].

Aerobic vaginitis (AV) is an imbalance of the vaginal flora. A decrease in the number of lactobacilli in the vaginal secretion reduces the defense ability and changes the pH value of the vaginal environment, which favors the development of bacterial inflammation [4]. Patients with AV may suffer from abnormal vaginal discharge and vulvae itching and discomfort, which severely affect their quality of life. AV has a complex microbiology. AV is more common than anaerobic vaginitis among all bacterial vaginitis [5], and the pathogens of AV include aerobic Gram-negative and Gram-positive microorganisms [6-8].

According to literature, the occurrence of AV may worsen the outcomes of pregnant women, resulting in more spontaneous preterm delivery and premature rupture of membranes [2,9]. However, previous studies mainly focused on early or late stage pregnancy, and it is hard to understand the incidence of vaginitis across the whole of pregnancy.

The study of risk factors of vaginitis in pregnant women also has important epidemiological and clinical significance. Many studies have explored the risk factors of vaginitis in non-pregnant women, which may differ significantly from those of non-pregnant women, due to hormonal and physiological changes. However, few studies have explored this issue to date, and the risk factors of AV in pregnant women remain unclear. Previous studies have identified the unmarried status, frequent vaginal douching, and long-term use of pregnancy-preventing drugs, and previous history of vaginal infection as the associated risk factors for AV [8-10].

Postoperative infection continues to be significant complications of major gynecologic surgery. The increasing resistance of microorganisms to drugs used in therapy healthcare associated infections (HAI) after gynecological surgeries in female is remarkable, since women report the recurrence of these infections and associated comorbidities. Many studies identified high incidence rates of HAI after hysterectomy for benign gynecological disease, and most cases were caused by pathogens that are resistant to antibiotics [11-14]. Majority of these cases were detected post discharge [11-14]. Few studies have examined the characteristics of aerobic vaginal flora samples in female, and no studies have examined them in women with postoperative infection and adverse pregnancy outcome. In Ukraine, similar studies on AV have not been carried out.

AIM

The aim of this study was to determine prevalence of AV after gynecologic surgery, risk factors and antimicrobial resistance of responsible pathogens, and adverse pregnancy outcomes in Ukraine.

MATERIALS AND METHODS

DESIGN, SETTINGS AND STUDY PARTICIPANTS

We performed a multicenter retrospective cohort study from January 1st, 2020 to December 31st, 2022. Our study included 3,125 women's (pregnant and non-pregnant) reproductive age (15 to 49 years) with symptomatic vaginal discharge, attending the fifteen medical clinic from eight regions of Ukraine. Our study population included women had history of gynecological surgery. All study participants were local residents. Exclusion criteria: Chlamydial infections, Syphilis or other sexually transmitted bacterial infections, patients with diagnosis of bacterial vaginosis, candidiasis and trichomoniasis, participation in a clinical trial using antibiotics or genital microbicides.

DEFINITION

Definitions of HAIs after gynecological surgery were adapted from the Centers for Disease Control and Prevention's National Healthcare Safety Network. Aerobic vaginitis (AV) was diagnosed if smears were deficient in lactobacilli, positive for cocci or coarse bacilli, positive for parabasal epithelial cells, and positive for vaginal leukocytes [15]. We focused on AV, and smears were analyzed using Donders' classification method and Dong's modified AV diagnosis for Gram stains [16, 17]. 'Any AV' was defined as an AV score of 4 or more, with a subclassification of 'light AV' if the score was 4–5, 'moderate AV' if it was between 6–7, and 'severe AV' when it was 8–10.

DATA COLLECTION

We developed a special questionnaire. Following enrolment, the baseline characteristics of patients was collected including age, body mass index, multifetal pregnancy, parity, history of cesarean delivery, microbiological, and clinical data, including invasive procedures, history surgical procedure and post-operative infections, previous hospitalization within one year after the current hospitalization, antibiotics usage (preoperative and postoperative antibiotic use), history of vaginal infection, history of hypertension and diabetes mellitus, level of education, history of smoking, and occupational status. All pregnant women were followed up until 1 month after delivery. Some pregnant outcomes were recorded in this study for further analysis, including delivery mode, preterm birth, premature rupture of membranes, birth weight, Apgar score, neonatal jaundice, neonatal infection, and stillbirth. This study includes interviews, questionnaires, and examinations medical records. Information was collected at baseline visit. Ambulatory medical records and relevant hospital records were reviewed for the study participants.

ETHICS

Institutional ethical committee clearance was taken. The samples were collected after obtaining informed consent from the patients. They were explained the purpose of the study and the procedures involved.

MICROBIOLOGICAL ANALYSIS

All enrolled participants underwent a gynecological examination, and a sterile cotton swab was used to obtain samples of vaginal discharge. Vaginal swab specimens were collected from females with symptomatic vaginal discharge, attending the medical clinics. Two high vaginal swabs were collected using sterile cotton swabs and were then immediately brought to the laboratory for processing. The first swab was used for Gram stain examination under 400x (for determining AV score) and 1000x magnification (for identification of organism). Smears were analyzed using Donders' classification method and Dong's modified AV diagnosis for Gram stains. Species identification was performed with standard microbial methods. The antibiotic susceptibility of the isolates was tested using the Kirby–Bauer disc diffusion method with Mueller Hinton agar and 5% sheep blood agar for the exigent strains. Thereafter, resistance data were interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) -2020 guidelines (http://eucast.org).

STATISTICAL ANALYSIS

In this study for all patients, demographic data, information about pregnancy outcomes, and genital symptoms (AB) were recorded. SPSS 24.0 software was used for data

processing and statistical analysis. Both bivariate analysis and multivariate regression analysis were used to evaluate the correlation of different variables. For bivariate analysis, the significance of differences between the two groups was evaluated using the Student T-tests and the Pearson's chi-square $\chi 2$ test. To express any significant difference, estimates with 95% confidence intervals were obtained using regression analysis. A $P<0.05$ significance level was used for all statistical tests.

RESULTS

PREVALENCE OF POST-OPERATIVE AEROBIC VAGINITIS

During the study period, 2147 of 3125 women's undergoing gynecologic surgery were found to have Aerobic Vaginitis (AB). Of the total postoperative AV cases, 70.3% (1509/2147) were in non-pregnant and 29,7% (638/2147) in pregnant women. The prevalence of AV among study participants was 68.7% (95% CI: 67.9–69.5). The differences in age distribution between the vaginal infection and no vaginal infection groups were statistically significant ($P < 0.001$). Twenty-nine percent of women had normal vaginal flora on microscopy, while 15.3% suffered from severe AV, 32.3% had moderate AV, and 16.9% had mild AV, compared to 0%, 2%, and 10%, respectively, in the normal group ($p < 0.0001$). Demographic and clinical characteristics of participants are shown in Table 1.

BACTERIAL PATHOGENS AND ANTIMICROBIAL RESISTANCE

In this study of 2256 culture positive samples, 80.8% (1823/2256) samples yielded single organism on culture and 19.23% (433/2256) yielded dual organisms (mixed). The most common pathogen of AV in this study was *Escherichia coli* (28.5%), followed by *Enterococcus faecalis* (17.5%), Group B *Streptococcus* (8.7%), *Staphylococcus aureus* (8.4%), *Enterococcus faecium* (8.2%), *Klebsiella pneumoniae* (7.4%), Coagulase-negative staphylococci (7.1%), *Pseudomonas aeruginosa* (5.9%), *Acinetobacter baumannii* (3.9%), *Lactobacillus* (2.9%), and other pathogens (1.4%). The distribution of bacterial pathogens in pregnant women with AV is summarized in Table 2.

There were 40% AV cases of mixed infections with *E. faecalis* and *E.coli* followed by 20% case each of *E.coli* + *P. aeruginosa*, *S. aureus* + *E.coli* and *K. pneumoniae* + CoNS. There was a greater predominance of gram-positive organisms in this study which seemed to show more resistance to penicillin and ampicillin except for Group B *Streptococcus* (*S. agalactiae*), which showed 100% sensitivity. Among the *E. faecalis* isolates, only 10% of them showed high level resistance to gentamicin. Among the *S. aureus* strains, 22 cases of MRSA (Methicillin resistant *S.aureus*) were isolated whereas none of the CoNS were cefoxitin resistant. The gram-positive organisms were maximum sensitive towards β–lactams/ β–lactamase inhibitor combinations, vancomycin and linezolid. The gram-negative isolates were least sensitive to ampicillin but showed moderate sensitivity towards third generation cephalosporin, aminoglycosides and fluoroquinolones but were highly sensitive to amoxyclav and meropenem. The most effective antibiotics against Pseudomonas aeruginosa were gentamicin, tobramycin and meropenem.

RISK FACTORS OF AEROBIC BAGINITIS AND PREGNANCY OUTCOMES

In this study risk factors of AV among study participants were analyzed using logistic regression as shown in Table 3. Age, history of cesarean delivery, history of vaginal infection, history of post-operative infection, antibiotic use, college education or above, and occupational status showed significant effects on the incidence of AV according to univariable logistic regression. However, after adjustment using multivariable logistic regression, a history of vaginal infection, history of post-operative infection and antibiotic use acted as an important risk factor of AV incidence, and a history of cesarean delivery, college education or above, and occupational status could protect study participants from the incidence of AV.

In this study pregnancy outcomes of women with AV are listed in Table 4. Vaginal delivery took place in 59.4% and 66.5% women in the without AV group and with AV group, respectively, and preterm birth occurred in 79 women (8.1%) in the without AV group and 412 women (19.2%) in the with AV group, showing significant difference ($P<0.001$). Similarly, premature rupture of membranes occurred in 91 women (9.3%) in the without AV group and 567 women (26.4%) in the with AV group, showing significant difference ($P<0.001$). Miscarriage occurred in 84 (8.6%) women in the without AV group and 599 women (27.9%) in the with AV group, showing significant difference ($P<0.001$). Neonatal jaundice was observed in 79 neonates (8.1%) of the without AV group and 318 neonates (14.8%) of the with AV group, showing a significant difference ($P=0.007$), and neonatal infection was observed in 40 neonates (4.1%) of the without AV group and 177 (8.2%) of the with AV group, also showing a significant difference ($P=0.025$). Only 11 stillbirth was observed in all enrolled women of both groups.

DISCUSSION

The results of present study provide valuable data as first research in Ukraine that focuses on the prevalence of AV after gynecological surgeries, bacterial pathogens and antimicrobial resistance, risk factors, and its impact on adverse pregnancy outcomes. In our study the prevalence of AV among study participants was 68.7%. Of the total postoperative AV cases, 70.3% were in non-pregnant and 29,7% in pregnant women. According to literature, the frequency of AV varies from 12% to 23.7% in symptomatic women who are not pregnant and 4 to 8% during pregnancy [18].

One of the most controversial issues is that the specific increasing pathogens and specific decreasing *Lactobacillus* species that contribute to AV remain poorly recognized. Based on classical cultivation methods, the most common bacteria related to AV in prior studies were Group B *Streptococcus* (*Streptococcus agalactiae*); *S. aureus*;

Table 1. Demographic and clinical characteristics of study participants in Ukraine

Variable	Number of women (n=3125)	Aerobic Vaginitis		P value
		Yes (n=2147)	No (n=978)	
Age (years), n (%)				0,072
15-21	192	174 (8.1)	18 (1.8)	
22-26	326	317 (14.8)	9 (0.9)	
27-31	406	339 (15.8)	67 (6.8)	
32-36	708	502 (23.4)	206 (21.1)	
37-41	816	522 (24.3)	294 (30.1)	
42-49	677	293 (13.6)	384 (39.3)	
Marital status, n (%)				0.056
Married	2,573	1,702 (79.3)	871 (89.0)	
Unmarried	552	445 (20.7)	107 (11.0)	
Education level, n (%)				0.004
High or below	2,247	1,627 (75.8)	620 (64.0)	
College of above	878	520 (24.2)	358 (36.0)	
Smoking habits, n (%)				0.362
No	2,995	2,044 (95.2)	951 (97.2)	
Yes	130	103 (4.8)	27 (2.8)	
Alcohol consumption, n (%)				0.128
No	2,008	1,427 (66.5)	581 (59.4)	
Yes	1,117	720 (33.5)	397 (40.6)	
Occupational status, n (%)				0.039
Unemployed	694	531 (24.7)	163 (16.7)	
Employed	2,431	1,616 (75.3)	815 (83.3)	
Pregnant status, n (%)				0.046
Non-pregnant	1,799	1,509 (70.3)	290 (29.7)	
Pregnant	1,326	638 (29.7)	688 (70.3)	
Multifetal pregnancy, n (%)	43	35 (1.6)	8 (0.8)	0.39
Parity, n (%)				0.283
0	1,947	1,381 (64.3)	566 (57.9)	
1	1,098	719 (33.5)	379 (38.8)	
2	80	47 (2.2)	33 (3.4)	
History of Cesarean delivery, n (%)	629	432 (9.9)	197 (20.1)	0.002
History of vaginal infection, n (%)	577	484 (22.5)	93 (9.5)	<0.001
History of hypertension, n (%)	77	48 (2.2)	29 (3.0)	0.793
History of diabetes mellitus, n (%)	38	23 (1.1)	15 (1.6)	1.0012
History of post-operative infection, n (%)	2,079	1,883 (87.7)	196 (20.0)	<0.0001
Antibiotic use, n (%)				<0.0001
Preoperative antibiotics not given	903	168 (7.8)	735 (75.2)	
Preoperative antibiotics given	577	466 (21.7)	111 (11.3)	
Post-operative long-term use of antibiotics	1,645	1,513 (70.5)	132 (13.5)	

E. faecalis; CoNS, such as *S. epidermidis*; and *E. coli* [18-20]. However, cultivation studies on vaginal bacteria from patients with AV exhibited heterogeneous results. We hypothesized that multiple aerobic microorganisms were involved or the causative bacteria were difficult to cultivate by conventional methods. In our study the most common pathogen of AV in this study was *E. coli*, followed by *E. faecalis*, *S. agalactiae*, *S. aureus*, *E. faecium*, *K. pneumoniae,* CoNS, *P. aeruginosa*, *A. baumannii*, *Lactobacillus*, and other pathogens.

Table 2. Distribution of bacterial pathogens in study participants with AV in Ukraine

Organisms	Total no. of isolates	Percentage (%)
Escherichia coli	642	28.5
Enterococcus faecalis	395	17.5
Group B Streptococcus (S. agalactiae)	197	8.7
Staphylococcus aureus	190	8.4
Enterococcus faecium	185	8.2
Klebsiella pneumoniae	167	7.4
Coagulase-negative staphylococci	161	7.1
Pseudomonas aeruginosa	134	5.9
Acinetobacter baumannii	88	3.9
Lactobacillus	65	2.9
Others	32	1.4
Total	2,256	100.0

Table 3. Risk factors of AV in study participants in Ukraine

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (years)	0,972 (0,944-1.004)	0,072	-	
History of Cesarean delivery	0,438 (0,257-0,746)	0,002	0,428 (0,248-0,738)	0,002
History of vaginal infection	2,754 (1,743-4,355)	<0,001	2,616 (1,638-4,174)	<0,001
History of post-operative infection	1.132 (1.092-1.172)	<0,001	1.142 (1.098-1.185)	<0,001
Antibiotic use	3.476 (2.226-5.427)	<0,001	2.506 (1.536-4.083)	<0,001
Education of college or above	0,566 (0,387-0,835)	0,004	0,578 (0,388-0,856)	0,006
Occupational status	0,647 (0,429-0,982)	0,039	0,637 (0,415-0,977)	0,04

Table 4. Pregnancy outcomes of women with post-operative Aerobic Vaginitis in Ukraine

Variable	Number of women	Aerobic Vaginitis		*P* value
		Yes (n=182)	No (n=503)	
Delivery mode, n (%)				0.095
Vaginal delivery	2,009	1,428 (66.5)	581 (59.4)	
Cesarean section	1,116	719 (33.5)	397 (40.6)	
Preterm birth, n (%)	491	412 (19.2)	79 (8.1)	0.001
Premature rupture of membranes, n (%)	658	567 (26.4)	91 (9.3)	0.001
Miscarriage	683	599 (27.9)	84 (8.6)	0.001
Birth weight, n (%)				0.572
<2500	209	152 (7.1)	57 (5.8)	
2500-4000	2,740	1,864 (86.8)	876 (89.7)	
>4000	176	131 (6.1)	45 (4.6)	
Apgar score, n (%)				0.613
<7	30	24 (1.1)	6 (0.6)	
≥7	3,095	2,123 (98.9)	972 (99.4)	
Neonatal jaundice, n (%)	397	318 (14.80	79 (8.1)	0.007
Neonatal infection, n (%)	217	177 (8.2)	40 (4.1)	0.025
Stillbirth, n (%)	11	11 (0.5)	0 (0)	0.266

Our study looks at the significance of AV, characterized by an increase in the number of resistant aerobic bacteria, including strains of both gram-positive and gram-negative microorganisms. In this study, many patients with AV had a history of post-operative infections associated surgical gynecological procedures. The reported incidence of healthcare-associated infection (HAI) after gynecological surgeries in Ukraine among women ranges from 9,9 to 25% [12-14, 21, 22]. The predominant HAI types were Cervicitis, Pelvic abscess or cellulitis, Salpingitis, Oophoritis, Adnexa uteri, Vaginal cuff infections, Endometritis, and Chorioamnionitis. 93.8% of HAIs were detected post discharge [13]. The most commonly identified pathogen was *E. coli, Enterobacter* spp., followed by *Klebsiella* spp., *Streptococcus* spp., and *P. aeruginosa*. The overall proportion of extended spectrum beta-lactamase production (ESBL) among Enterobacteriaceae was 17.1% and of methicillin-resistance in *S. aureus* (MRSA) 15.8%. Resistance to third-generation cephalosporins was observed in 13.7% *E.coli* and 8.5% *Klebsiella* spp. isolates. Carbapenem resistance was in 9.7% of *P.aeruginosa* strains [13].

Aerobic vaginitis is an imbalance of the vaginal flora and the main characteristic is an abnormal vaginal flora that contains aerobic and intestinal pathogens with varying degrees of vaginal inflammation. Essential treatment should result in the establishment of homeostasis of the vaginal environment where Lactobacilli play a role a charming role. Intensive treatment of AV could be a very important factor in preventing of precancerous lesions and cervical cancer.

The recommended treatment of AV includes a combination of therapy such as: antibacterial (antiseptic and antibiotic), hormonal, non-steroidal anti-inflammatory and/or probiotics, which can be prescribed in the form of local or systemic therapy. There is no generally accepted clinical strategy for the treatment of AV caused by multi-resistant strains Gram-negative and Gram-positive organisms. Therapy should be based on microbiological findings using a topical antibiotic for the infectious agent, a topical steroid to reduce inflammation, and estrogen to treat atrophy.

We in present study determined the risk factors of AV according to multivariable logistic regression and found the most important risk factor to be a history of vaginal infection, history of post-operative infection and antibiotic use. This is consistent with the results of other authors [2, 23]. Previous studies have shown intrauterine device use, external hemorrhoids, long-term antibiotic use, and frequent vaginal douching were independent risk factors for AV [2].

We found that the presence of AV worsened pregnancy outcomes, by increasing the incidence of preterm birth, the premature rupture of membranes, miscarriage, neonatal jaundice, and neonatal infection. Previous studies also confirmed that AV would increase the incidence of neonatal jaundice and neonatal infection [9], and preterm birth and premature rupture of membranes [24]. However, it also found that AV would increase the proportion of neonates with low birth weight. Only 209 neonates with low birth weight were delivered in our study and there was no significant difference between the two groups. After adjustment using multivariable logistic regression, older age, especially older than 40 years, was also seen as an important risk factor of adverse pregnant outcomes, which is similar to the results of a previous study [25].

Our study emphasized on the need to identify the aerobic vaginal pathogens associated with vaginitis especially in reproductive age group women which can go a long way in preventing the adverse outcomes associated with pregnancy and also ensures the necessity to determine the antibiotic sensitivity pattern of the pathogens which can aid in making a suitable therapeutic choice for 'aerobic vaginitis' by considering an antibiotic that is characterized by an intrinsic activity against the majority of bacteria, bactericidal effect and without any interference with the vaginal microbiota.

Finally, this study determined the prevalence and risk factors for AV among pregnant women after gynecological surgeries in Ukraine to generate findings that could guide the design of interventions for prevention of infection and associated poor pregnancy outcomes.

STRENGTH AND LIMITATION

The results of present study provide valuable data as first research in Ukraine that focuses on the prevalence of AV after gynecological surgeries, antimicrobial resistance pathogens, and risk factors for adverse pregnancy outcomes, and potential for comparison with data from other countries. The results of present study provide valuable data as first research focused on AV in Ukraine and potential for comparison with data from other countries.

Limitations: Firstly, as a retrospective study, the types of data that can be collected are relatively limited. Some other data such as the results of serological and immunological examinations could not be obtained, which may affect the final result. Secondly, follow-up and data collection were performed when women attended hospital for prenatal examination and delivery, and some risk factors of AV and adverse pregnancy outcomes that may have existed out of hospital and after delivery could also not be collected. Thirdly, different pathogens of AV were identified in our study, and it is still unclear what effect each of these pathogens has on pregnancy outcomes. Studies focusing on the effect of a single pathogen may improve the quality of future studies.

CONCLUSIONS

Aerobic Vaginitis after gynecological surgeries in Ukraine is a common medical problem in women that is associated with substantial discomfort, significant morbidity, adverse pregnancy outcome (preterm birth, preterm premature rupture of membranes, miscarriage, low birth weight, neonatal and maternal infections), and hence frequent medical visits. Most number of cases of AV are associated with vaginal infections and long-term use of antibiotics to treat post-operative infections. These infections must be identified and treated promptly. Antibiotics used to treat vaginitis must be very selective in order not to kill the

beneficial bacteria (*Lactobacilli*) that help in preservation of vaginal health and ecosystem, being one of the probiotic bacteria. Therapy should be based on microbiological findings using a topical antibiotic for the infectious agent, a topical steroid to reduce inflammation, and estrogen to treat atrophy. The high incidence of AV-associated with postoperative infections highlights, further research is needed to determine the etiology and understand potential causal linkages between AV after gynecological surgeries, and adverse pregnancy outcomes.

REFERENCES

1. Rigo GV, Tasca T. Vaginitis: Review on Drug Resistance. Curr Drug Targets. 2020;21(16):1672-1686. doi: 10.2174/1389450121666200804112340.
2. Han C, Li H, Han L et al. Aerobic vaginitis in late pregnancy and outcomes of pregnancy. Eur J Clin Microbiol Infect Dis. 2019;38(2):233-239. doi: 10.1007/s10096-018-3416-2.
3. Abdul-Aziz M, Mahdy MAK, Abdul-Ghani R et al. Bacterial vaginosis, vulvovaginal candidiasis and trichomonal vaginitis among reproductive-aged women seeking primary healthcare in Sana'a city, Yemen. BMC Infect Dis. 2019;19(1):879. doi: 10.1186/s12879-019-4549-3.
4. Krauss-Silva L, Almada-Horta A, Alves MB et al. Basic vaginal pH, bacterial vaginosis and aerobic vaginitis: prevalence in early pregnancy and risk of spontaneous preterm delivery, a prospective study in a low socioeconomic and multiethnic South American population. BMC Pregnancy Childbirth. 2014;14:107. doi: 10.1186/1471-2393-14-107.
5. Tao Z, Zhang L, Zhang Q et al. The Pathogenesis Of Streptococcus anginosus In Aerobic Vaginitis. Infect Drug Resist. 2019;12:3745-3754. doi: 10.2147/IDR.S227883.
6. Zhang HT, Wang H, Wu HS et al. Comparison of viromes in vaginal secretion from pregnant women with and without vaginitis. Virol J. 2021;18(1):11. doi: 10.1186/s12985-020-01482-z.
7. Lin Z, Lin Y, Zhang Z et al. Systematic analysis of bacteriostatic mechanism of flavonoids using transcriptome and its therapeutic effect on vaginitis. Aging (Albany NY). 2020;12(7):6292-6305. doi: 10.18632/aging.103024.
8. Wang C, Fan A, Li H et al. Vaginal bacterial profiles of aerobic vaginitis: a case-control study. Diagn Microbiol Infect Dis. 2020;96(4):114981. doi: 10.1016/j.diagmicrobio.2019.114981.
9. Tang Y, Yu F, Hu Z et al. Characterization of aerobic vaginitis in late pregnancy in a Chinese population: A STROBE-compliant study. Medicine (Baltimore). 2020;99(25):e20732. doi: 10.1097/MD.0000000000020732.
10. Wang H, Huang Z, Wu Z et al. An epidemiological study on vaginitis in 6,150 women of reproductive age in Shanghai. New Microbiol. 2017;40(2):113-118.
11. Salmanov A, Shchehlov D, Svyrydiuk O et al. Epidemiology of healthcare-associated infections and mechanisms of antimicrobial resistance of responsible pathogens in Ukraine: Results of a multicentre study (2019-2021). J Hosp Infect. 2023; 131:129-138. doi: 10.1016/j.jhin.2022.10.007.
12. Salmanov AG, Koctjuk IM, Ihnatieva OK et al. Prevalence of healthcare-associated cervicitis and antimicrobial resistance of the responsible pathogens in Ukraine: results of a multicenter study (2019-2021). Wiad Lek. 2022;75(9):2189-2197. doi: 10.36740/WLek202209202.
13. Salmanov AG, Vitiuk AD, Kovalyshyn OA et al. Surgical site infection after laparoscopic hysterectomy for benign gynecological disease in Ukraine. Wiad Lek. 2022;75(1):251-258. doi: 10.36740/WLek202201218.
14. Salmanov AG, Baksheev SM, Kuflovskyi DV et al. Healthcare-associated infection after legal induced abortions in Ukraine: results a multicenter study. Wiad Lek. 2021;74(7):1559-1565. doI: 10.36740/WLek202107103.
15. Donders GG, Vereecken A, Bosmans E et al. Definition of a type of abnormal vaginal flora that is distinct from bacterial vaginosis: aerobic vaginitis. BJOG. 2002;109(1):34-43. doi: 10.1111/j.1471-0528.2002.00432.x.
16. Liu Y, Wong KK, Ko EY et al. Systematic Comparison of Bacterial Colonization of Endometrial Tissue and Fluid Samples in Recurrent Miscarriage Patients: Implications for Future Endometrial Microbiome Studies. Clin Chem. 2018;64(12):1743-1752. doi: 10.1373/clinchem.2018.289306.
17. Dong M, Wang C, Li H et al. Aerobic Vaginitis Diagnosis Criteria Combining Gram Stain with Clinical Features: An Establishment and Prospective Validation Study. Diagnostics (Basel). 2022;12(1):185. doi: 10.3390/diagnostics12010185.
18. Donders GGG, Bellen G, Grinceviciene S et al. Aerobic vaginitis: no longer a stranger. Res Microbiol. 2017;168(9-10):845-858. doi: 10.1016/j.resmic.2017.04.004.
19. Fan A, Yue Y, Geng N et al. Aerobic vaginitis and mixed infections: comparison of clinical and laboratory findings. Arch Gynecol Obstet. 2013;287(2):329-35. doi: 10.1007/s00404-012-2571-4.
20. Han C, Wu W, Fan A et al. Diagnostic and therapeutic advancements for aerobic vaginitis. Arch Gynecol Obstet. 2015;291(2):251-7. doi: 10.1007/s00404-014-3525-9.
21. Salmanov AG, Artyomenko V, Koctjuk IM et al. Cervicitis as a cause of preterm birth in women. Wiad Lek. 2022;75(11):2715-2721. doi: 10.36740/WLek202211201.
22. Salmanov AG, Terekhov VA, Baksheev SM et al. Infections associated with obstetric and gynecological surgeries as a cause of female infertility in Uktaine. Wiad Lek. 2022;75(7):1634-1641. doi: 10.36740/WLek202207104.
23. Li N, Yue Y, Chen Q. Pathogen profile and risk factors of aerobic vaginitis in pregnant women: a retrospective cohort study. Ann Palliat Med. 2021;10(8):8881-8888. doi: 10.21037/apm-21-1710.
24. Juliana NCA, Suiters MJM, Al-Nasiry S et.al. The Association Between Vaginal Microbiota Dysbiosis, Bacterial Vaginosis, and Aerobic Vaginitis, and Adverse Pregnancy Outcomes of Women Living in Sub-Saharan Africa: A Systematic Review. Front Public Health. 2020;8:567885. doi: 10.3389/fpubh.2020.567885.
25. Xie D, Xiang Y, Wang A et al. The risk factors of adverse pregnancy outcome for pre-pregnancy couples in Hunan, China: a cross-sectional study based on population. Medicine (Baltimore) 2020;99:e23094. doi: 10.1097/MD.0000000000023094.

ACKNOWLEDGEMENTS

We would like to thank all physicians who contributed to the prevalence surveys.

ORCID AND CONTRIBUTIONSHIP
Aidyn G. Salmanov: 0000-0002-4673-1154[A,C-F]
Iryna P. Netskar: 0000-0003-4162-7179[B-D,F]
Valerii V. Kostikov: 0009-0008-6716-4858[B-D,F]
Volodymyr Artyomenko: 0000-0003-2490-375X[B-D,F]
Svitlana M. Korniyenko: 0000-0003-3743-426X[B-D,F]
Victor O. Rud: 0000-0002-0768-6477[B-D,F]
Orusia A. Kovalyshyn: 0000-0002-9710-0694[B-D,F]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 10.04.2023
ACCEPTED: 03.09.2023

ADDRESS FOR CORRESPONDENCE
Aidyn G. Salmanov
Shupyk National Healthcare University of Ukraine,
9 Dorohozhytska St., 04112 Kyiv, Ukraine
tel: +380667997631
e-mail: mozsago@gmail.com

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 464-474

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305104

DRUG MISUSE AND SELF-MEDICATION AMONG PHARMACY STUDENTS IN JORDAN

Ahmed Maslat[1,9], Nadia Al-Atoom[2] Manal Al-Najdawi[3] Loay Khaled Hassouneh[4], Ahmed Mashaal[5], Yazan Alrashdan[6], Naser Hamad Al-Rawashdeh[7], Mohammed Elhamrawy[8]

[1]DEPARTMENT OF PHARM-D, FACULTY OF PHARMACY, JADARA UNIVERSITY, AMMAN, JORDAN
[2]DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY, SCHOOL OF MEDICINE, INDIANA UNIVERSITY, INDIANA, USA
[3]DEPARTMENT OF APPLIED PHARMACEUTICAL SCIENCES AND CLINICAL PHARMACY, FACULTY OF PHARMACY, ISRA UNIVERSITY, AMMAN, JORDAN
[4]DEPARTMENT OF RESPIRATORY THERAPY, FACULTY OF ALLIED MEDICAL SCIENCES, ISRA UNIVERSITY, AMMAN, JORDAN
[5]DEPARTMENT OF PHYSICAL THERAPY, FACULTY OF ALLIED MEDICAL SCIENCES, ISRA UNIVERSITY, AMMAN, JORDAN
[6]DEPARTMENT OF PHARMACY, FACULTY OF PHARMACY, AMMAN ARAB UNIVERSITY, AMMAN, JORDAN
[7]COMMUNICABLE DISEASES DIRECTORATE, MINISTRY OF HEALTH, AMMAN, JORDAN
[8]DEPARTMENT OF PHYSICAL THERAPY, FACULTY OF ALLIED MEDICAL SCIENCES, MIDDLE EAST UNIVERSITY, AMMAN, JORDAN
[9]DEPARTMENT OF BIOLOGICAL SCIENCES, FACULTY OF SCIENCE, YARMOUK UNIVERSITY, IRBID, JORDAN

ABSTRACT

Aim: To estimate risks and prevalence of self-medication and potential abuse risk among pharmacy students in Jordanian Universities.
Materials and Methods: A cross-sectional study design was conducted with 450 students, selected using multistage sampling methods, from seven different universities. Data was collected by self-administrated questionnaires covering demographic and academic information, health-related information, use of self-medication, and pattern of self-medication among pharmacy students.
Results: Out of 394 students who answer the questions, 76.9% reported that they had usually treated themselves in case of simple cases without physician or pharmacist consultation. Most commonly used drugs among the surveyed students were Paracetamol 60%, multivitamins supplement 74.25%, and herbal products 37.2%, combination of NSAIDs and Paracetamol 20.6%, and laxatives 19.4%. Cold and flu 25.5%, headache 22.3%, abdominal pain 7.9%, gastric pain 7.9%, cold and flu, headache, abdominal pain, and gastric pain 14.9% were the main conditions which contribute to self-medication practice. It was also found that Pharmacy students were over-confident with the type of cases they could treat without referral to a specialist physician, despite knowing that some of the symptoms may be due to serious health problems. Misuse of analgesics and laxatives was clear, and there was a weakness in knowledge of the indications for the use of the most common drug.
Conclusions: The prevalence of self-medication among pharmacy students in Jordan is high, and medical teaching institutions need to educate students about the proper use of medicines. Strict legislation and more education on self-medication are necessary for effective use of medicines.

KEY WORDS: cross-sectional, self-medication, drug, pharmacy, Jordan

INTRODUCTION

Self-medication was prevalent in 86.7% of pharmacy students. 56.6% of students reported getting their medication from pharmacies, and roughly 30.5% admitted to consuming pharmaceuticals 5–6 times last year without a prescription. Before using the medicine, the majority of students (83.2%) read the informational leaflet [1]. Jordanian university students studying both medical and non-medical disciplines frequently self-medicate. If employed inappropriately, this behavior can represent a health issue that requires education and attention from Jordan's health care authorities [2]. Male students in their fifth year were more likely to self-medicate and utilize prescription-only drugs. While the rate of medication use was comparable in male and females, it varied between fifth- and first-year students. The most frequently utilized medications were paracetamol, antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs) [3]. 316 students were recruited. The majority of students, or 94.6%, had strong knowledge of self-medication, according to this survey. Additionally, being female and being a pharmacy student were substantially related to having good knowledge [4]. In Jordan, the rate of self-medication is alarmingly high. Misconceptions and misuse of drugs are viewed as important issues as well [5] based on students' views regarding self-medication, should create educational and preventative measures and establish a self-medication program. Drug regulatory and health authorities should strictly enforce the laws governing the sale and purchase of self-medication

and create public service announcements emphasizing the risks associated with self-medication [6]. More than two thirds of medical professionals self-medicate and describe the harmful effects of doing so. The pharmacy profession was a predictor of self-medication. For promoting sensible medication usage, it was suggested that relevant health education be provided [7]. Self-medication was shown to be more frequently used by females, third-year medical students, and people in good self-reported health. Fever (67.9%), muscle ache (54.0%), weariness (51.7%), sore throat (46.6%), and cough (44.4%) were the most frequently reported symptoms for self-medication. The most often prescribed medication for all symptoms was paracetamol [8]. Pharmacy students are the first medical care providers available for medication consultation, and the entrance to medical care, including access to fundamental medicines, is an earlier requirement. There are variations on the definition of a self-care concept, but all agree on its main components, which are self-diagnosis, self-medication, self-treatment, and patient's participation in professional care [9]. Strong actions should be taken to stop the sale of pharmaceuticals without a valid prescription, and national guidelines on medicine access should be adopted. Students should also be taught about the negative effects of self-medication [10]. Self-medication practice is popular worldwide in both developing and developed countries and despite its passive outlook it considered an important element of primary health care and accepted to have a strong role in the care of minor illness [11]. Ghadeer et al. (2012) study examined antibiotic self-medication among medical and non-medical students at the University of Jordan. Results revealed gaps in knowledge, attitudes and practice regarding the use of antibiotics in the study population and found no significant differences between medical and non-medical students in terms of self-medication [12]. In terms of gender, throughout different studies the majority of students who had reported the use of self-medication were female [13]. This study recommended having stricter measures to monitor the advertisements of medications. In 2006, a study among Chinese university students reported that self-medication prevalence was 94%. Among female university students in Malaysia, the prevalence was reported as 80.9% in 2010 [14]. The study results indicated that poorer individuals might rely on self-medication as an alternative to regular medical care [15]. In Jordan, the public has easy access to nearly many types of medications, as is similar in many other countries. Therefore, self-medication is an easy practice in Jordan. Jordanians can buy many medications without prescriptions and without consulting a doctor [16]. However, self-medication is not well explored area of research and has been studied by some researchers [17, 18].

Health expenditure in Jordan is high compared to other countries, with total health spending growing faster than GDP. The Health Care Utilization and Expenditure Survey found that Jordanians pay an average of 33JD (Jordanian dinars) annually for outpatient care of this, 75 % represent spending on drugs [19]. The total pharmaceutical expenditure in 2008 was 496.4 JD million (US $701 million dollars). This expenditure accounts for 3.08% of the GDP and makes up 35.94 of the Total Health Expenditure (THE) in the country [20]. Resistance increased use of healthcare facilities, lost workdays, and the spread of disease are all costs that outweigh the wasteful expenditure on the drug itself. These costs include increased drug resistance, increased use of healthcare facilities, lost workdays, and spread of disease [21]. Two studies investigated antibiotic self-medication among Jordanian. Sawair et al. (2009) studied antibiotic self-medication among the general population in Jordan. Six months' recall period was used to measure the prevalence of antibiotic self-medication. Previous experience with the same type of illness and the perception of saving time were the main reasons reported for antibiotic self-medication [16]. Self-medication with an antibiotic was higher among higher income and self-medication with antibiotics is more common among the general population than among university students. Self-medication prevalence among Jordanians is 42.5%, and is associated with age, where elderly and children being more susceptible to its troubles, with education level subjects in a sample of 1,943 households in Jordan [22]. A study by Alazzam et al. reported that the total cost of unused medication at home was estimated as JD 6,326,000 [24].

Self-medication and drug abuse are increasing globally due to lack of regulation and inadequate monitoring of prescription drugs. This is especially true in countries with no strict regulations [25]. The misuse of such drugs can cause serious outcomes such as serious side effects, drug interactions, and drug dependence. A study by Alkhatatbeh et al. found that self-medication was prevalent among medical and pharmacy students, regardless of their level of study. Drug authorities and healthcare faculties need to educate and encourage students about the proper use of medicines as a therapeutic tool. A study by Alsous et al. reported that self-medication is highly prevalent among pharmacy students at the University of Jordan [1, 20]. Pharmacy students in Jordanian universities must be effective communicators, providers of high-quality medications, trainers and managers, partners, and health promoters to contribute to society by promoting self-medication [26-28]. In our society, it is a common practice to treat most illnesses by self-medication. Self- medication is very common in medical students (pharmacists, doctors, nurses) [26-30]. Self-medication can lead to complications such as allergies, antibiotic resistance, kidney impairment, and dependency. Excessive use of vitamins and analgesics can lead to vitamin poisoning and analgesic poisoning [31]. As far as its prevalence is concerned, it has high rate all over the world. It has high prevalence rate that is ranging from 32.5-51.8% [32]. In another study, the main reasons were reported as not having serious diseases and being familiar with the disease and its remedy [33]. In one another study, the main reason for self-medication practice was reported as lack of time [34]. In an additional study, previous experience with a similar illness and saving time were the main reasons for self-medication with antibiotic [20]. Previously prescribed antibiotics stored in the household and purchased from retail pharmacies were reported in one another study as

the main sources of medication used [20]. Many studies have investigated the symptoms leading to self-medication [35]. Among university student's headache continued to be the main symptoms of self-medication, followed by the flu. Another study, reported fever and headache as the main symptoms of self-medication by the study participants [36]. The primary reason for not practicing self-medication among teaching healthcare professionals in Malaysia is the risk of adverse reactions [37]. Self-medication was associated with gender, field of study, and study year in Tigray, Ethiopia, with increased prevalence among female, pharmacy, and higher study year students [28].

AIM

The aim of this study was to assess the risks and prevalence of self-medication and to establish the degree of potential risk of drug abuse among pharmacy students at Jordanian universities.

MATERIALS AND METHODS

SETTINGS

This study was carried out between February 2018 and May 2018 in Jordanian universities providing pharmacy program. It targeted the undergraduate college pharmacy students at seven Jordanian universities in different cities, two of which are public universities: University of Jordan and Jordan University of Science and Technology (JUST), and five private universities: Isra University, Al-Zaytoonah University, Petra University, Al-Ahliyya Amman University, and Middle East University.

STUDY POPULATION AND SAMPLING TECHNIQUE

The study population consists of all undergraduate students from the seven universities. These universities enroll students from both genders, different backgrounds, different socioeconomic levels, and from different geographic regions of Jordan. The minimum sample size required to detect a difference is 242 calculated using the following formula $N=(I.9622*p*q)/d^2$, where (N: sample size, p: expected prevalence of self-medication: (1-p), d: margin of error 0.05). The p was assumed to be 19.61% as observed in the neighbor country (19%). However, given the study design effect, a sample of 450 was identified as a target sample size.

Sampling technique in this study was multi-stage sampling as the following:

I. We selected the seven universities in Amman city and Irbid governorate.
II. A list of pharmacy faculties was obtained from the website of each university, from this list, three were randomly selected from each university.
III. From each faculty, few sites were selected to collect the data. Then, Time periods were classified in each faculty by the lecture times (8-10am, 12-2pm, and 3-5pm).
IV. A convenient sample of time periods and day was selected from each faculty.

Each period represented the data collection time. Students available at the time of the lecture were asked to participate in the study. The total number of pharmacy students in each university was obtained from the university website. A specific number of participants were selected proportionate to the size of pharmacy students. The questionnaire was distributed among students the researcher and a research assistant who was trained on how to distribute the questionnaires. The verbal consent was obtained and considered if the students agree to fill out the questionnaire and participate in the study. The researcher would wait for the students until they were finished and returned the questionnaire. The collected sample size was 394 out of 450 questionnaires distributed.

STUDY DESIGN

A quantitative approach utilizing a descriptive, cross-sectional study design was used to estimate the prevalence of self-medication and abuse risk among pharmacy students and to provide information regarding the pattern of self-medication among pharmacy students in Jordan.

STUDY INSTRUMENT

Data for this study was collected using self-administered questionnaire. The questionnaire was developed and adopted after extensive literature review for similar studies conducted previously [24, 28, 31, 32, 36, 37]. The questionnaire was tested on a sample of 25 students who were excluded from the study. The study questionnaire consisted of 24 questions. It is divided into five major parts composed and discussed the following topics: demographic data, measures of academic and profession condition, health-related questions, self-medication practice, and patterns of self-medication.

PILOTING AND VALIDATION PROCESS

The instrument was examined by a pilot test, which is a small version of the proposed research study, which was conducted in a lecture hall at Jadara University to refine and to check the research process. In addition, it aims to determine whether the research questions are clear easy to understand, and to assess time needed to complete the questionnaire. The pilot test was carried out in January 2018 using a convenient sample of 25 students and 3 doctors in college of pharmacy. Some modifications were made mainly in editing and changing some words to bold font. Some instructions were written and the general design of the questionnaire was changed to reduce the number of pages from the three to two papers in order to make the question easier to answer. It took ten to fifteen minutes to complete each of the questionnaires.

STATISTICAL ANALYSIS

Data were coded and analyzed using SPSS version 21 and presented using descriptive statistics (counts, percentages). The bivariant analysis included the distribution of the prevalence of self-medication by each independent variable and chi-square statistical test was used to determine statistically significant differences. It was examined in relation to many variables by using chi-square statistical test. Level of alpha 0.05 was used.

ETHICAL CONSIDERATION

The institutional research board (IRB) committee at Jadara University approved the study prior to data collection. Verbal

informed consent was obtained from each participant before the participants filled out the questionnaires. Participants were informed that the collected data would be used only for the study purposes. No names or student's number were needed on the questionnaire in order to protect the confidentiality.

RESULTS

A total of 394 out of 450 questionnaires were returned to the author, giving an overall response rate of 87.5%. Table 1 shows the response rate for each university. As shown in the table, the response rate was between 83% and 96%, the higher was in Al-Ahliyya Amman University 96%, while the lowest was in Al-Zaytoonah University 83.3%.

The characteristics of 394 pharmacy students who participated in the study are given in (Table 2). Regarding the distribution of participants between public and private universities, it was found that the number of participants in private universities was significantly higher than in public universities (53.8% and 46.2%, respectively). In terms of gender, approximately three-fourths were female (72.6%) while the male account for 27.4% of the study subjects. The number of male participants in private universities is more than twice than in public ones, 19.7%, and 8.2% respectively, while the female is slightly higher in public universities 37.9% *vs*. 34.1%. This difference reached a statistically significant difference with p-value less than 0.001 (Table 2). A 95.7% of the study subjects were their ages between 20-25 years and the difference in the age between public and private universities was statistically significant. The largest proportion, about 72%, of participants was their GPA either very good or excellent. The accepted GPA comprises of 10.8 % of the study subjects and was higher in private universities, while the good and very good were account for 17.24 % and 38.9 % respectively and it is similar to accepted GPA in terms of their distribution, was higher in private universities. Excellent GPA was the only honor which was higher in public universities with an overall percentage of both type of universities is 33.1%. The difference in the distribution of participants according to the GPA between public and private universities was statically significant (p-value 0.034).

Table 2 shows that 251 (64.2%) of the surveyed students have been taking a training in community pharmacy. The figure was approximately similar in public and private universities without a statistically significant difference. In terms of having medical insurance, the majorities of public pharmacy students have a medical insurance (153 *vs*. 27), while the only less than half of the students in private universities have a medical insurance (95 *vs*. 111). This difference reached a statistically significant difference with p-value less than 0.001 (Table 2). Finally, the distribution of study subjects between public and private universities according to taking any drugs currently was not statistically significant, p-value 0.556. The most drugs used by the participants were vitamin D, B12, C, and naproxen (Fig. 1).

As table 3 shows, 54 of the respondents reported that they visit the physician for follow up in the last year at least once, while 45% had not visited the clinic the previous year. The major number of visits among majority was once, 56.6% of the total number of follow up. It has been found that the participants who have medical insurance visit the physician for follow up purpose more than who have not medical insurance, but the difference was not statistically significant with p-value 0.711. Also, it has been observed that the pharmacy students enrolled in private universities visit their physicians more than whom in public universities. Regarding the type of cases that the respondents will contact their healthcare provider for, about 62% said that they will approach the physician for severe cases, while 10.7% reported that they did not like to contact the physician for any type cases. It has been found that the participants who have medical insurance tend to visit the physician for sever case followed by simple cases and the same trend for participants who have not medical insurance. Moreover, it has been observed that the pharmacy students enrolled in both private and public universities tend to visit their physicians for severe cases in similar proportion, while for simple cases, more subjects in private universities said they will go to the clinic than students in public universities but this difference did not reach statistical significance with p-value 0.337.

The relationship between the pattern and practice of self-medication and academic year and type of university were examined. When participants were asked about self-medication in general, not specifies a time period, there was no significant difference in the practicing of self-medication between pharmacy students according to the academic year as well as the type of the university. When participants were asked if they deal with prescribed drugs with more caring than non-prescribed, 80.5% of the participants said yes and

Table 1. Response rate *per* university

University	No. of response	Response rate
Jordan University of Science and Technology	90	87.7%
University of Jordan	80	84.4%
Al-Zaytoonah University	50	83.3%
Isra University	55	89%
Petra University	69	87.7%
Al-Ahliyya Amman University	40	96%
Middle East University	10	90%
Overall response rate		87.5%

Table 2. Demographic characteristics of the sample

Demographic characteristics	Public university No (%)	Private university No (%)	p-value
Age (Year)			
20-25	180 (45.8%)	196 (50%)	0.556
26-30	1 (0.25%)	12 (3%)	
Older than 30	0 (0%)	4 (1%)	
Gender			
Male	32 (8.2%)	77 (19.7%)	≤0.001
Female	148 (37.9%)	133 (34.1%)	
Academic year			
3rd	37 (9.6%)	77 (20%)	≤0.001
4th	65 (17%)	63 (16.4%)	
5th	46 (12%)	65 (17 %)	
Overall GPA			
Accepted	10 (2.6%)	32 (8.2%)	≤0.001
Good	27 (6.94%)	40 (10.3%)	
Very Good	71 (18.3%)	80 (20.6%)	
Excellent	72 (18.5%)	57 (14.6%)	
Training in community pharmacy			
Yes	119 (30.4%)	132 (33.7%)	0.556
No	62 (15.8%)	78 (20%)	
Have medical insurance			
Yes	153 (39.6%)	95 (24.6%)	≤0.001
No	27 (6.9%)	111 (28.7%)	
Taking any drug currently			
Yes	37 (9.5%)	46 (11.8%)	0.556
No	144 (36.9%)	163 (41.8%)	

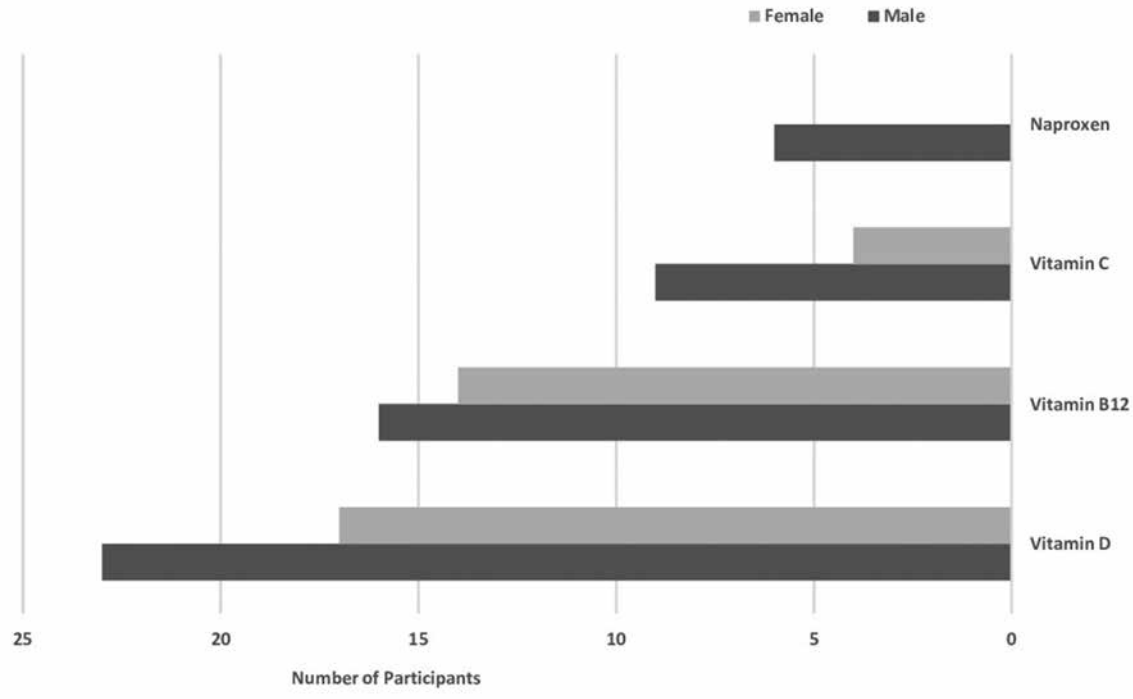


Fig. 1. Drugs used by the respondents regularly.

Table 3. Participants' responses to their health status and its relationship to medical insurance

	Do you have a medical insurance			University		
	Yes	No	*P*-value	Public	Private	*P*-value
How many times did you visit the physician the last year to conduct a regular checkup?						
Once	72	43		51	66	
Twice	33	27		26	36	
Three	18	8	0.771	13	14	0.941
More than four	1	1		0	2	
None	112	55		82	86	
What is the type of cases that you contact the physician for?						
Simple cases	32	24		17	39	
Sever cases	159	80	0.566	119	125	0.337
Most of the cases	28	20		27	22	
I do not go to the clinic	27	14		17	24	

the percentage was higher among fourth and fifth-year students. The different of subjects' response to this question was clear in term of an academic year and approaches the statistically significant, p-value 0.055 (Table 4). With regard to the difference in term of the type of university, there was no statistical difference between students studied in public and private universities. Amongst 380 students who answered the question (if does he/she become able to take drug without physician's consultation after joining pharmacy school), 209 (55%) said yes, and the figure for who responded positively was higher among fourth, fifth, and sixth year, while majority of third-year students answered no to this question, with p-value less than 0.001. Likewise, the previous question, there was no statistical difference between students studied in public and private universities (Table 4). Regarding the most type of analgesic that the surveyed students used frequently without prescription, the majority (60.8%) reported Paracetamol followed a combination of Paracetamol & NSAIDS with 20.9% (Table 4). Most of the Paracetamol users were third and fourth-year students while its using was less popular with sixth-year peers and this difference was statistically significant p-value 0.002. Similarly, there was no statistical difference between students studied in public and private universities. The distribution of used drugs is depicted in Figure 2.

Interestingly, when we asked the pharmacy students, who you usually consult in case of simple diseases like cold and headache, 76.9% said they usually treat their self, 19.4% go to the pharmacy and consult the pharmacist, while only 3.7% stated that they go to the clinic and consult the physician. With regards the distribution of the response according to the academic year, the confidence of the students to treat themselves in case of simple cases increased as the percentage in the third year 70.1% and reached approached 80% in the

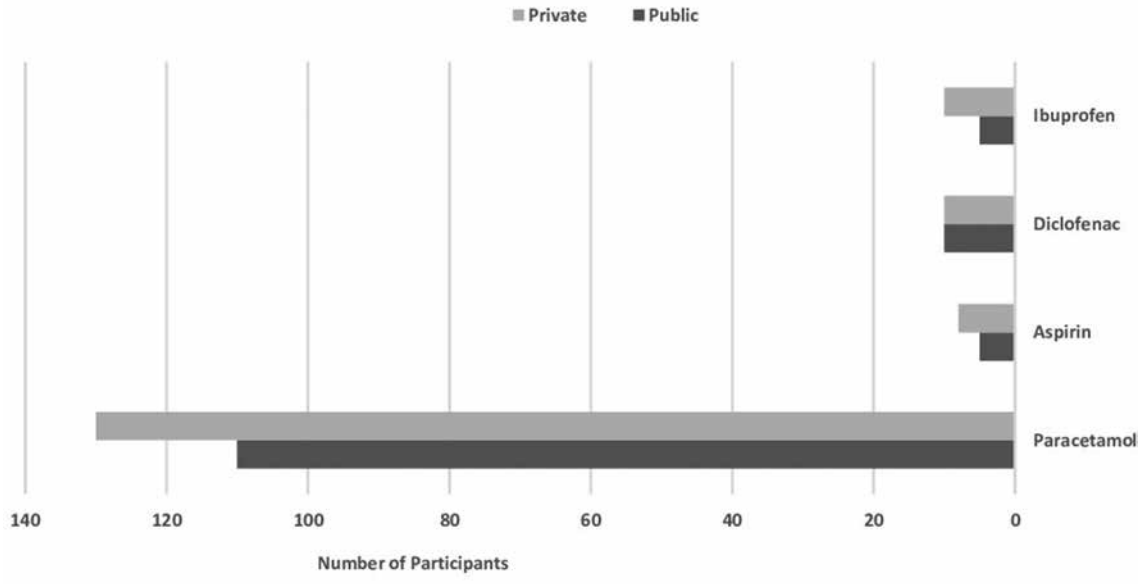


Fig. 2. Distribution of drugs intake by the participants.

sixth year. On the other hand, consultation of the pharmacist decreases as the academic year increase (from 27% in the third year to 4.7% in the fifth year). So, this difference was statistically significant with p-value, 0.013. Looking to the answer for this question form university type side, we found that 79.6% of the students enrolled in the public universities prefer to treat themselves compared to 74% in the private ones, but going to the pharmacy was higher in the private universities 23.6% *vs.* 15.3%. Regarding the physician consultation, 5.1% was from the public universities' compared to 2.35% from the private universities and this difference was not statistically significant. When participants were asked which of the following diseases can you treat yourself without healthcare provider consultation, 25% selected cold and flu, 21% chooses a headache, and 14.6% answered abdominal pain, headache, gastric pain, and cold and flu. There was no statistical difference in the answers according to the academic year, but it has occurred between public and private universities with (p-value less than 0.001) (Table 4). In terms of using herbal product, 143 (37.2%) reported that they use herbal product, and the large section of these users was in the fourth year (36.4% among herbal product intakes), while the lowest percentage 9.8% of usage was in the sixth year and the figure was similar for third and fifth year with 26.5% for each. It was clear that using herbal products are more popular among students who enrolled in public universities than private universities with p-value less than 0.001, (Table 4). Table 4 also shows that 172 (45.3%) of the surveyed students take vitamin supplements and the distribution of vitamin consumers is approximately similar in term of academic year and type of university. In addition, the types of multivitamins that the user reported are shown in Figure 3.

Furthermore, 140 (36.8%) of the participants reported that using two tablets instead of one provides a better outcome. The biggest cohort who claimed that was third-year students 38.5% and the number decreases as the academic year increases. According to the university, 41% of students in public university said yes compared to 31.9% for private universities. Similarly, only 19.9 % of the sample reported that they found a complication after using a specific drug, and the number was similar in all academic years except the sixth year which was much lower (7.9%) and the same was observed in the distribution of subjects who claimed. In addition, there was no difference between universities in terms of complication reported of the self-medication (Table 4). When participants were asked what is the indication for the first generation of antihistamine, 239(61.8%) selected allergy, 10.3% chose cold, 4.4% for sleep, 3.1% for the three indications, and 9.3% for none. It has been shown that the distribution of the answers was approximately similar between academic years except in group who said none; the majority of them were in the third year. Looking for the answers form universities view, there was no robust difference except that in the group who selected all the indication was higher in the public universities and this difference was not statically significant.

Table 5 shows that 103 (27.1%) of the surveyed students who take the drug regularly, 60 of them have training in a community pharmacy, while 277 (72.9%) do not take the drug regularly, 182 of them have training in a community pharmacy. Linking using the drug by the participants with if there is anyone in your family take prescribed analgesic, 63% do not use the drug regularly and there is no one in their families taking any type of analgesic. In addition, 31% of the students use complementary products such as herbal or multivitamins and have a training in a community pharmacy, while only half of this percentage 16.75% use complementary products such as herbal or multivitamins and have not a training in a community pharmacy. This difference was not statistically significant (Table 5).

Out of 386 participants, 305 (79%) members stated that they follow the leaflet instruction when you use the drug

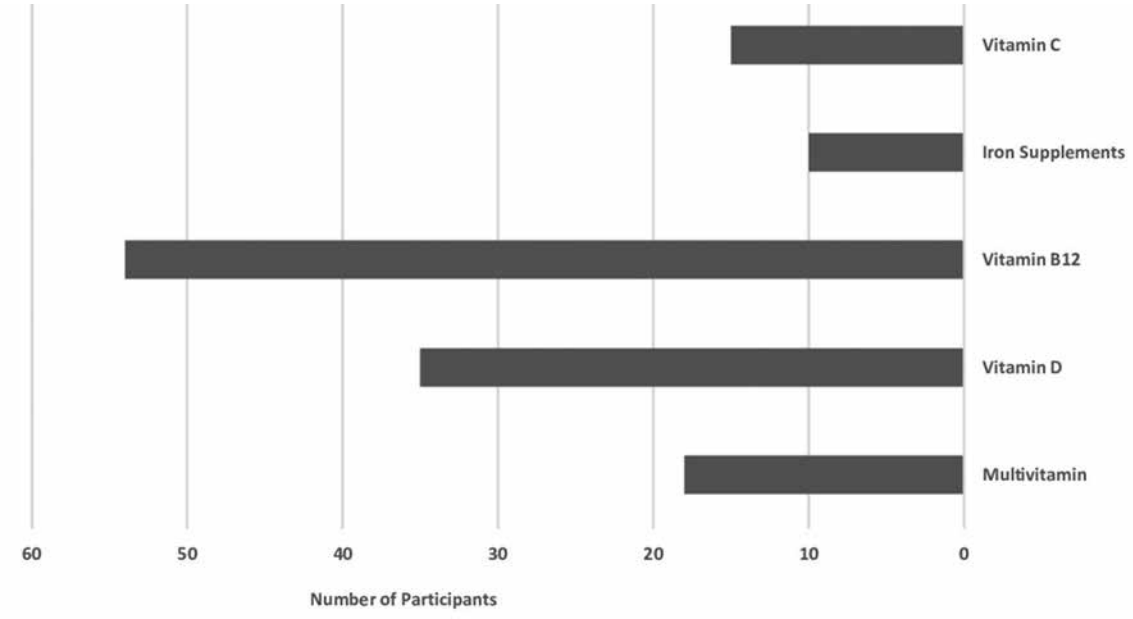


Fig. 3. Vitamin supplements used by the respondents.

Table 4. Participants response to the pattern and practice of self-medication

	Year					University		
	3rd	4th	5th	6th	*P*- value	Public	Private	*P*- value
Do you take any drug regularly without a prescription?								
Yes	21	28	22	10	0.749	37	46	0.556
No	92	98	84	27		144	163	
Do you deal with prescribed drugs with more caring than non-prescribed?								
Yes	80	110	88	29	0.055	148	163	0.766
No	33	17	16	8		31	47	
After joining pharmacy school, do you become able to take a drug without physician's consultation?								
Yes	34	74	76	25	0.000	103	111	0.591
No	78	52	30	11		77	97	
What type of analgesic you frequently use without a prescription?								
Paracetamol	91	69	57	19	0.002	107	134	0.982
Aspirin	2	5	1	1		3	6	
Diclofenac	0	4	8	0		6	6	
Ibuprofen	0	6	5	2		4	9	
Paracetamol& NSAIDS	16	30	23	12		45	37	
Combination of NSAIDS	1	16	11	4		18	12	
All	0	7	8	0		8	9	
None	5	3	2	3		5	8	
In case of simple diseases like cold and headache, who you usually consult?								
Physician	1	4	5	4	0.013	9	5	0.094
Pharmacist	33	20	17	4		27	50	
Treated by your self	80	101	83	29		141	157	
Which of the following diseases can you treat yourself without healthcare provider consultation?								
Abdominal pain	14	8	6	2	0.228	13	18	0.00
A headache	22	29	25	8		31	56	
Gastric pain	5	3	21	1		4	7	
Cold and flu	23	32	28	13		39	57	
All	15	19	16	6		35	22	
None	6	3	4	1		11	5	
Dou you use the herbal product?								
Yes	39	52	38	14	0.771	89	56	0.000
No	75	75	68	23		91	156	
Do you use vitamins supplements?								
Yes	51	60	50	11	0.258	76	98	0.687
No	63	65	54	26		102	112	
Do you think that using two tablets instead of one provides a better outcome?								
Yes	54	44	28	14	0.076	84	59	0.567
No	59	82	76	23		119	126	
Did you find any complication after using a specific drug?								
Yes	21	24	25	6	0.494	34	42	0.378
No	93	105	78	29		145	160	
What is the indication for the first generation of antihistamine?								
Cold	13	17	9	1	0.008	15	25	0.407
Allergy	66	82	69	22		109	134	
Sleep	4	5	5	3		9	9	
Cold and allergy	0	6	6	0		8	5	
Allergy and sleep	5	4	6	4		13	6	
All	1	6	4	1		10	4	
None	22	6	3	5		11	25	

without a prescription and most of these respondents were their GPA good (41%), very good (31.8%), and excellent (16%), while who said no, 69% was their GPA either good or very good. However, there was no statistically significant difference regarding the GPA or the type of university (Table 6). Likewise, when we asked the subjects if they look for the adverse effects, the interactions when using OTC, 310 (79.9%) selected yes, and the pattern of the destitution was similar to the previous question (Table 6). Finally, 73 (19.4%) of the surveyed students reported that they use laxative compared to 306 (80.7%) those who were not taking laxative and most of the laxative consumers were females compared to males (67.1% vs. 32.9%) and the answers for the reasons to take laxative was either for constipation, weight loss, and dyspepsia (Table 7).

DISCUSSION

Self-medication use is an increasingly hot topic in health care. We acknowledge that this type of study, using a self-administered questionnaire, is largely dependent upon information given by respondents. Although students were encouraged to complete the questionnaire independently, mutual influence between the students could not be entirely ruled out. This study was conducted to estimate the prevalence and pattern of self-medication risks among pharmacy students in Jordan, identify the main demographic, academic, and health associated with self-medication, and obtain information regarding the pattern of self- medication practices among the studied population. The study was conducted on a sample of 394 students from seven universities in Amman city and Irbid governorate. It was found that the prevalence of a self-medication was dependent on the type of university, in our study the prevalence did not significantly differ according to university type. Our results showed that 96.7% of participants use analgesic frequently without a prescription (60% Paracetamol, 8.6% NSAIDs, and 20.6% combination of Paracetamol and NSAIDs), 37.2% take herbal products, and 47.25% and 19.4% use vitamins and laxative respectively. These findings are similarly the study by Suleiman Ibrahim Sharif et al [38] revealed that the most common types of self-medication used by participants include, vitamins and minerals 67%, laxatives 10%, Paracetamol 83%, other NSAIDs 67%, are self-medicated which was found in a study by Sonia Imtiaz et. al. [39]. Laxative abuse was higher among female participants, possibly due to the belief that castor oil helps to lose weight. It is important for academic staff and healthcare providers to increase awareness of the rumors. There is an alarming trend among pharmacy students that they are able to treat themselves for simple cases without physician or pharmacist consultation.

Table 5. Students responses toward using drugs and complementary products

	Have you trained in community pharmacy?			Is there anyone in your family take prescribed analgesic?		
	Yes	No	*P*- value	Yes	No	*P*-value
Did you use a specific drug regularly?						
Yes	63	40	0.633	22	80	0.189
No	182	95		38	239	
Did you use any complementary products like herbal or multivitamins products?						
Yes	124	65	0.625	29	159	0.948
No	125	74		34	165	

Table 6. Students' responses regarding dealing with OTC and their academic year

	Overall GPA					University		
	Accepted	Good	Very good	Excellent	*P*- value	Public	Private	*P*-value
Do you follow the leaflet instruction when you use the drug without a prescription?								
Yes	34	125	97	49	0.193	147	158	0.283
No	8	25	31	17		31	53	
When you use OTC, do you look for adverse effects and the interactions?								
Yes	34	123	105	48	0.513	144	167	0.593
No	8	29	23	18		35	45	

Table 7. Participants' abuse for laxative

	Gender			University		
	Male	Female	*P*- value	Public	Private	*P*-value
Have you used a laxative without a prescription?						
Yes	24	49	0.708	33	40	0.074
No	84	222		139	169	

Professional and advanced education in pharmacy at the university starts when the students have progressed from the preparatory year into 2nd year and especially the fourth and fifth year. Professional education may influence their perception towards self-medication practice and treat the simple cases. The current study states that the ailments that do not need to contact a physician and for which self-medication was practiced include the cold and flu 25.5%, headache 22.3%, abdominal pain 7.9%, gastric pain 7.9%, cold and flu, headache, abdominal pain, and gastric pain 14.9%. This result is comparable to a study conducted by Sonia et al., [38] showed the high prevalence rates of self-medication were seen in conditions of common cold, headache, and other pains, and to another study by Sohair E Ali et al. [11] Furthermore, we also found that student's private university students were more visited by doctors than public university students due to their financial situation and high-income areas. This is due to the economic level of caring to the participants' health and the financial situation of private university students. We also found that their Pharmacy students in public and private universities lack knowledge of drugs and their indications, which was highlighted by the question of what is the indication for the first generation of antihistamine. The percentage of those who responded very correctly was so little, not more than 4%, and this is considered a serious warning message that it is necessary to focus more on the topics of pharmacotherapy and pharmacology because most graduates of the colleges of pharmacy are working in community pharmacies.

CONCLUSIONS

Self-medication is a common practice among pharmacy students in Jordan, with misuse of analgesics and laxatives. There was a weakness in the knowledge of indications for the most common drug, and pharmacy students were over-confident with regard to the type of cases that could be treated without reference to a specialist physician. This over-confidence was evident in the student's response to the qualification exam conducted by the Ministry of Higher Education. A well-structured training on the identification, prevention, and management of prescription and OTC drug misuse and abuse is needed in university pharmacy curricula in Jordan. A continuing pharmacy education program for practicing pharmacists is also needed since most Jordanian pharmacists work in community pharmacies, which are the most accessible primary health care facilities. Medical knowledge increases students' awareness of the risk of self-medication, which can lead to responsible self-medication. Medical teaching institutions need to educate students about the proper use of medicines as a therapeutic tool.

REFERENCES

1. Alsous M, Elayeh E, Abdel Jalil MH, et al. Evaluation of Self-Medication Practice among Pharmacy Students in Jordan. Jordan J Pharmaceut Sci. 2018;11(1):21-30.
2. Alshogran OY, Alzoubi KH, Khabour OF, et al. Patterns of self-medication among medical and nonmedical University students in Jordan. Risk Manag Healthc Policy. 2018;11:169-176. doi:10.2147/RMHP.S170181.
3. Daanish AF, Mushkani EA. Influence of Medical Education on Medicine Use and Self-Medication Among Medical Students: A Cross-Sectional Study from Kabul. Drug Healthc Patient Saf. 2022;14:79-85. doi:10.2147/DHPS.S360072.
4. Alduraibi RK, Altowayan WM. A cross-sectional survey: knowledge, attitudes, and practices of self-medication in medical and pharmacy students. BMC Health Serv Res. 2022;22(1):352. doi:10.1186/s12913-022-07704-0.
5. Mukattash T, Jarab A, Khawaldeh A, et al. Parental self-treatment of their children in Jordan, a qualitative study. Journal of Pharmaceutical Health Services Research. 2019;10 (3):317-323.
6. Malak MZ, AbuKamel AM. Self-medication Practices among University Students in Jordan. Malays J Med Health Sci. 2019;15(2):112-119.
7. Mohammed SA, Tsega G, Hailu AD. Self-Medication Practice and Associated Factors Among Health Care Professionals at Debre Markos Comprehensive Specialized Hospital, Northwest Ethiopia. Drug Healthc Patient Saf. 2021;13:19-28. doi:10.2147/DHPS.S290662.
8. Yasmin F, Asghar MS, Naeem U, et al. Self-Medication Practices in Medical Students During the COVID-19 Pandemic: A Cross-Sectional Analysis. Front Public Health. 2022;10:803937. doi:10.3389/fpubh.2022.803937.
9. World Health Organization. Guidelines for developing national drug policies. World Health Organization, 1988. [Access: January 2023]. https://iris.who.int/handle/10665/40427?&locale-attribute=ar
10. Araia ZZ, Gebregziabher NK, Mesfun AB. Self medication practice and associated factors among students of Asmara College of Health Sciences, Eritrea: a cross sectional study. J Pharm Policy Pract. 2019;12(3):1-9. doi:10.1186/s40545-019-0165-2.
11. White A, South J, Bagnall AM, et al. The self-care for people initiative: the outcome evaluation. Prim Health Care Res Dev. 2012;13(4):382-394. doi:10.1017/S146342361200014X.
12. Suaifan GARY, Shehadeh M, Darwish DA et al. A cross-sectional study on knowledge, attitude and behavior related to antibiotic use and resistance among medical and non-medical university students in Jordan. Afr J Pharm Pharmacol. 2012;6(10):763-770.
13. Lau GSN, Lee KKC, Luk MCT. Self-medication among university student in Hong Kong. Asia Pac J Public Health. 1995;8(3):153-157.
14. Ali SE, Ibrahim MI, Palaian S. Medication storage and self-medication behaviour amongst female students in Malaysia. Pharm Pract (Granada). 2010;8(4):226-232. doi:10.4321/s1886-36552010000400004.
15. Yousef AM, Al-Bakri AG, Bustanji Y, et al. Self-medication patterns in Amman, Jordan. Pharm World Sci. 2008;30(1):24-30. doi:10.1007/s11096-007-9135-x.
16. Sawair FA, Baqain ZH, Abu Karaky A, et al. Assessment of self-medication of antibiotics in a Jordanian population. Med Princ Pract. 2009;18(1):21-25. doi:10.1159/000163041.
17. Nandakumar AK, Wilwerding J, Bhawalkar M. Jordan Healthcare Utilization and Expenditure Survey. Jordan Ministry of Health; 2000. [Access: January 2023] https://scholarworks.brandeis.edu/esploro/outputs/9924147756701921

18. Chautrakarn S, Khumros W, Phutrakool P. Self-Medication With Over-the-counter Medicines Among the Working Age Population in Metropolitan Areas of Thailand. Front Pharmacol. 2021;12:726643. doi:10.3389/fphar.2021.726643.
19. Barnett A, Creese AL, Ayivor EC. The economics of pharmaceutical policy in Ghana. Int J Health Serv. 1980;10(3):479-499. doi:10.2190/UKU9-4XK5-VYMG-ELB4.
20. Alkhatatbeh MJ, Alefan Q, Alqudah MA. High prevalence of self-medication practices among medical and pharmacy students: a study from Jordan. Int J Clin Pharmacol Ther. 2016;54(5):390-398. doi:10.5414/CP202451.
21. Jaber D, Bulatova N, Suyagh M, et al. Knowledge, Attitude and Opinion of Drug Misuse and Abuse by Pharmacy Students: A Cross-Sectional Study in Jordan. Trop J Pharm Res. 2015;14(8):1501-1508.
22. Al-Azzam SI, Al-Husein BA, Alzoubi F et al. Self-medication with antibiotics in Jordanian population. Int J Occup Med Environ Health. 2007;20(4):373-380. doi:10.2478/v10001-007-0038-9.
23. Al-Azzam S, Khader Y, Rawashdeh S et al. An assessment of the Extent of Medication Wastage among Families in Jordan. Jordan J Pharm Sci 2012;5(1):65-73.
24. Bennadi D. Self-medication: A current challenge. J Basic Clin Pharm. 2013;5(1):19-23. doi:10.4103/0976-0105.128253.
25. Aljinović-Vucić V, Trkulja V, Lacković Z. Content of home pharmacies and self-medication practices in households of pharmacy and medical students in Zagreb, Croatia: findings in 2001 with a reference to 1977. Croat Med J. 2005;46(1):74-80.
26. Awad AI, Eltayeb IB. Self-medication practices with antibiotics and antimalarials among Sudanese undergraduate university students. Ann Pharmacother. 2007;41(7):1249-1255. doi:10.1345/aph.1K068.
27. Sharma R, Verma U, Sharma CL, et al. Self-medication medication among urban population of Jammu city. Ind J Pharmacol. 2005;37(1):40-43.
28. Kassie AD, Bifftu BB, Mekonnen HS. Self-medication practice and associated factors among adult household members in Meket district, Northeast Ethiopia, 2017. BMC Pharmacol Toxicol. 2018;19(1):15. doi:10.1186/s40360-018-0205-6.
29. Auta A, Banwat S, Sariem C, et al. Medicines in Pharmacy Students' Residence and Self-medication Practices. J Young Pharm. 2012;4(2):119-123. doi:10.4103/0975-1483.96627.
30. Naïm RO, Escher M. Antalgiques en automédication: quels sont les risques? [Self medication with analgesics: what are the risks?]. [in French] Rev Med Suisse. 2010;6(255):1338-1341.
31. Sanghani S, Zaveri HG, Patel VJ. Self medication: prevalence and pattern in urban community. J Pharmacovigilance Drug Safety. 2008:5:95-98.
32. Sweileh M. W. Self–Medication and Over-the-Counter Practices: A Study in Palestine. Al-Aqsa University Journal (Natural Sciences Series) 2004;8(1):1-9.
33. Gutema GB, Gadisa DA, Kidanemariam ZA, et al. Self- Medication Practices among Health Sciences Students: The Case of Mekelle University. J Appl Pharm Sci. 2011;10:183-189.
34. Ali AN, Kai JT, Keat CC, et al. Self-Medication Practices among health care professionals in a Private University, Malaysia. Int Curr Pharmaceutical Journal. 2012;1(10):302-310.
35. Osomene KP, Lamikanra A. Study of the Prevalence of self-Medication Practice among University Students in Southwestern Nigeria. Trop J Pharm Res. 2012;11(4):683-689.
36. Albusalih FA, Naqvi AA, Ahmad R, et al. Prevalence of Self-Medication among Students of Pharmacy and Medicine Colleges of a Public Sector University in Dammam City, Saudi Arabia. Pharmacy (Basel). 2017;5(3):51. doi:10.3390/pharmacy5030051.
37. Bollu M, Vasanthi B, Chowdary PS, et al. Prevalence of self-medication among the pharmacy students in Guntur: a questionnaire based study. World J Pharm Pharmaceut Sci. 2014;3(12):810-826.
38. Sharif SI, Mouslli L, Waisi R. Evaluation of Self-Medication among Pharmacy Students. Am J Pharmacol Toxicol. 2012; 7(4): 135-140.
39. Imtiaz S, Kamran SNA. Conditions, frequencies, and sociodemographic factors leading self medication practice in Sargodha area of Punjab Pakistan. J App Pharm. 2013;5(4):819-826.

ACKNOWLEDGMENTS

All the Authors acknowledge Jadara University in Jordan for providing material facilities.

ORCID AND CONTRIBUTIONSHIP

Ahmed Maslat: 0000-0003-3808-2788[B]
Nadia Al-Atoom: 0009-0008-3089-8030[C,F]
Manal Al-Najdawi: 0000-0003-4372-997X[C,E]
Loay Hassouneh: 0000-0002-8278-7278[A,F]
Ahmed Mashaal: 0000-0003-1586-5376[C,E]
Yazan Alrashdan: 0000-0002-8980-4616[B-C]
Naser Hamad Al-Rawashdeh: 0009-0009-0113-0126[D-E]
Mohammed Elhamrawy: 0000-0002-5758-3468[D-E]

ADDRESS FOR CORRESPONDENCE

Loay Hassouneh
Department of Respiratory Therapy
Faculty of Allied Medical Sciences
Isra University, Amman
e-mail: Loay.Hassouneh@iu.edu.jo

CONFLICT OF INTEREST

The Authors declare no conflict of interest

RECEIVED: 06.05.2023
ACCEPTED: 12.09.2023

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 475-481

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305105

INFLUENCE OF THE PATIENT'S SEX AND AGE, VOLUMES OF THE SALIVARY GLAND AND PLEOMORPHIC ADENOMA ON THE TUMOR HISTOLOGICAL VARIANTS

Igor S. Brodetskyi[1], Vladislav A. Malanchuk[1], Mykhailo S. Myroshnychenko[2], Stanislav O. Riebienkov[3], Oleksandr V. Arseniev[4], Oleksandr E. Kotenko[2], Liudmyla O. Brodetska[1]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE
[2]KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE
[3]NATIONAL SPECIALIZED CHILDREN HOSPITAL "OHMATDYT", KYIV, UKRAINE
[4]KHARKIV INTERNATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

Aim: The purpose of the study was to identify the influence of the patient's sex and age, the volumes of the salivary gland and pleomorphic adenoma on the histological variants of the tumor.

Materials and Methods: The study included 21 women and 9 men with pleomorphic adenomas of the salivary gland. In 15 cases, a mesenchymal variant of pleomorphic adenoma was identified, in 5 cases – an epithelial variant, in 10 cases – a mixed variant. The average age of the patients was 39.7±2.9 years. Patients with pleomorphic adenomas underwent magnetic resonance imaging using a Siemens MAGNETOM Aera 1.5T device (Germany), during which three projections of the tumor and salivary gland were measured (antero-posterior, lateral, vertical) with subsequent calculation of their volumes, and then the ratios of these volumes. Classification trees were used to determine whether patients belonged to one of three variants of pleomorphic adenoma. The CART (Classification And Regression Tree) algorithm was used as a branching option. Stopping branching was carried out using the FACT (Fact-style direct stopping) method until each terminal (final) node of the tree does not contain incorrectly classified observations or when their number becomes less than a given proportion of the total group size (less than 5%). Determination of the structure and relationships between the tumor variants and such indicators as gender, age and radiological indicators (volume of the tumor, volume of the salivary gland, ratio of tumor volume to salivary gland volume) was carried out using correspondence analysis.

Results: Epithelial variant of pleomorphic adenoma is more typical for women, and the mixed and mesenchymal variant is more common for patients of both sexes. The epithelial variant can develop in patients of any age, while the mixed variant occurs mainly in patients older than 41 years, and the mesenchymal variant – mainly in patients younger than 41 years. The ratio of the volume of the tumor to the volume of the salivary gland will be predominantly >0.17 in the epithelial variant of pleomorphic adenoma, predominantly ≤0.17 in the mesenchymal variant, and can take any value in the mixed variant.

Conclusions: The authors conducted a study in order to identify the influence of sex, age of the patient, and the ratio of the volume of pleomorphic adenoma to the volume of the salivary gland on the histological variant of the tumor. The revealed data will be useful in the treatment and diagnostic process in patients with pleomorphic adenoma of the salivary gland.

KEY WORDS: sex, age, patient, salivary gland volume, pleomorphic adenoma volume, pleomorphic adenoma histological variants

INTRODUCTION

Salivary gland tumors widely heterogeneous group that comprise about 3% of all head and neck tumors the annual incidence of which varies worldwide and ranges from 1.0 to 6.5 cases per 100,000 population [1-3]. They are the most complex due to broad histological spectrum resulting from a multiple tumor cell differentiation, cellular arrangements and extracellular matrix synthesis produced by certain tumor cells [4].

Benign tumors of salivary gland are more common when compared to malignant [5]. Pleomorphic adenoma is the most common salivary glands benign tumor, comprising 50-70% of all cases [5-6].

Pleomorphic adenoma was first termed by Willis. Its name comes from the architectural pleomorphism that may be seen with a light microscope [7]. Histological variants of pleomorphic adenoma, their immunohistochemical and morphometric characteristics have been described in our previous studies, as well as by many scientists [8-10].

Literature data regarding the age and gender characteristics of pleomorphic adenomas are contradictory [11]. Pleomorphic adenoma occurs in all ages but is most common in the third

to sixth decades of life. The average age of presentation is approximately 45 years with a female-to-male ratio of 2:1 [2].

Tumor size is an important pathological and clinical variable for benign and malignant salivary gland tumors [12]. Literature data regarding the relationship between the histological variants of pleomorphic adenoma and its size are controversial. Some scientists have not identified such a relationship [12], while other scientists describe it for some histological tumor variants [13].

AIM

The purpose of the study was to identify the influence of the patient's sex and age, the volumes of the salivary gland and pleomorphic adenoma on the histological variants of the tumor.

MATERIALS AND METHODS

The study included 21 women and 9 men with pleomorphic adenomas of the salivary gland. In 15 cases, a mesenchymal variant of pleomorphic adenoma was identified, in 5 cases – an epithelial variant, in 10 cases – a mixed variant. The average age of the patients was 39.7±2.9 years. Patients with pleomorphic adenomas underwent magnetic resonance imaging using a Siemens MAGNETOM Aera 1.5T device (Germany), during which three projections of the tumor and salivary gland were measured (antero-posterior, lateral, vertical) with subsequent calculation of their volumes, and then the ratios of these volumes. The average value of the salivary gland volume was 35041.91±11802 mm^3, the pleomorphic adenoma volume was 6141.86±4887.23 mm^3, and the ratio of tumor volume to salivary gland volume was 0.24±0.27.

Classification trees were used to determine whether patients belonged to one of three variants of pleomorphic adenoma [14]. The purpose of constructing a classification tree is to predict whether an object belongs to a particular class (tumor variant). The classification tree is a hierarchical structure with decision nodes and decisive selection rules. The CART (Classification And Regression Tree) algorithm was used as a branching option.

CART is an algorithm for constructing a classification tree that searches through all possible options for one-dimensional branching and selects the best one. Stopping branching was carried out using the FACT (Fact-style direct stopping) method until each terminal (final) node of the tree does not contain incorrectly classified observations or when their number becomes less than a given proportion of the total group size (less than 5%).

Determination of the structure and relationships between the tumor variants and such indicators as gender, age and radiological indicators (volume of the tumor, volume of the salivary gland, ratio of tumor volume to salivary gland volume) was carried out using correspondence analysis [15].

RESULTS

In this study, two qualitative indicators (gender, tumor type) and four quantitative indicators (age, tumor volume, salivary gland volume, ratio of tumor volume to salivary gland volume) were used for analysis.

For this analysis, the classification tree method [14] was used because it is a nonparametric method, which allows the use of data measured at any scale and under any distribution law. Another advantage of this method is the possibility of graphical presentation of results and ease of interpretation, which allows us to clearly explain why a particular object belongs to a particular class. In this case, it is possible to rank the indicators according to the degree of importance when determining the classified variants of pleomorphic adenomas.

It was applied a complete search of trees with one-dimensional branching using the CART algorithm to solve the classification (analysis) problem. Branching was stopped using a direct stopping algorithm according to FACT method with the established proportion of unclassified observations being less than 5%. Five-fold cross-validation was performed to assess quality.

Classification tree is built on the principle of a hierarchical structure, which consists of decision-making nodes. The decision nodes contain selection criteria. At each branching step, a rule generated at a node divides the set of patients into two parts. The left side of the node is the group where the condition is met; the right side is the group where the condition is not met. The number above the rectangles shows the number of patients included in it. Inside the rectangle is a qualitative diagram in three colors of the relationship between the variants of pleomorphic adenoma that are present at the input.

The resulting model (classification tree) (fig. 1) showed an optimal decision tree with 11 terminal vertices (red rectangles) and 10 branches. At the same time, the classification accuracy was 97% (29 out of 30 cases), the cost of cross-validation was 82.6%, which are very good indicators of the quality of the model.

Thus, we can conclude that indicators such as age and gender turned out to be significant parameters for classification and are associated with the type of pleomorphic adenoma. At the same time, it remains unclear how they are connected. It would be possible to use two-entry contingency tables and Pearson's χ^2 test to establish such relationship for qualitative indicators gender and tumor type. Unfortunately, the obtained values of χ^2 test had no significant differences ($p>0.05$). Therefore, multivariate analysis of contingency tables was used for several indicators (gender, age, ratio of tumor volume to salivary gland volume). This analysis is called corresponding analysis [15], but it requires converting all indicators into dichotomous ones. Figure 2-3 shows the principle of converting numerical indicators into dichotomous ones. After sorting the indicator by tumor type and indicator value, a line graph was constructed and a threshold value of the indicator was selected, which corresponded to the maximum average value of the χ^2 test between tumor types. The original quantitative indicator was transformed into a dichotomous one with the following values: 1 – less than the threshold value, 2 – more.

Multidimensional two-entry frequency table was used for three dichotomous predictors (sex, age, ratio of tumor

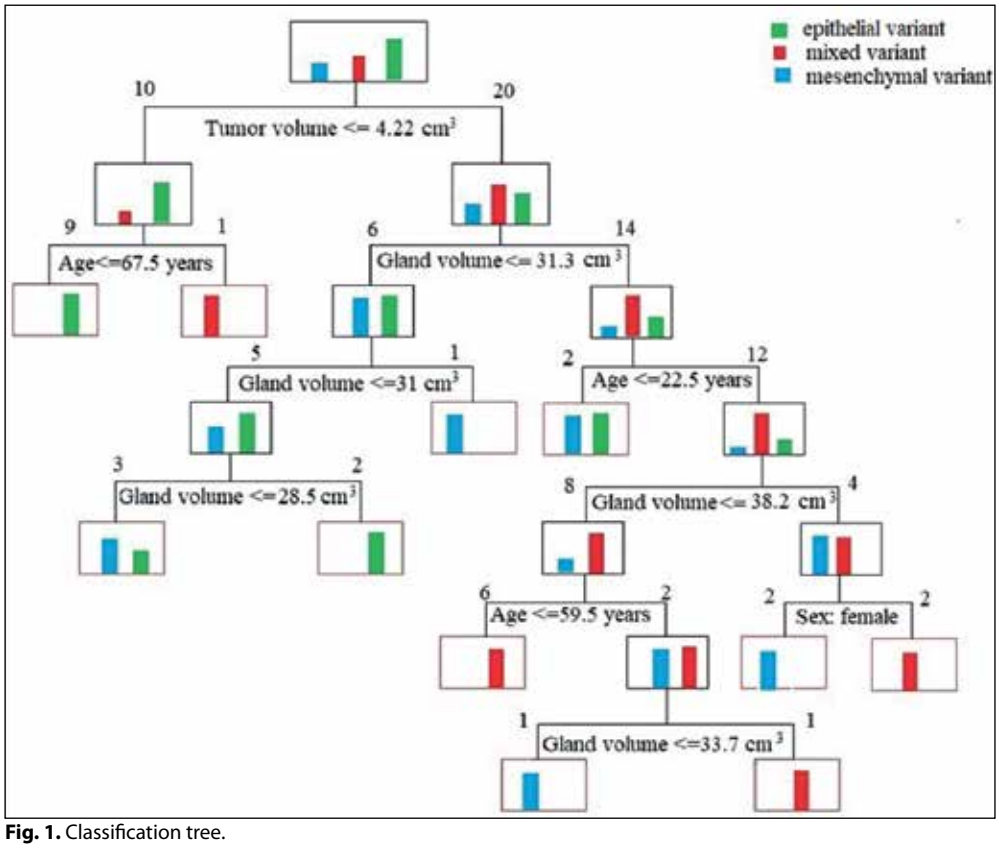


Fig. 1. Classification tree.

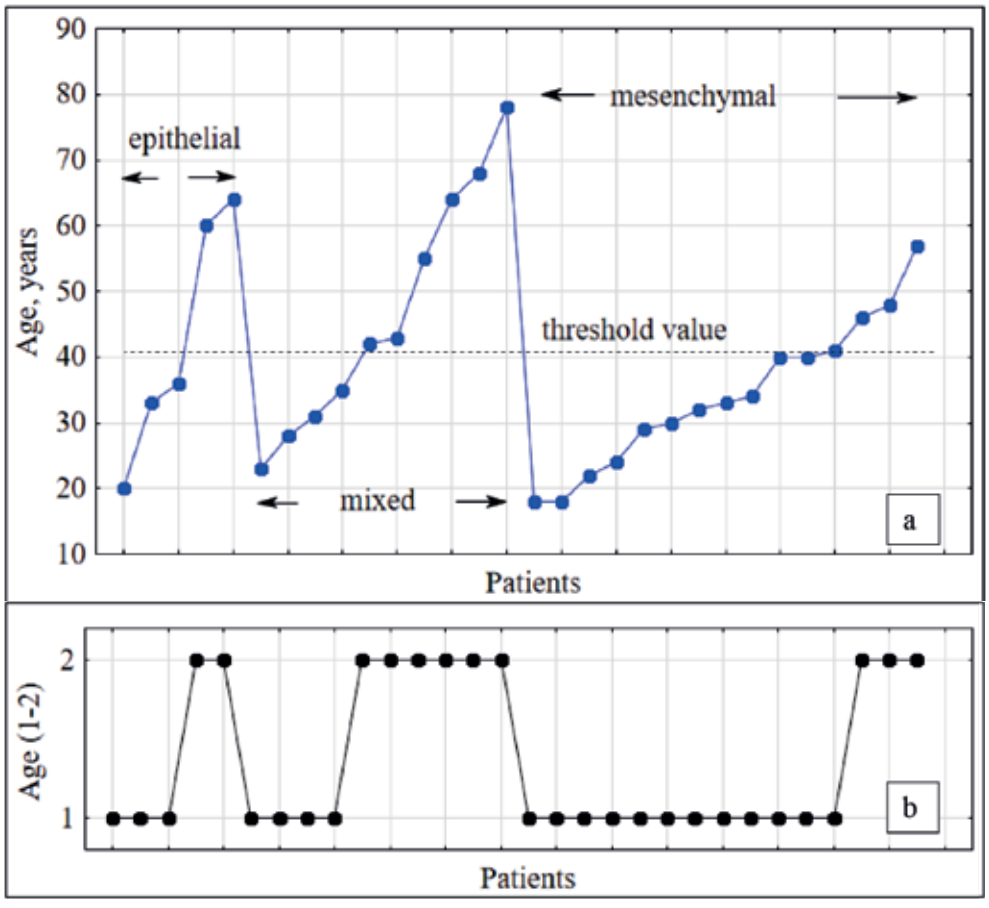


Fig. 2 (a, b). Determining the threshold value for age in order to convert it to the dichotomous indicator.

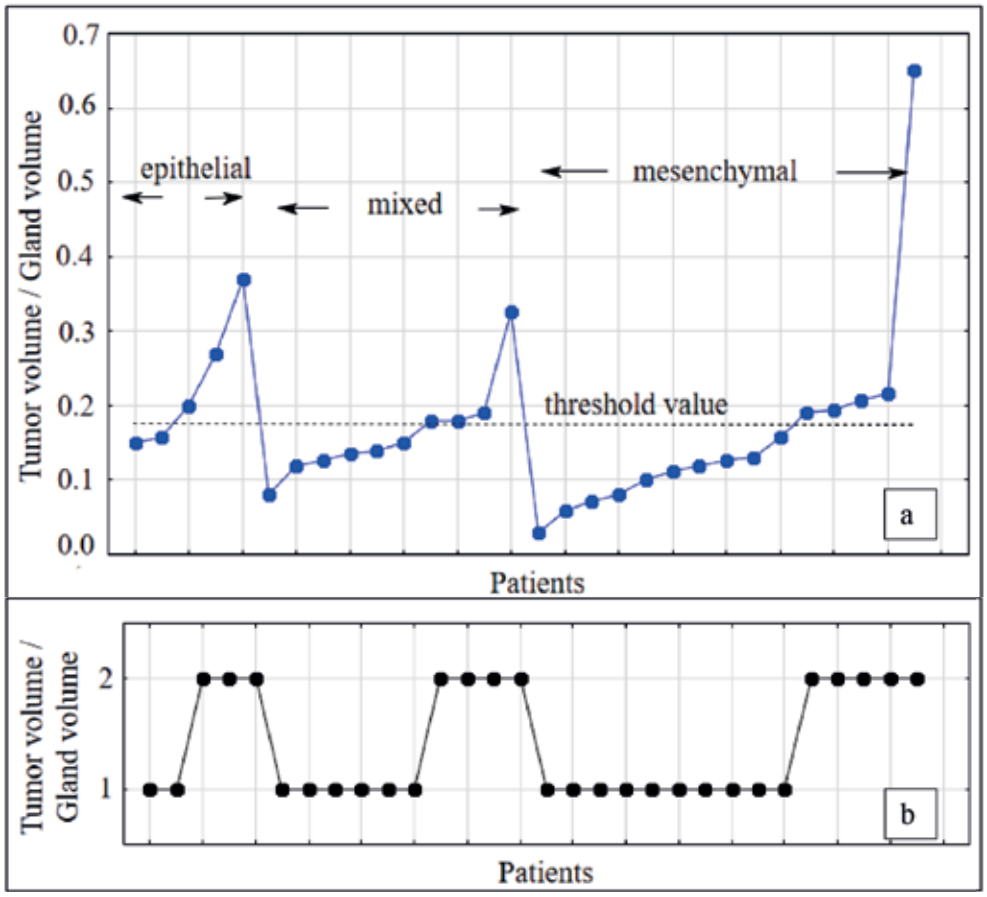


Fig. 3 (a, b). Determining the threshold value for the ratio of tumor volume to gland volume in order to convert it to the dichotomous indicator.

Table 1. 9×9 dimensional Burt matrix

	Gender: female	Gender: male	Age: ≤41 years	Age: >41 years	Type: epithelial	Type: mixed	Type: mesen-chymal	Tumor/ gland volume: ≤0.17	Tumor/ gland volume: >0,17	Total
Gender: female	21	0	15	6	5	6	10	12	9	84
Gender: male	0	9	4	5	0	4	5	6	3	36
Age: ≤41 years	15	4	19	0	3	4	12	10	9	76
Age: >41 years	6	5	0	11	2	6	3	8	3	44
Type: epithelial	5	0	3	2	5	0	0	2	3	20
Type: mixed	6	4	4	6	0	10	0	6	4	40
Type: mesenchymal	10	5	12	3	0	0	15	10	5	60
Tumor/gland volume: ≤0.17	12	6	10	8	2	6	10	18	0	72
Tumor/gland volume: >0,17	9	3	9	3	3	4	5	0	12	48
Total	84	36	76	44	20	40	60	72	48	750

volume to gland volume) and three tumor types, which was transformed into a 9×9 dimensional Burt matrix for correspondence analysis (Table 1).

Using multidimensional correspondence analysis, the contents of the Burt matrix can be represented as points that correspond to the rows and columns of a table in a lower dimensional space. In the case of the initial nine-dimensional space, it was enough to consider only 4 dimensions with a cumulative contribution to inertia of at least 91.14%. Table 2 shows the coordinates of the original 9 points in four-dimensional space.

Figure 4 shows a graph of one of its two-dimensional projections of the considered 9 indicators, which are specified by the coordinates indicated in Table 2. It should be noted

Table 2. Coordinates of indicators in 4-dimensional space

Indicators	Coordinates			
	Dimension 1	Dimension 2	Dimension 3	Dimension 4
Gender: female	-0.431	0.186	-0.265	-0.326
Gender: male	1.01	-0.435	0.617	0.761
Age: ≤41 years	-0.556	-0.328	0.17	-0.16
Age: >41 years	0.96	0.566	-0.293	0.277
Type: epithelial	-0.958	1.459	-0.715	1.061
Type: mixed	0.855	0.573	0.397	-0.839
Type: mesenchymal	-0.251	-0.868	-0.026	0.206
Tumor/gland volume: ≤0.17	0.353	-0.314	-0.632	-0.091
Tumor/gland volume: >0,17	-0.529	0.472	0.948	0.136

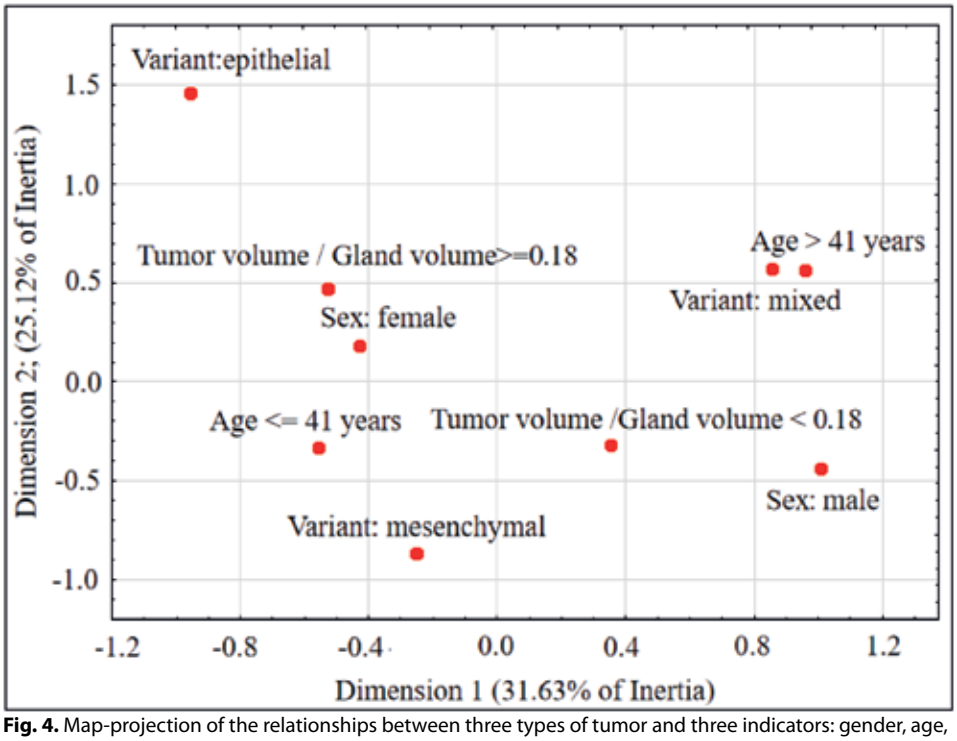


Fig. 4. Map-projection of the relationships between three types of tumor and three indicators: gender, age, ratio of tumor volume to gland volume.

that the distances between 9 indicators shown on figure 4 only illustrate their relative positions. Euclidean metric was used in accordance with the coordinates of table 2 to calculate real distances. They are shown in Table 3.

Distances between points can be considered as a measure of the relationship between indicators, i.e. the closer the points are to each other, the more connected they are and the more likely the events they represent are to co-occur. Therefore, the inverse distances between points can be interpreted as the probabilities of their joint occurrence. Taking into account that tumor type-dependent indicators are dichotomous and the probability normalization condition, we can write the probabilities of indicators for the three types of adenoma (Table 4).

Thus, the data in table 4 indicate that the epithelial variant of pleomorphic adenoma is more typical for women, and the mixed and mesenchymal variant is more common for patients of both sexes. The epithelial variant can develop in patients of any age, while the mixed variant occurs mainly in patients older than 41 years, and the mesenchymal variant – mainly in patients younger than 41 years. The ratio of the volume of the tumor to the volume of the salivary gland will be predominantly >0.17 in the epithelial variant of pleomorphic adenoma, predominantly ≤0.17 in the mesenchymal variant, and can take any value in the mixed variant.

DISCUSSION

The authors conducted a study in order to identify the influence of sex, age of the patient, and the ratio of the volume of pleomorphic adenoma to the volume of the salivary gland on the histological variant of the tumor.

Table 3. Euclidean distances between adenoma types and indicators

Indicators	Gender: female	Gender: male	Age: ≤41 years	Age: >41 years	Tumor/ gland volume: ≤0.17	Tumor/ gland volume: >0.17
Type: epithelial	1.377	2.729	1.832	2.295	2.489	1.077
Type: mixed	1.343	1.019	1.673	0.105	1.02	1.387
Type: mesenchymal	1.07	1.33	0.62	1.877	0.819	1.368

Table 4. Probability of indicators for different types of adenoma

Indicators	Gender: female	Gender: male	Age: ≤41 years	Age: >41 years	Tumor/ gland volume: ≤0.17	Tumor/ gland volume: >0.17
Type: epithelial	66.5%	33.5%	55.6%	44.4%	30.0%	70.0%
Type: mixed	43.0%	57.0%	5.9%	94.1%	57.6%	42.4%
Type: mesenchymal	55.4%	44.6%	75.2%	24.8%	62.6%	37.4%

Research carried out by many scientists, including our earlier analysis of archival material, revealed that pleomorphic adenoma most often develops in women [16, 17]. This study showed that the epithelial variant of pleomorphic adenoma is more typical for women, whereas the mixed and mesenchymal variant is more common for patients of both sexes.

Pleomorphic adenoma of the salivary gland, according to the literature, can develop at any age, including children, but with predominance in the third to sixth decades of life [2]. Our research showed that the epithelial variant of pleomorphic adenoma can develop in patients of any age, while the mixed variant occurs mainly in patients older than 41 years, and the mesenchymal variant – mainly in patients younger than 41 years.

Many scientists in their studies did not analyze the size of salivary gland, the size of pleomorphic adenoma in various types of tumor. In a few studies, tumor size and histological variant were analyzed, and the results obtained were contradictory. Chau and Radden reported that stroma-poor (epithelial variant) pleomorphic adenoma were larger than stroma-rich (mesenchymal variant) ones, and suggested that cellular variant may grow at a faster rate. Cesinaro et al., Alves FA et al. observed that stroma-rich pleomorphic adenoma were significantly larger than other variant [13]. Erkul E et al. did find a significant association between tumor size and its histological subtype [12]. In this study, we noted that the ratio of the volume of the tumor to the volume of the salivary gland will be predominantly >0.17 in the epithelial variant of pleomorphic adenoma, predominantly ≤0.17 in the mesenchymal variant, and can take any value in the mixed variant.

CONCLUSIONS

The epithelial variant of pleomorphic adenoma is more typical for women, but the mixed and mesenchymal variant is more common for patients of both sexes. The epithelial variant can develop in patients of any age, while the mixed variant occurs mainly in patients older than 41 years, and the mesenchymal variant – mainly in patients younger than 41 years. The ratio of the volume of the tumor to the volume of the salivary gland will be predominantly >0.17 in the epithelial variant of pleomorphic adenoma, predominantly ≤0.17 in the mesenchymal variant, and can take any value in the mixed variant.

REFERENCES

1. Shamloo N, Ghanadan A , Hashemiyan F S, Ghorbanpour M. Epidemiologic characteristics of salivary gland tumors in an Iranian population. Shiraz E-Med J. 2021;22(9):e107675. doi:10.5812/semj.107675.
2. Ghartimagar D, Ghosh A, Shrestha MK, Thapa S, Talwar OP. Histopathologic Profile of Salivary Gland Tumors among Specimens from a Tertiary Care Hospital: A Descriptive Cross-sectional Study. JNMA J Nepal Med Assoc. 2020;58(230):729-735. doi: 10.31729/jnma.4898.
3. Toper MH, Sarioglu S. Molecular Pathology of Salivary Gland Neoplasms: Diagnostic, Prognostic, and Predictive Perspective. Adv Anat Pathol. 20211;28(2):81-93. doi: 10.1097/PAP.0000000000000291.
4. Nonitha S, Yogesh TL, Nandaprasad S, Maheshwari BU, Mahalakshmi IP, Veerabasavaiah BT. Histomorphological comparison of pleomorphic adenoma in major and minor salivary glands of oral cavity: A comparative study. J Oral Maxillofac Pathol. 2019;23(3):356-362. doi: 10.4103/jomfp.JOMFP_91_19.
5. Lai CC, Lin CT, Lin YH. Cellularity and its relation with capsular characteristics as an influencing factor for operative strategies of pleomorphic adenoma. Cir Cir. 2022;90(4):439-446. doi: 10.24875/CIRU.21000626.

6. Brodetskyi IS, Malanchuk VA, Sorokin BV, Myroshnychenko MS, Beketova YI, Dyadyk OO, Kapustnyk NV, Krotevych MS, Brodetskyi SB. Tumors and tumor-like lesions of the salivary glands: morphological characteristics of the surgical material. Wiad Lek. 2021;74(4):929-933.
7. Kalwaniya DS, Meena R, Kumar D, Tolat A, Arya SV. A Review of the Current Literature on Pleomorphic Adenoma. Cureus. 2023;15(7):e42311. doi: 10.7759/cureus.42311.
8. Brodetskyi IS, Dyadyk OO, Myroshnychenko MS, Zaritska VI. Morphological characteristics of pleomorphic adenomas of salivary glands (analysis of the surgical material). Wiad Lek. 2020;73(11):2339-2344.
9. Brodetskyi IS, Dyadyk OO, Malanchuk VA, Myroshnychenko MS, Krotevych MS. Immunohistochemical features of the expression of human papilloma virus type 16 in pleomorphic adenomas of salivary gland. Wiad Lek. 2021;74(1):7-10.
10. Ito FA, Jorge J, Vargas PA, Lopes MA. Histopathological findings of pleomorphic adenomas of the salivary glands. Med Oral Patol Oral Cir Bucal. 2009;14(2):E57-61.
11. Adiyodi NV, Sequeira J, Mehra A. Twinning of Pleomorphic Adenoma: A Case Report. Cureus. 2020 Jan 9;12(1):e6608. doi: 10.7759/cureus.6608.
12. Erkul E, Yilmaz I, Issin G, Gungor A, Cekin E, Demirel D. Correlation of Histopathological Sub Typing and Adverse Morphological Features of Pleomorphic Adenoma of the Parotid Gland. Am J Otolaryngol Head Neck Surg. 2018;1(5):1022.
13. Alves FA, Perez DEC, Almeida OP, Lopes MA, Kowalski LP. Pleomorphic Adenoma of the Submandibular Gland: Clinicopathological and Immunohistochemical Features of 60 Cases in Brazil. Arch Otolaryngol Head Neck Surg. 2002;128(12):1400-1403. doi:10.1001/archotol.128.12.1400
14. Breiman L, Friedman JH, Olshen RA, Stone CJ. Classification and regression trees. New York: Springer, 2017. 368 p.
15. Greenacre M. Correspondence Analysis in Practice, 2nd edition. London: Chapman & Hall/CRC, 2007. 274 p.
16. Brodetskyi IS, Malanchuk VO. Analysis of archive material of patients with salivary gland neoplasms according to the department of O.O. Bogomolets National Medical University for the last five years. J Stoma. 2019;72(2):70-76.
17. Reinheimer A, Vieira DS, Cordeiro MM, Rivero ER. Retrospective study of 124 cases of salivary gland tumors and literature review. J Clin Exp Dent. 2019 Nov 1;11(11):e1025-e1032. doi: 10.4317/jced.55685. PMID: 31700577; PMCID:PMC6825733.

ORCID AND CONTRIBUTIONSHIP
Igor S. Brodetskyi: 0000-0002-9434-4079[D]
Vladislav A. Malanchuk: 0000-0001-8111-0436[A]
Mykhailo S. Myroshnychenko: 0000-0002-6920-8374[E]
Stanislav O. Riebienkov: 0000-0001-8116-5277[F]
Oleksandr V. Arseniev: 0000-0002-9807-0853[C]
Oleksandr E. Kotenko: 0000-0001-8497-4811[B]
Liudmyla O. Brodetska: 0000-0002-0570-3085[E]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 02.06.2023
ACCEPTED: 09.09.2023

ADDRESS FOR CORRESPONDENCE
Mykhailo S. Myroshnychenko
Department of General and
Clinical Pathological Physiology
named after D.O. Alpern,
Kharkiv National Medical University,
4 Nauky avenue, Kharkiv, 61022, Ukraine
e-mail: msmyroshnychenko@ukr.net

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 482-488

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305106

SURGICAL INTERVENTION IN PATIENTS WITH IDIOPATHIC INFLAMMATORY BOWEL DISEASE AND PERIANAL DISEASE

Ioannis Triantafyllakis[1], Maria Saridi[2], Aikaterini Toska[2], Eleni N. Albani[3], Constantinos Togas[4], Dimitrios K. Christodoulou[1], Konstantinos H Katsanos[1]

[1]DEPARTMENT OF GASTROENTEROLOGY, UNIVERSITY HOSPITAL OF IOANNINA, IOANNINA, GREECE
[2]LABORATORY OF CLINICAL NURSING, DEPARTMENT OF NURSING, UNIVERSITY OF THESSALY, LARISSA, GREECE
[3]DEPARTMENT OF NURSING, UNIVERSITY OF PATRA, PATRA, GREECE
[4]PANTEION UNIVERSITY OF SOCIAL AND POLITICAL SCIENCES, ATHENS, GREECE

ABSTRACT

Aim: The aim of the study was to investigate the incidence of IBD in gastrointestinal surgery patients and record the disease's characteristics and treatment.

Materials and Methods: A search was carried out in the archives of the gastroenterology clinics of the University General Hospital of Ioannina and the General Hospital of Ioannina "G. Hatzikosta" in Greece. All cases of operated patients from 1980 to 2018 were examined. The duration of the study was 4 months. Data were analyzed with the SPSS program, v.28.

Results: The total sample consisted of 1464 patients (n=1464). Most of them (915-62.5%) came from the University General Hospital of Ioannina, while the rest (549-37.5%) came from the GHI hospital "G. Hatzikosta". The mean age of the patients was 47 years (M=47.26, SD=17.34, Min=<1 month, Max=95 years). From the total sample, 58 patients (4%) suffered from IBD; most were men (42-72.41%). Their mean age was approximately 50 years (M=49.63, SD=16.48, Min=25 years, Max=77 years, range=52 years) and most belonged to the age groups of 31-40 years (11 patients- 19.6%) and 21-30 years and 61-70 years (10 patients-17.9%). The perianal disease was present in 43.1% (25 patients). The most frequent type of operation was fistula resection, ligation, curettage-biopsy (24.1%) and opening-drainage (22.4%-13 patients) and the most frequent type of anesthesia was general anesthesia (93.1%-54 patients).

Conclusions: This long-term study of the patients' data followed up over time showed that the possibility of surgery in patients with IBD is mitigated through systematic monitoring and multifaceted therapeutic treatment.The perianal disease which appeared more often in men shows that it can be diagnosed early and at an early stage and with the new minimally invasive techniques the patient with IBD can be treated with a better quality of life.

KEY WORDS: IBD, perianal disease, operation, file search, Ioannina hospitals, Greece

INTRODUCTION

The treatment of IBD is a multifaceted and multidisciplinary approach with pharmaceutical and often surgical treatment. These interventions aim to maintain patients' quality of life at as optimal a level as possible, keeping their disease in long-term remission and treating flare-ups supportively [1].

The surgical intervention appears to reach 30% of ulcerative colitis patients and 70% of Crohn's disease patients, although in recent years with available treatments and early diagnosis, and regular follow-up, these rates have decreased. Minimally invasive techniques have replaced the conventional open approach in many specialized centers worldwide [2-4]. Perianal diseases in Crohn's Disease (CD) occurs in approximately 50% of patients, and usually, these perianal symptoms appear as the first manifestation of CD [5], while the estimated incidence of perianal fistulas in Europe is 1.2–2.8 per 10,000 people [6]. It is an indicator of more severe disease and is associated with multiple surgeries and frequent recurrences [7], while it appears from the literature that it may likely be a combination of genetic, microbiological, and immunological factors [8].

Treatment of complex perianal fistulas (CPF) in patients with CD is particularly challenging for surgeons and gastroenterologists and although not desirable, it is still recommended as first-line treatment, with surgery reserved for sepsis control or laying open surface tracks (is typically still recommended as a first-line treatment, with surgery being reserved for sepsis control or laying open superficial tracks) 7.Treatment of perianal fistulizing disease (PFCD) has traditionally been surgical, and seton placement is the most common technique. However, it seems that the advent of biological therapy, especially anti-tumor necrosis factor (TNF) agents (infliximab and adalimumab), helped to reduce surgery in these cases [9-12].

Also, new therapeutic approaches to perianal disease aim to promote long-term fistula healing while maintaining continence and avoiding stomy diversion [13]. Related studies show that quality of life is better in patients undergoing surgery than in those undergoing biologic maintenance therapy, and this may be due to the element of the ongoing

chronic disease still experienced by those undergoing maintenance therapy because complete remission is rarely achieved [14-16].

AIM

The purpose of the present research was to examine the frequency of surgery in patients with IBD, who suffer from perianal or complicated bowel disease, and record the characteristics of the disease and treatment.

MATERIALS AND METHODS

A file search was carried out in the cases recorded at the Gastroenterology Clinic of the University General Hospital of Ioannina and the General Hospital of Ioannina "G. Hatzikosta" in Greece. All incidents were recorded for the period from 1980 to 2018. So, the study covers a very long period of 38 years. More specifically, in the study, the details of the patients who came with a diagnosis of IBD and a diagnosis of perianal or intestinal complicated disease were recorded. The duration of the study was 4 months.

LOG VARIABLES

Patient demographics (gender, age), diagnosis, conservative methods, and types of surgical treatment, as well as other important data (endoscopic/radiological), were recorded. Furthermore, the clinical outcome of the patients was recorded.

STATISTICAL PROCESSING OF THE DATA

The statistical processing of the data has done with the statistical program SPSS v. 26 (Statistical Package for Social Sciences). The mean value, standard deviation, maximum and minimum value, and range were calculated to describe the quantitative variables.Absolute (n) and relative (%) frequencies were used to describe the categorical variables. Also, both the quantitative and categorical variables were presented with appropriate diagrams for each case (eg histogram, bar graph, pie chart, population pyramid, etc.).In those cases where it was deemed necessary, the x2 test was used to investigate the possible difference in the subcategories of two categorical variables as well as the ratio of relative probabilities (odds ratio).

ETHICS

This study was approved from the from the Departments ethics committee : 876α/18-12-2018. In every case, care was taken to ensure the anonymity and sensitive personal data of the patients, and the General Data Protection Regulation was observed.

RESULTS

The total sample consisted of 1464 patients (n=1464) and their mean age was 47 years (M=47.26, SD=17.34, Min=<1 month, Max=95 years). The rest of their characteristics are presented in Table 1.

Three out of four patients (1098-75%) had a perianal disease. The male-female difference in having cervical disease was statistically significant (Continuity Correction value=57.145, p<0.001).Males were approximately 2.6 times more likely than females to have perianal disease (OR=2.64). Since the confidence interval does not include unity, the value of the relative odds ratio differs from 1 with at least 95% confidence.

The most frequent types of operation were fistula excision, ligation, scraping-biopsy (41.2%), and opening drainage (35.5%). Smaller percentages were recorded in the other types of interventions. Most patients underwent general anesthesia (89.5%), while small percentages were recorded in the remaining categories of anesthesia (local=5.4%, intraspinal=4.5%, intoxication=0.6%, other=0.1%).

Overall, 58 patients (4%) suffered from IBD,and most were men (42-72.41%). Most IBD patients were male (42/58) and the remaining 16 were female, with most of these patients hospitalized at the University General Hospital of Ioannina (44/58).Their mean age was about 50 years (M=49.63, SD=16.48, Min=25 years, Max=77 years, range=52 years) and most belonged to the age groups of 31-40 years (11 patients-19.6%) and 21-30 years old and 61-70 years old (10 patients-17.9%).

The perianal disease was present in 43.1% (25 patients). The most frequent diagnoses in these patients are presented in Table 2.

In patients with IBD, the most frequent diagnoses were cervical abscesses (24.1%), followed by cervical fistulas, ulcerative colitis, and Crohn's disease with the same percentage (11%). Some diagnoses occurred exclusively in men (perianal abscesses, perianal fistulas, obstructive ileus, Fournier's gangrene, and torsion).

On the other hand, necrosis and intestinal bleeding occurred exclusively in women. Ulcerative colitis was more common in women than in men, and 33patients (56.9 %) with IBD did not have a perianal disease.Conversely, a high percentage (25 patients-43.1%) had perianal disease. Most cases of cervical disease were recorded in the 31-40 and 61-70 age groups. The perianal disease occurred overwhelmingly in men (24/25).

A statistically significant difference was recorded between men and women in the occurrence of cervical disease (Continuity Correction value= 57.145, p<0.001). Men in the sample were 20 times more likely than women to have perianal disease (OR=20). Since the confidence interval does not include unity, the value of the relative odds ratio differs from 1 with at least 95% confidence.

The most frequent operations were fistula resection, ligation, scraping-biopsy (24.1%), opening-drainage (22.4%), and typhlostomy, colostomy, ileostomy, sigmoidostomy (17.24%).

The most frequent operation in men was opening-drainage and fistula resection, ligation, and scraping biopsy, and in women typhlostomy, colostomy, ileostomy, sigmoidostomy, and colectomies. Most patients with IBD underwent general anesthesia (93.1%), while much smaller percentages were recorded under spinal anesthesia (3.4%) and local anesthesia and intoxication (1.7%).

General anesthesia was the most common choice of anesthesia in patients with IBD,concerning both sexes and all age groups, being the exclusive form of anesthesia in women and in some age groups (41-50 years and 51-60 years).

Table 1. Patients' characteristics in the total sample

	Frequency	Percentage %
Hospital		
University General Hospital of Ioannina	915	62.5%
GHI «G. Chatzikosta»	549	37.5%
Gender		
Man	1082	73.91%
Woman	382	26.09%
Age group		
Newborn -10 years old	24	1.7%
11-20 old	48	3.4%
21-30 old	181	12.9%
31-40 old	266	19%
41-50 old	327	23.3%
51-60 old	237	16.9%
61-70 old	178	12.7%
71-80 old	100	7.1%
81-90 old	36	2.6%
91-100 old	5	0.4%
Diagnosis		
Perianal fistulas	609	41.6%
Perianal abscess	500	34.2%
Stenosis	20	1.4%
Obtructive ileus	78	5.3%
Gangrene Fournier	27	1.8%
Ulcerative colitis	20	1.4%
Crohn disease	20	1.4%
Necrosis	43	2.9%
Rupture of intestine	23	1.6%
Colitis	4	0.3%
Intestinal bleeding	14	1%
Ileum	31	2.1%
Appendectomy	33	2.3%
Granulation	2	0.1%
Twist	21	1.4%
Orthovaginal fistula	3	0.2%
Colostomy	2	0.1%
Intestinal fistula	7	0.5%
Inflammations	5	0.3%
Orthocystic fistula		0.1%

DISCUSSION

In the present research, the data from surgical operations of patients with inflammatory bowel disease in the prefecture of Ioannina were examined. The data came from file research in the two hospitals of the prefecture of Ioannina (University General Hospital of Ioannina and GHI "G. Chatzikosta"). All cases operated on for gastrointestinal reasons at the above hospitals and covering a very long period of 38 years (from 1980 to 2018) were examined. The key finding is that a very small percentage of these cases involved inflammatory bowel disease. Specifically, from the total of operated cases (1464) only 58 patients (3.96%) suffered from inflammatory bowel disease (ulcerative colitis and Crohn's disease).This finding shows that possibly the prevalence of inflammatory bowel diseases in the Ioannina region is low and the number of patients with such diseases requiring surgical treatment is limited.

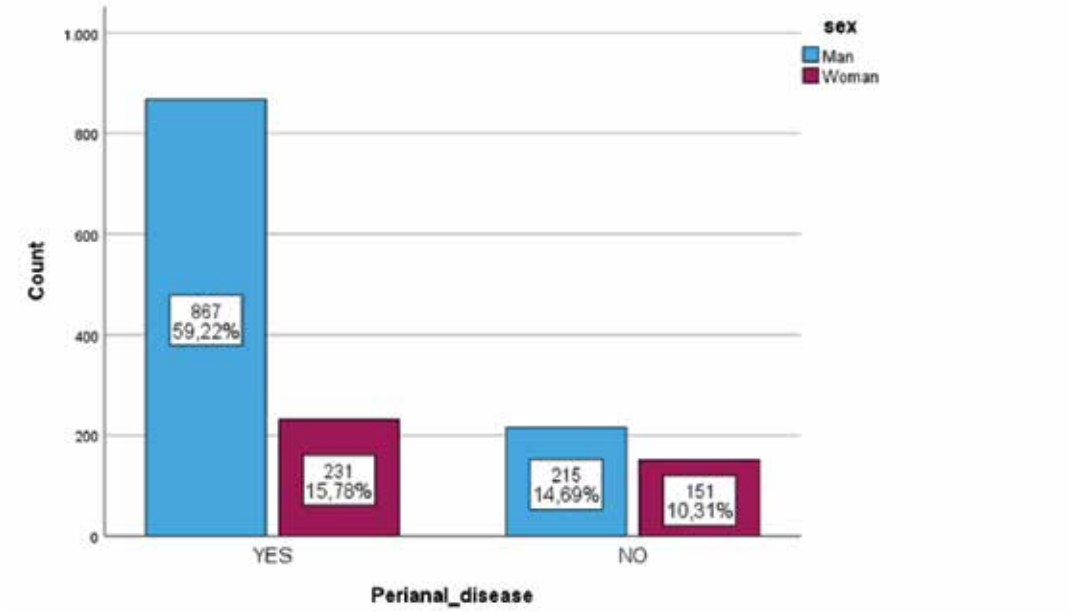


Fig. 1. Perianal disease by gender.

Table 2. Diagnosis of patients with IBD

	Frequency	Rate %
Perianal fistulas	11	19%
Perianal abscess	14	24,1%
Stenosis	3	5,2%
Obstructive ileus	3	5,2%
Gangrene Fournier	2	3,4%
Ulcerative colitis	11	19%
Crohn disease	11	19%
Necrosis	1	1,7%
Intestinal bleeding	1	1,7%
Twist	1	1,7%
Total	58	100%

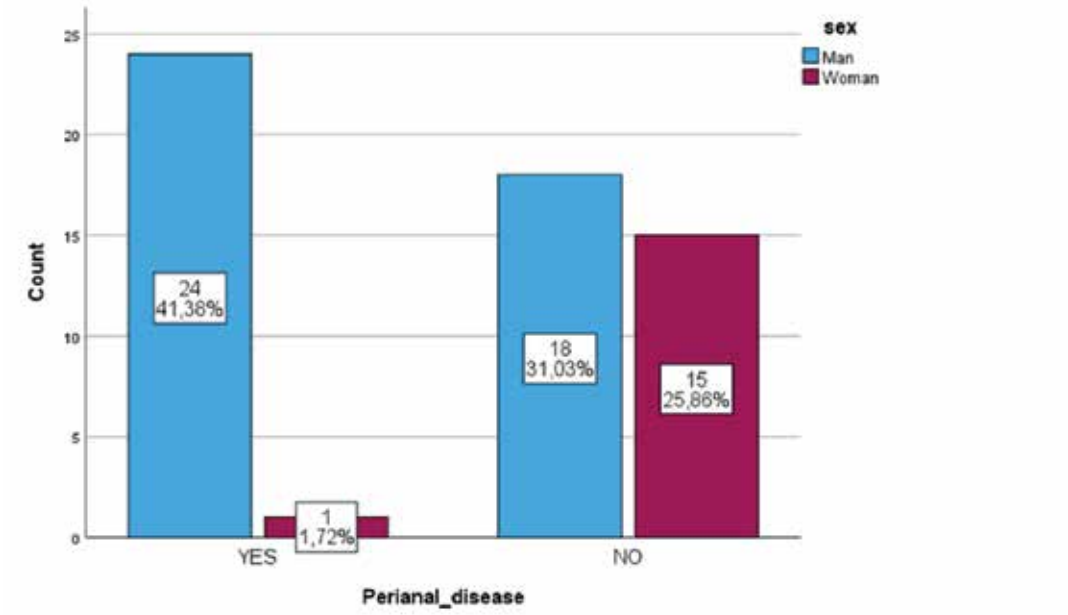


Fig. 2. Perianal disease by patients' gender with ID.

Consequently, there is adequate management and treatment of these diseases in a conservative way and medical treatment [17]. So, there is close monitoring and long-term care of patients with inflammatory bowel disease in the area. This is also achieved by the semi-urban character of the area covered by the two hospitals.Patients have easy and immediate access to these hospitals, and continuity of care is ensured over time. This has a positive effect on the functioning of the health system, as patients with inflammatory bowel disease do not need to travel to large urban centers,since monitoring,management, and treatment of their disease,is achieved close to their place of residence.In this way, the large hospitals of Attica are decongested, and financial resources are saved for the health care system as wellas for the patients themselves.Most patients with IBD came from the University General Hospital of Ioannina, a finding that is to be expected, as University Hospitals manage a larger number of patients for all diseases every day.

Both men and women who were hospitalized at the GHI "G. Hatzikosta" was older than the patients treated at the University General Hospital of Ioannina.Most of the patients were men, and the mean age of IBD patients was approximately 49.5 years (Mean=49.63, SD=16.48). Regarding the age variable, the youngest age was 25 years and the oldest was 77 years, so, an age range of 52 years was recorded, with most patients with IBD belonging to the age group of 31-40 years (19.6%). These findings are compatible with what is reported in the international literature, according to which the disease affects people of any age, but mainly people of young productive age.Furthermore, although IBDs can be diagnosed at any age (from infancy to the eighth decade of life), most new diagnoses occur in adolescence and early adulthood (Loftus, 2004). But this concerns the age of initial diagnosis and not the age of examination and submission to surgical treatment.In patients with IBD, the most frequent diagnoses were perineal abscesses (24.1%), followed by perineal fistulas, ulcerative colitis, and Crohn's disease with the same percentage (11%).

Some diagnoses occurred exclusively in men (perianal abscesses, perianal fistulae, obstructive ileus, Fournier's gangrene, and torsion). On the other hand, necrosis and intestinal bleeding occurred exclusively in women. Ulcerative colitis was more common in women than in men.Most of the diagnoses concerned patients from the University General Hospital of Ioannina. On the contrary, the stenosis was diagnosed two times at the GHI "G. Hatjikosta" and one time at the University General Hospital of Ioannina. Also, the only case of necrosis and the only case of torsion was diagnosed in patients from the GHI "G. Hatzikosta".

Regarding the relation between IBD and perianal disease, it was found that most patients with IBD did not have a perianal disease (56.9%), while a high percentage (43.1%) had this disease. Several other researchers have pointed out that perianal disease affects a significant number of patients with Crohn's disease [18], and its incidence ranges from 17% to 43% of patients with this disease [19]. Other researchers emphasize that this percentage is up to 47% [20] or up to 90% of patients with Crohn's disease [21].

It was also found a greater incidence of perianal disease in men. More specifically, men in the sample were 20 times more likely than women to develop perianal disease. Different results are reported by other researchers [9], pointing out that the incidence of the perianal disease is similar in men and women,but they further emphasize that women have an increased chance of greater complications.

In our study, most cases of perianal disease were recorded in the 31-40 and 61-70 age groups. Likewise, in the retrospective study by Kühn et al [22], at the Rostock University Hospital, the mean age at first operation was 38 years (range: 17 – 66 years). Also, in Han et al's research [23], the mean age of patients with perianal disease was 33.8 years.Regarding the cases of old age, which were recorded with high frequency in this research, it is pointed out that they have an increased risk for perioperative complications [22].The most frequent operations were fistula resection, ligation, curettage-biopsy, opening-drainage and typhlostomy, colostomy, ileostomy, and sigmoidostomy. The most frequent operation in men was opening-drainage and fistula resection, ligation, and curettage-biopsy, and in women the typhlostomy, colostomy, ileostomy, sigmoidostomy, and colectomies.These data provide sufficient evidence regarding the frequency of surgery in these patients and their distribution by gender.

Most patients with IBD underwent general anesthesia (93.1%), while much smaller percentages were recorded under spinal anesthesia (3.4%) and local anesthesia and intoxication (1.7%).General anesthesia was the most common form of anesthesia in those suffering from IBD for both sexes and for all age groups, being the exclusive form of anesthesia in women and in age groups of 41-50 years and 51-60 years. This element enriches the existing knowledge, as few studies have examined the issue of anesthesia in these surgical cases. Conversely, the topic of anesthesia has been extensively examined in diagnostic procedures [19,24, 25].

Regarding the advantages of this study, the main ones are the following: First, the subject examined covers a large gap in the scientific literature and presents originality for the Greek data. It enriches the existing knowledge about the specific scientific field and creates questions for its further investigation. So, its contribution to the promotion of scientific knowledge is judged to be sufficient and important.

Second, evidence was examined over a long period of approximately 38 years. Based on the type of research (archive research), a simple sample examination of the data under study was not done, but a complete inventory of them.In other words, all the recorded cases of IBD in the two hospitals of the Prefecture of Ioannina for the above time (1980-2018) were examined. The complete recording helps to overcome the disadvantages that come from the sampling surveys (representativeness of the sample, reduction of the conclusions to the population, etc.).

On the other hand, a key limitation of the research is the fact that only the variables for which there were already recorded data were examined. But this is an inherent disadvantage of the relevant research (archive research) and there was no possibility of overcoming it.Thus, data

were recorded on only certain variables of interest and the researcher was not able to study additional data of interest.

The subject of the present research can be examined in the future with various other research designs, for example with prospective or retrospective studies or with a comparison between patients with ulcerative colitis and Crohn's disease. Some additional variables (e.g., disease outcome, quality of life, etc.) could also be examined, which were not evaluated in the present study due to their nature (archive study with specific recorded variables). Would also be of particular interest a further examination of certain demographic and medical characteristics (eg gender, type of surgery) associated with perianal disease in IBD and its prognosis and outcome.Finally, the issue could also be examined in comparison with groups of patients with IBD but without perianal disease, to evaluate possible significant differences.

CONCLUSIONS

This long-term study of the data of patients who are monitored over time showed that the possibility of surgery in patients with IBD is mitigated when there is systematic monitoring and multifaceted therapeutic treatment.The perianal disease which appeared more often in men shows that it can be diagnosed early and at an early stage and with the new minimally invasive techniques the patient with IBD can be treated with a better quality of life.The results obtained from the present study provide sufficient information for the surgical treatment of IBD patients with perianal disease. Therefore, they can be used to further evaluate them and make recommendations for the optimal care of these patients.The results can be used by health professionals for the supportive care and management of these patients, with the goal of maintaining and improving their quality of life.

REFERENCES

1. Bemelman WA. S-ECCO collaborators, Evolving Role of IBD Surgery. Journal of Crohn's and Colitis. 2018;12(8):1005-1007. doi: 10.1093/ecco-jcc/jjy056.
2. Carter MJ, Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2004;53 Suppl 5:V1-16.
3. Fousekis FS, Mitselos IV, Tepelenis K, Pappas-Gogos G, Katsanos KH, Lianos GD, Frattini F, Vlachos K, Christodoulou DK. Medical, Endoscopic and Surgical Management of Stricturing Crohn's Disease: Current Clinical Practice. J Clin Med. 2022 Apr 23;11(9):2366. doi: 10.3390/jcm11092366. PMID: 35566492; PMCID: PMC9104530.
4. Katsanos KH, Saridi M, Albani E, Mantzouranis G, Zmora O, Christodoulou DK. Sexual Dysfunction in Patients With Inflammatory Bowel Disease. Inflamm Bowel Dis. 2018 Oct 12;24(11):2348-2349. doi: 10.1093/ibd/izy206. PMID: 30312432.
5. Zabot GP, Cassol O, Saad-Hossne R, Bemelman W. Modern surgical strategies for perianal Crohn's disease. World J Gastroenterol. 2020 Nov 14;26(42):6572-6581. doi: 10.3748/wjg.v26.i42.6572. PMID: 33268947; PMCID: PMC7673971.
6. García-Olmo D, Van Assche G, Tagarro I, Diez MC, Richard MP, Mona J. Prevalence of anal fistulas in Europe: systematic literature reviews and population-based database analysis. Adv Ther. 2019;36:3503-18.
7. Tarrant KM, Barclay ML, Frampton CM, Gearry RB. Perianal disease predicts changes in Crohn's disease phenotype-results of a population-based study of inflammatory bowel disease phenotype. Am J Gastroenterol. 2008;103(12):3082-3093.
8. Tozer PJ, Whelan K, Phillips RK, Hart AL. Etiology of perianal Crohn's disease: role of genetic, microbiological, and immunological factors. Inflamm Bowel Dis. 2009;15(10):1591-1598.
9. Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. Gastroenterology. 2003;125:1508-1530.
10. Steele SR, Kumar R, Feingold DL, Rafferty JL, Buie WD. Practice parameters for the management of perianal abscess and fistula-in-ano. Dis Colon Rectum. 2011;54:1465-74. doi:10.1097/DCR.0b013e31823122b3.
11. Truong A, Zaghiyan K, Fleshner P. Anorectal Crohn's Disease. Surg Clin North Am. 2019;99:1151-1162.
12. Bislenghi G, Wolthuis A, Van Assche G, Vermeire S, Ferrante M, D'Hoore A. Cx601 (darvadstrocel) for the treatment of perianal fistulizing Crohn's disease. Expert Opin Biol Ther. 2019;19:607-616.
13. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2004;63(9):1381-92.
14. van Gennep, SahamiS, BuskensCJet al. Comparison of health-related quality of life and disability in ulcerative colitis patients following restorative proctocolectomy with ileal pouch-anal anastomosis versus anti-tumor necrosis factor therapy Eur J Gastroenterol Hepatol 2017;29:338-44.
15. Ponsioen CY, de Groof EJ, Eshuis EJ, et al. LIR!C study group. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. Lancet Gastroenterol Hepatol2017;2:785-92.
16. Fousekis FS, Katsanos AH, Kourtis G, Saridi M, Albani E, Katsanos KH, Christodoulou DK. Inflammatory Bowel Disease and Patients With Mental Disorders: What Do We Know? J Clin Med Res. 2021 Sep;13(9):466-473. doi: 10.14740/jocmr4593. Epub 2021 Sep 30. PMID: 34691320; PMCID: PMC8510650.
17. Gerontoukou EI, Michaelidoy S, Rekleiti M, Saridi M, Souliotis K. Investigation of Anxiety and Depression in Patients with Chronic Diseases. Health Psychol Res. 2015 Oct 19;3(2):2123. doi: 10.4081/hpr.2015.2123. PMID: 26973961; PMCID: PMC4768533.
18. Kelley KA, Kaur T, Tsikitis,VL. Perianal Crohn's disease: challenges and solutions. Clin Exp Gastroenterol. 2017;10:39-46.
19. Schwartz DA, Loftus EVJr, Tremaine WJ, Panaccione R, Harmsen WS, Zinsmeister AR, et al. The natural history of fistulizing Crohn's disease in Olmsted County. Minnesota Gastroenterology. 2002;122(4):875-880.
20. Baumgart DC, Sandborn WJ. Crohn's disease. The Lancet. 2012;380(9853):1590-1605.
21. Platell C, Mackay J, Collopy BT, Fink R, Ryan P, Woods R. Anal pathology in patients with Crohn's disease. Aust NZ J Surg. 1996;66:5-9.

22. Kühn F, Nixdorf M, Schwandner F, Klar E. Risikofaktoren für einenfrühen OP-Zeitpunkt und chirurgischeKomplikationenbei Morbus Crohn [Risk Factors for Early Surgery and Surgical Complications in Crohn's Disease]. ZentralblChir. 2018 Dec;143(6):596-602. German. doi: 10.1055/a-0645-1489
23. Han YM, Kim JW, Koh SJ, Kim BG, Lee KL, Im JP, et al. Patients with perianal Crohn's disease have poor disease outcomes after primary bowel resection. J Gastroenterol Hepatol. 2016;31(8):1436-1442.
24. Regueiro M. The role of endoscopy in the evaluation of fistulizing Crohn's disease. GastrointestEndosc Clin N Am. 2002;12(3):621-633.
25. Komarovskyi M, Mykytenko R, Onofreichuk K, Hryshchenkova O, Podhorna A, Kosolapov O, et al. "Clinical Case of Catatonic Stupor Developed As a Result of Acute Respiratory Disease COVID-19". Mental Health: Global Challenges Journal. 2021;4(1). doi:10.32437/mhgcj.v4i1.129. [cited 2021-10-25] https://mhgcj.org/index.php/MHGCJ/article/view/129

ORCID AND CONTRIBUTIONSHIP
Ioannis Triantafyllakis: 0009-0004-5108-0992[A,B,D,E,F]
Maria Saridi: 0000-0002-1042-5323[B,E,F]
Aikaterini Toska: 0000-0002-6888-3394[B,D,E,F]
Eleni N. Albani: 0000-0001-7340-4696[B,E,F]
Constantinos Togas: 0000-0002-1042-5323[B,E,F]
Dimitrios K. Christodoulou: 0000-0001-9694-1160[A,B,D,E,F]
Konstantinos H Katsanos: 0000-0002-3273-0417[A,B,D,E,F]

ADDRESS FOR CORRESPONDENCE
Maria Saridi
Gaiopolis, Larissa-Trikalon Ring Road,
T.K 41500, Larissa, Greece
e-mail: msaridi@uth.gr

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 22.04.2023
ACCEPTED: 07.09.2023

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 489-495

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305107

THE NEUROLOGICAL MANIFESTATIONS AND FUNCTIONAL INDEPENDENCE IN PATIENTS WITH ENCEPHALOPATHIES OF DIFFERENT TYPES

Khrystyna V. Duve, Svitlana I. Shkrobot

I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY OF THE MINISTRY OF HEALTH OF UKRAINE, TERNOPIL, UKRAINE

ABSTRACT

Aim: To access the neurological manifestations and activities of daily living in patients with encephalopathy of one of the following types: post-infectious, chronic traumatic encephalopathy, alcohol-induced, and microvascular ischemic disease of the brain.

Materials and Methods: In the period of 2021-2022 we examined 520 patients, who signed the informed consent, taking into account their age, sex, occupation, the cause, and the disease duration. Such parameters were evaluated, as the data of neurological manifestations, the activities of daily living (Barthel index), cognitive functioning (MoCA-test), and statistical methods (Statistica 13.0).

Results: A probable influence of the age factor on the frequency of occurrence of different types of encephalopathies was established ($\chi 2=235.05$; $p<0.001$). The cognitive impairment was diagnosed in 53.79 % of patients with CTE, 66.21% with SVD, and 58.82% with AE. 40% of patients with CTE are dependent on their activities of daily living, among patients with SVD – 31,72 %, among patients with AE – 44.12%, among patients with PIE – 53.91%. 17.97% of patients with PIE had moderate dependence by the Barthel index. Thus, the severity of disability doesn't depend on the age or sex of patients but is correlating with the duration of the disease.

Conclusions: The neurological manifestations in patients with encephalopathies and their activities of daily living were studied profoundly and the data obtained opened new directions in the following research.

KEY WORDS: encephalopathy, TBI, cognitive functioning, microvascular ischemic disease, Barthel index

INTRODUCTION

Encephalopathies – are the diffuse non-inflammatory lesions of the brain which cause impaired brain function. The question is still open about the common classification of encephalopathies, in order to categorize all the types. Peculiarities of one encephalopathy course depend on the etiological factor and its influence on the pathophysiology of the disease course, the rate of progression of the lesion, its prevalence, and the predominance of damage to certain areas of the brain [1-8].

The statistical analysis of the frequency of different types of encephalopathies, performed in 2021-2022 has shown the predominance of the main 4 types, as they accounted for about 15,20 % of all neurological disorders admitted to the hospital in 2021 and 11,37 % in 2022 years. Therefore, such types were chosen for further research, as post-infectious, chronic traumatic encephalopathy, alcohol-induced, and microvascular ischemic disease of the brain.

A growing number of researchers and clinicians are indicating that even mild TBI can lead to lasting effects and, in some cases, to progressive neurodegeneration and chronic traumatic encephalopathy (CTE). CTE is a unique neurodegenerative tauopathy, that was first described in boxers and later in contact sports athletes, military veterans, and civilians exposed to repeated mild TBI. The exact mechanism that explains how repeated TBI leads to neurodegeneration has not yet been established. Morphologically, CTE is characterized by the accumulation of phosphorylated tau (p-tau) in apices and perivascular areas, microgliosis, and astrocytosis, which leads to progressive neurodegeneration [9-12].

Post-infectious encephalopathy (PIE) is a syndrome characterized by acute cerebral insufficiency, that is, the inability of the brain to provide central regulation of the body's functioning. In infectious patients, encephalopathy is caused by a violation of blood circulation, cerebrospinal fluid circulation, and brain metabolism as a result of an intoxication syndrome against the background of an infectious disease and due to a violation of the functions of the excretory organs. The mechanism of occurrence of post-infectious encephalopathy is caused by a cytokine storm, which leads to a violation of the integrity of the brain-blood barrier and damage to the brain parenchyma [1, 13-18].

Alcohol-induced encephalopathy (AE) is a persistent dystrophic lesion of the central nervous system of toxic (alcoholic) genesis, which is a consequence of long-term, systematic alcohol intoxication. Organic changes in the central nervous system at the biochemical and cellular level, including permanent disturbances of homeostasis,

processes of degeneration, demyelination, and apoptosis. Chronic alcoholism leads to brain damage and a number of psycho-neurological manifestations, which include cognitive dysfunction, Wernicke-Korsakoff syndrome, alcoholic cerebellar degeneration, and alcoholic dementia [6, 19-21].

The microvascular ischemic disease of the brain (or cerebral small vessel disease, (SVD)) is a slowly progressive insufficiency of blood supply to the brain, which leads to the development of multiple small focal necroses of brain tissue and is manifested by gradually increasing defects in brain functions. At the same time, on the one hand, chronic cerebrovascular insufficiency is a risk factor for the development of acute cerebrovascular disorders, on the other hand, it is the cause of the gradual increase in various neurological and mental disorders. Among the main etiological forms of SVD, atherosclerotic, hypertensive, and mixed etiologies are distinguished, although, by definition, other causes leading to chronic vascular cerebral insufficiency (vasculitis, rheumatism, blood diseases) are also possible. [3, 22-29].

A promising direction of research remains the elucidation of theoretical and practical issues related to the problems of studying clinical and neurological peculiarities of different types of encephalopathies, and the impact of these signs on the patient's activity of daily living and social functioning and prognosis [25, 27, 29].

AIM

The aim was to access the neurological manifestations and activities of daily living in patients with encephalopathy of one of the following types: post-infectious, chronic traumatic encephalopathy, alcohol-induced, and microvascular ischemic disease of the brain.

MATERIALS AND METHODS

In the period of 2021-2022 we examined 520 patients, who were undergoing the treatment in Communal Non-commercial Enterprise "Ternopil Regional Clinical Psychoneurological Hospital" of Ternopil Regional Council. The patients previously signed the informed consent. The age, sex, occupation, possible cause, and disease duration were taken into the account. The following distribution of encephalopathies was found: CTE (n=145), SVD (n=145), AE (n=102) та PIE (n=128). It was established that the percentage of males was 69.6 (n=362), and the percentage of females was 30.4 (n=158). The age of patients was analyzed due to the World Health organization's standard classification (young age is from 25 to 44, middle age is 44-60, elderly age is 60-75, senile age is 75-90 years). The duration of the disease was classified by the following time intervals: up to 1 year, 1-5 years, 6-10 years, and more than 10 years.

The study was carried out in accordance with the Helsinki Declaration and was approved by the university ethics committee. Full clinical and neurological examinations were performed in order to mark out the main complaints, focus on the neurological syndromes, and distinguish the main pathology or reason, which led to encephalopathy. The patient's physical independence in every-day-life was evaluated by means of the Barthel index, which accesses the activities of daily living. The cognitive functioning and severity of impairment were detected by the Montreal Cognitive Assessment (MoCA-test). We used (Statistica 13.0).

The results of the study were processed using Microsoft Excel. For the statistical analysis, we used the advanced analytics software package Statistica originally developed by StatSoft.

RESULTS

During the distribution of patients with different types of encephalopathies depending on the age category, a probable influence of the age factor on the frequency of occurrence of different types of encephalopathies was established ($\chi 2=235.05$; $p<0.001$). In particular, in the group of patients with CTE, young people probably predominated (57.24%), in the group of patients with SVD – elderly (48.79%), in the group of patients with AE – middle-aged (53.92%) and in the group of patients with PIE is young (49.22%).

Analyzing the distribution of patients with various types of encephalopathies by age, characteristic differences were statistically significant (Table 1).

In particular, the age of patients with CTE was probably lower than that of patients with SVD (by 64.34%), AE (by 26.23%) and PIE (by 14.65%). In turn, patients with SVD were the oldest, their age statistically significantly exceeded the age of patients with AE by 30.19% and the age of patients with PIE by 43.34%. It should also be noted that the age of patients with AE probably exceeded the age of patients with PIE by 10.10%. During the distribution of patients with different types of encephalopathies depending on the age category, a probable influence of the age factor on the frequency of occurrence of different types of encephalopathies was established ($\chi 2=235.05$; $p<0.001$).In particular, in the group of patients with CTE,

Table 1. The distribution of patients with encephalopathies by age

Group	The age interval		Age, years	p
	Min	Max		
CTE	18	66	40,41±12,18	$p_{1-2, 1-3, 1-4, 2-3, 2-4, 3-4}<0,05$*
SVD	39	88	66,41±9,90	
AE	22	79	51,01±10,11	
PIE	17	82	46,33±15,39	

*Note. * – statistically significant result.*

young people probably predominated (57.24%), in the group of patients with SVD – elderly (48.79%), in the group of patients with AE – middle-aged (53.92%) and in the group of patients with PIE is young (49.22%).

The type of activity and education of the patients were taken into account, which turned out to be likely influencing factors in patients with various types of encephalopathies ($\chi2=15.92$; $p<0.05$ and $\chi2=14.82$; $p=0.002$, respectively). A probable predominance of unemployed persons was established in all observation groups. Regarding the type of activity, among patients with various types of encephalopathies, the highest percentage of mental work (21.88) was recorded in the PIE group, and physical work was recorded equally in the CTE group (11.03%) and the PIE group (10.94%).

Analyzing the duration of the disease in patients with various types of encephalopathies, a predominance of individuals with catamnesis up to 1 year was established among patients with SVD (15.86%), AE (36.27%) and PIE (51.56%); within 1-5 years – among patients with CTE (30.34%). It is also worth noting the small number of patients with SVD (6.21%) and PIE (4.69%), whose catamnesis was 6-10 years. As for patients with a disease duration of more than 10 years, their number was almost the same in the CTE, AE, and PIE groups and slightly lower in the SVD group.

Analyzing the presence/absence of concomitant somatic diseases in patients with various types of encephalopathies, the presence of comorbid pathologies was established in 32.41% of patients with CTE, 91.03% of patients with SVD, 70.59% of patients with AE, and 60.94% of patients with PIE. The frequency of registration of concomitant somatic diseases in patients with SVD probably exceeded the similar indicator of patients with AE and PIE.

In the structure of comorbidity of encephalopathies, cardiovascular diseases (CVD), diseases of the digestive tract, COPD, and other diseases of the respiratory system, endocrinopathy prevailed; diseases of the eyes, genitourinary system, and rheumatological pathology were significantly less common.

The most common complaints of patients are shown in Figure 1.

Analyzing the syndromes of patients with various types of encephalopathies, such were detected most often in the group of patients with CTE: cephalgic (96.55 %), asthenic (73.79 %), cognitive impairment (53.79 %) and cerebellar ataxia (34.48 %), pyramidal insufficiency (46.21%).

In the group of patients with SVD: cephalgic (70.34%), extrapyramidal (60.00%), vestibular (61.38%), and asthenic (53.79%) syndromes were most often registered, as well as the syndrome of cognitive disorders (66.21%).

In the group of patients with AE, the syndrome of cognitive disorders (58.82%), convulsive (31.37%), amiostatic (37.25%), and emotional lability (30.39%) dominated.

In the group of patients with PIE, cephalgic (59.38 %), asthenic (73.44 %), meningeal (43.75 %) syndromes, pyramidal insufficiency (55.47 %), as well as motor syndromes (motor neuron lesion syndrome) (32.81 %) and sensory (38.28%) disorders, cerebellar ataxia (37.50%).

A statistically significant difference in the frequency of registration of cephalgic syndrome in patients with various types of encephalopathies was established ($\chi2=148.93$; $p<0.001$). In patients with various types of encephalopathies, a statistically significant difference in the frequency of registration of the syndrome of cognitive disorders was found ($\chi2=43.04$; $p<0.001$). At

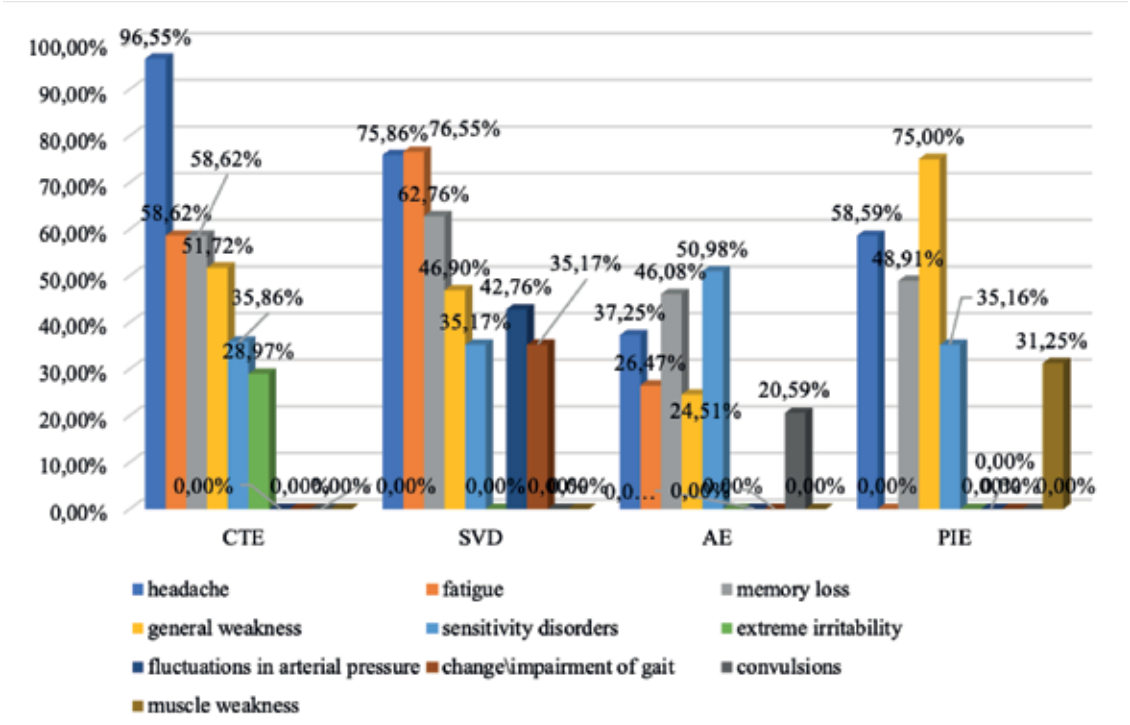


Fig. 1. The complaints, predominating in the patients with CTE, AE, SVD, PIE.

the same time, in the group of patients with SVD, the syndrome of cognitive disorders was registered more often than in the group with CTE – by 12.42% and PIE – by 38.03%, p<0.05. A statistically significant difference in the frequency of registration of cerebellar ataxia in patients with various types of encephalopathies was established (χ2=23.14; p<0.001). Thus, the frequency of registration of this syndrome in patients with TE and PIE practically did not differ and exceeded SVD data by an average of 20%. A statistically significant difference in the frequency of registration of extrapyramidal syndrome in patients with various types of encephalopathies was established (χ2=32.37; p<0.001). At the same time, with SVD, the percentage of patients with diagnosed extrapyramidal syndrome probably exceeded the data of the group with CTE – by 26.21% and PIE – by 31.09%, p<0.05. In patients with various types of encephalopathies, a statistically significant difference in the frequency of registration of vestibular syndrome was also found (χ2=75.32; p<0.001). At the same time, with SVD, the percentage of patients with vestibular syndrome probably exceeded the data of the group with CTE – by 15.17%, AE – by 48.63%, and PIE – by 37.16%, p<0.05. Seizure syndrome also reliably differed in the frequency of diagnosis among the studied encephalopathies (χ2=42.77; p<0.001) with the highest frequency of registration in patients with AE, which probably exceeded the data of SVD by 29.99% and PIE by 11.06%, p <0.05. In patients with various types of encephalopathies, the presence of a statistically significant difference in the frequency of registration of movement disorder syndrome was also found (χ2=31.56; p<0.001). In patients with PIE, this percentage exceeded the data of the group with CTE – by 12.12%, AE – by 25.91%, and PIE – by 18.10%, p<0.05. The frequency of meningeal syndrome in patients with PIE was probably higher than in patients with AE by 35.91%, p<0.05.

It should be noted that analyzing the syndromes of patients with various types of encephalopathies revealed a number of syndromes that are unique to patients with a certain type of encephalopathies. In particular, epileptic syndrome was recorded in patients with CTE, apraxia – in patients with SVD, amiostatic, emotional lability, psycho-organic, general cerebral, delirious syndrome, vegetative-vascular disorders, cortical-sensitive ataxia, cerebellar- sensitive ataxia – with AE, in patients with PIE – prosoparesis, myopathic syndrome, as well as the syndrome of pelvic disorders.

Analyzing the distribution of patients with various types of encephalopathies according to functional incapacity in everyday life according to the Barthel scale, it was established that among patients with CTE, 60.00% were completely independent of the help of others, among patients with SVD – 68.28%, among patients with AE – 55.88%, among patients with PIE – 46.09% (Table 2).

Mild dependence in daily life was found in 28.28% of patients with CTE, 19.31% of patients with SVD, 28.43% of patients with AE and 35.94% of patients with PIE. Moderate dependence in everyday life was found in 11.72% of patients with CTE, 12.41% of patients with SVD, 15.69% of patients with AE, and 17.97% of patients with PIE. At the same time, statistically significant differences were found only between the groups of patients with SVD and PIE. It should be noted that there were no persons with pronounced/complete dependence in everyday life according to the Barthel scale among the patients of all observation groups.

Table 2. The distribution of patients with encephalopathy by the activity in daily living (Barthel index)

Grade of dependence	CTE		SVD		AE		PIE		χ^2, p
	n	%	n	%	n	%	n	%	
Totally independent (100 points)	87	60,00	99	68,28	57	55,88	59	46,09	χ^2_{1-2}=3,25; p_{1-2}=0,197; χ^2_{1-3}=0,89; p_{1-3}=0,645; χ^2_{1-4}=5,52; p_{1-4}=0,063; χ^2_{2-3}=4,08; p_{2-3}=0,130; χ^2_{2-4}=14,11; p_{2-4}<0,001*; χ^2_{3-4}=2,23; p_{3-4}=0,327
Mild dependence (91–99 points)	41	28,28	28	19,31	29	28,43	46	35,94	
Moderate dependence (61–90 ponts)	17	11,72	18	12,41	16	15,69	23	17,97	
Severe dependence (21–60 points)	0	0	0	0	0	0	0	0	
Fully dependent (0–20 points)	0	0	0	0	0	0	0	0	

Note 1. χ^2 – Pearson's criteria, p – level of significance.
*Note 2. * – statistically significant result.*

Table 3. The results of cognitive function testing in patients with encephalopathy (by MoCA test)

Group of patients	MoCA-test results interval		Average MoCA-test	p
	Min	Max		
CTE	15	28	23,99±2,40	$p_{1-2,\ 1-3,\ 2-4,\ 3-4}$<0,001*
SVD	7	28	21,26±4,06	
AE	7	27	21,74±4,24	$p_{1-4,\ 2-3}$>0,05
PIE	16	29	23,48±3,33	

*Note. * – statistically significant result.*

Table 4. The assessment of dependence in activities of daily living (Barthel index) according to the disease duration

Type of encephalopathy	Level of dependence	Disease duration (years)							
		up to 1 tyear		1-5		6-10		> 10	
		n	%	n	%	n	%	n	%
CTE	Mild	6	26,09	13	29,55	8	21,05	14	35,00
	Moderate	4	17,39	5	11,36	3	7,89	5	12,50
χ^2=3,74; p=0,712									
SVD	Mild	10	16,13	3	7,32	1	11,11	14	42,42
	Moderate	3	4,84	7	17,07	2	22,22	6	18,18
χ^2=23,40; p<0,001*									
AE	Mild	8	21,62	8	34,78	4	26,67	9	33,33
	Moderate	6	16,22	5	21,74	2	13,33	3	11,11
χ^2=3,07; p=0,799									
PIE	Mild	26	39,39	6	33,33	4	66,67	10	26,32
	Moderate	8	12,12	4	22,22	1	16,67	10	26,32
χ^2=6,96; p=0,325									

*Note. * – statistically significant result.*

Analyzing the average number of points gained on the MOCA-test in patients with various types of encephalopathies, weak cognitive impairments were found in patients of all studied groups (Table 3).

At the same time, statistically significant differences were found between groups of patients with CTE and SVD and AE; SVD and PIE; AE and PIE.

During the distribution of patients with different types of encephalopathies depending on gender, no probable influence of the gender factor and age on the degree of dependence on external assistance in everyday life according to the Barthel scale in patients of all observation groups was established (CTE (χ2=4.20; p=0.123); SVD (χ2=1.90; p=0.386); AE (χ2=0.96; p=0.619); PIE (χ2=3.96; p=0.138)) The assessment of functional disability in everyday life according to the Barthel scale, depending on the age category, did not show statistically significant differences in patients with CTE (χ2=6.15; p=0.188); SVD (χ2=9.23; p=0.161) and AE (χ2=3.81; p=0.703). As for patients with PIE, it has been established that the age category has a probable influence on the degree of functional incapacity in everyday life, in particular, the predominance in patients aged 60-74 years of light dependence on external assistance, and in the age category of 45-59 years – moderate dependence on external assistance (χ2=14.21; p=0.027))

The assessment of functional disability in everyday life according to the Barthel scale in patients with various types of encephalopathies depending on the duration of the disease indicates a probable influence of the catamnesis factor only in patients with SVD. In particular, in the group of patients with catamnesis up to 1 year, mild dependence on external assistance in everyday life was found in 16.13%, and moderate – in 4.84% of people; in the group of patients with catamnesis of 1-5 years, mild dependence on external assistance in everyday life was found in 7.32%, and moderate – in 17.07% of people; in the group of patients with catamnesis aged 6-10 years, mild dependence on external assistance in everyday life was found in 11.11%, and moderate dependence in 22.22% of people; in the group of patients with catamnesis for more than 10 years, mild dependence on external assistance in everyday life was found in 42.42%, and moderate dependence in 18.18% of people (Table 4).

DISCUSSION

The multifariousness of neurological signs and syndromes is typical for patients with post-infectious, chronic traumatic encephalopathy, alcohol-induced, and microvascular ischemic disease of the brain. Some of the syndromes may be unique and typical for a certain encephalopathy, for example, seizure and amiostatic syndromes were found in patients with CTE, apraxia – in SVD, amiostatatic and different types of ataxia – in AE, while in case of PIE – prosoparesis, myopathic syndrome, and pelvic disorder were found.

As the study has shown, weak cognitive impairments were predominating in patients of all studied groups. Cognitive dysfunction is affecting the day-to-day functioning of the patient and evokes decreasing in the patient's quality of life [13, 25].

Despite the fact, that those syndromes, predominating in the majority of patients, don't cause disability, however, 40% of patients with CTE are dependent in their activities of daily living, among patients with SVD – 31,72 %, among patients with AE – 44.12%, among patients with PIE – 53.91%. Thus, the severity of disability doesn't depend on the age or sex of patients but is correlating with the duration of the disease in a group with SVD.

Therefore, future studies should analyze the other correlations, such as the correlation of the disability level from the neurological syndromes and neuroimaging data.

The role of genetic polymorphisms in the patogenesis of encephalopathy should be investigated thoroughly. As due to several studies, inflammation, oxidative stress, and apoptosis, which are happening during certain periods of encephalopathy, may be modified by genetic variability [3, 5, 8, 30, 31]. Such valuable data would also let us to apply various statistical methods in order to predict the prognosis.

CONCLUSIONS

This research shows the diversity of neurological manifestations in patients with the following encephalopathies: post-infectious, chronic traumatic encephalopathy, alcohol-induced, and microvascular ischemic disease of the brain. The activities of daily living were studied profoundly and the data obtained opened new directions in the following research.

REFERENCES

1. Öznur AK et al. Influenza B-associated encephalopathy in two adults. Journal of Infection and Chemotherapy. 2012;18(6):961-964.
2. Almqvist J et al. Neurological manifestations of coronavirus infections–a systematic review. Annals of clinical and translational neurology. 2020;7(10):2057-2071.
3. Benameur K et al. Encephalopathy and encephalitis associated with cerebrospinal fluid cytokine alterations and coronavirus disease, Atlanta, Georgia, USA, 2020. Emerging infectious diseases. 2020;26(9).
4 Wiseman S, Marlborough F, Doubal F et al. Blood markers of coagulation, fibrinolysis, endothelial dysfunction and inflammation in lacunar stroke versus non-lacunar stroke and non-stroke: systematic review and meta-analysis. Cerebrovasc Dis. 2014;37(1):64-75.
5. Cechetti F et al. Chronic brain hypoperfusion causes early glial activation and neuronal death, and subsequent long-term memory impairment. Brain research bulletin. 2012;87(1):109-116.
6. Chamorro AJ et al. Differences between alcoholic and nonalcoholic patients with Wernicke encephalopathy: a multicenter observational study. In: Mayo Clinic Proceedings. Elsevier. 2017, p.899-907.
7. Douglas-Escobar M, Michael D. Hypoxic-ischemic encephalopathy: a review for the clinician. JAMA pediatrics. 2015; 169(4):397-403.
8. Farhadian Sh et al. Acute encephalopathy with elevated CSF inflammatory markers as the initial presentation of COVID-19. BMC neurology. 2020;20(1):1-5.
9. Fateeva VV, Vorob'eva OV. Cerebral markers of endothelial dysfunction in chronic brain ischemia. Zhurnal Nevrologii i Psikhiatrii Imeni SS Korsakova. 2017;117(4):107-111.
10. Feng Chao et al. The'silence'of silent brain infarctions may be related to chronic ischemic preconditioning and nonstrategic locations rather than to a small infarction size. Clinics. 2013;68:365-369.
11. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. Journal of Neurology. 2017; 264(8):1608-1616.
12. Garg RK, Vimal K. GUPTA, Ankit. Encephalopathy in patients with COVID-19: a review. Journal of Medical Virology. 2021; 93(1):206-222.
13. Hrytsiuk T, Gerasymchuk R, Mykhalchuk D. The peculiarities of cognitive impairment and their association with structural changes in the carotid artery of the patients after ischemic stroke. The Pharma Innovation Journal. 2018;7(4):444-447.
14. Kim TE et al. Wernicke encephalopathy and ethanol-related syndromes. Seminars in Ultrasound, CT and MRI. WB Saunders. 2014,p.85-96.
15. Kim Y, Jae W. Toxic encephalopathy. Safety and health at work. 2012; 3(4):243-256.
16. Palacio S, Mcclure LA, Benavente OR et al. Lacunar strokes in patients with diabetes mellitus: risk factors, infarct location, and prognosis: the secondary prevention of small subcortical strokes study. Stroke. 2014;45(9):2689-94.
17. Levin OS, Chimagomedova A. Sh. Cognitive disorders in discirculatory encephalopathy. Psikhiatriya. 2018;78:158-166.
18. Fudong L, Mccullough LD. Inflammatory responses in hypoxic ischemic encephalopathy. Acta Pharmacologica Sinica. 2013;34(9):1121-1130.
19. Mamurova M et al. Neurological disorders and conditions of cerebral hemodynamics in patients with discirculatory encephalopathy on the background of arterial hypotension. European Journal of Molecular & Clinical Medicine. 2020; 7(2):2504-2508.
20. Manzo G et al. MR imaging findings in alcoholic and nonalcoholic acute Wernicke's encephalopathy: a review. Biomed research international. 2014, p.63.
21. Mckee AC et al. The neuropathology of chronic traumatic encephalopathy. Brain pathology. 2015;25(3):350-364.
22. Mckee AC et al. The spectrum of disease in chronic traumatic encephalopathy. Brain. 2013;136(1):43-64.
23. Mez J, Stern RA, McKee AC. Chronic traumatic encephalopathy: where are we and where are we going?. Current neurology and neuroscience reports. 2013;13(12):1-12.
24. Montenigro PhH et al. Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. Alzheimer's research & therapy. 2014; 6(5):1-17.
25. Omalu B. Chronic traumatic encephalopathy. Concussion. 2014; 28:38-49.
26. Parfenov VA. Vascular cognitive impairment and chronic cerebral ischemia (dyscirculatory encephalopathy). Neurology, Neuropsychiatry. Psychosomatics. 2019; 11(3): 61-67.
27. Saulle M, Greenwald BD. Chronic traumatic encephalopathy: a review. Rehabilitation research and practice. 2012, p.78.
28. Tabarki B et al. Acute necrotizing encephalopathy associated with enterovirus infection. Brain and Development. 2013; 35(5):454-457.
29. Zhang Sh, Feng J, Shi Y. Transient widespread cortical and splenial lesions in acute encephalitis/encephalopathy associated with primary Epstein-Barr virus infection. International Journal of Infectious Diseases. 2016;42:7-10.
30. Esih K, Goričar K, Soltirovska-Šalamon A et al. Genetic Polymorphisms, Gene-Gene Interactions and Neurologic Sequelae at Two Years Follow-Up in Newborns with Hypoxic-Ischemic Encephalopathy Treated with Hypothermia. Antioxidants (Basel). 2021;10(9):1495. doi:10.3390/antiox10091495.
31. Zhang F et al. Investigation of the relationship between MBP gene polymorphisms and delayed encephalopathy after acute carbon monoxide poisoning. NeuroToxicology. 2023;94:217-222.

The presented work was performed within the theme of research work of the Neurology Department "Clinical and pathogenetic characteristics of diseases of the nervous system, improvement of diagnostics, optimization of treatment" (state registration number 0123U100059) of I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine.

ORCID AND CONTRIBUTIONSHIP
Khrystyna V. Duve: 0000-0001-9036-2459[A-D]
Svitlana I. Shkrobot: 0000-0002-5115-0207[A,E,F]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 14.04.2023
ACCEPTED: 03.09.2023

ADDRESS FOR CORRESPONDENCE
Khrystyna V. Duve
I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine
14 Troleybusna St., 46000 Ternopil, Ukraine
e-mail: duve.khrystyna@gmail.com

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305108

ASSOCIATION OF SOLUTE CARRIER ORGANIC ANION TRANSPORTER 1B1 GENE POLYMORPHISM WITH RESPONSE TO ATORVASTATIN AND ASSOCIATED MYOPATHY IN IRAQI DYSLIPIDEMIA PATIENTS

Noor Dheyaa Aziz[1], Sameer H. Abbood[2], Ahmed H. Al-Mayali[3], Najah Rayish Hadi[4]

[1]DEPARTMENT OF CLINICAL PHARMACY, COLLEGE OF PHARMACY, UNIVERSITY OF KERBALA, KERBALA, IRAQ
[2]DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS, SCHOOL OF MEDICINE, KUFA UNIVERSITY, KUFA, IRAQ
[3]DEPARTMENT OF INTERNAL MEDICINE, COLLEGE OF MEDICINE, UNIVERSITY OF KERBALA, KERBALA, IRAQ
[4]DEPARTMENT OF PHARMACOLOGY & THERAPEUTICS, FACULTY OF MEDICINE, UNIVERSITY OF KUFA, KUFA, IRAQ

ABSTRACT

Aim: The study aims to investigate the effect of solute carriers organic anions transporters 1B1 (SLCO1B1) gene polymorphisms rs4149056, rs2306283, rs55901008, and rs729559745 in a sample of patients with dyslipidemia, and relate it to atorvastatin response and associated myopathy.

Materials and Methods: A cross sectional enrolled 200 patients both males and females of Arabic race, Iraqi nationality aged between 30-65 years. The patients were divided into two groups: Group 1 (Atorvastatin responders and tolerant), Group 2 (Atorvastatin non responder and intolerant). Blood samples collected from the patients for biochemical studies and analyzed statistically by Student T-test and Chi-square, and DNA extracted for polymerase chains reactions (PCR).

Results: The results showed insignificant association $P \geq 0.05$ between the demographic characteristics of the study population with different genotypes, and significant difference $P < 0.05$ in the biochemical parameters regarding (T-cholesterol, triglycerides, low density lipoproteins, and Creatine kinase-MM) when comparing the two groups. Odds ratio (OR) with confidence intervals CI (95%) used to evaluate the risk association to develop myopathy and poor response to atorvastatin therapy show relevant association for CC and CT genotype of rs4149056, while rs2306283 GG genotype show low association, also rs55901008 show low association for CC genotype, and moderate association for rs72559745 genotypes GG, AG.

Conclusions: The mutant allele's genotypes of rs4149056, rs55901008, and rs72559745, and the wild allele genotype of rs2306283 show significant association with the development of poor response to atorvastatin and elevated the level of CK-MM plasma concentration.

Key words: dyslipidemia, myopathy, atorvastatin, SLCO1B1 gene polymorphism

INTRODUCTION

Dyslipidemia is a significant risk factor for both stroke and coronary artery disease. Hydroxy-methyl glutaryl coenzyme A reductase inhibitors, like atorvastatin used for management despite the inter-individual variability, like the influx carrier organic anion transporter polypeptides (OATP1B1) genetic polymorphisms. Numerous genetic and acquired diseases that characterized by elevated lipid levels in the body are referred as dyslipidemia. Although dyslipidemia does not often result in severe symptoms on its own, this underlying illness frequently leads to major problems that may be cause death [1]. Strong evidence supports the use of moderate-dose statins as the most effective primary preventive therapy for high-risk individuals, with relative risk reductions in cardiovascular events and death of 20% to 30% over five years [2]. Statins reduce LDL-C and total cholesterol by preventing the reductase enzyme for 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA). Numerous researches have conclusively revealed that different statins may reduce the levels of LDL-C, limiting the disease progression and mortality of ASCVD and lowering the risk for developing CVD in those with elevated LDL-C. Statins remain the corner stone of dyslipidemia management [3]. Numerous researches have shown that variations in genes related to the pharmacokinetics are responsible for variation in effectiveness of statin across people. The variations in genetics of drug transporters gene and drugs metabolizing enzymes (phase 1 and phase 2) can play an important role within hepatocytes and plasma atorvastatin concentration, and then in the clinical response to the atorvastatin, as atorvastatin metabolized initially in the liver and inhibits "HMG-CoA reductase" by its major mechanism of action. Variations in genetics of efflux transporters, and influx transporters, including solute carrier organic anions transporters families member 1B1 (SLCO1B1) genes mutations, was linked to altered statin pharmacokinetics

and diminished statin-induced lipid-lowering effects [4]. It has been suggested that atorvastatin serve as OATP1B1 probe substrates. Hepatocytes and enterocytes both absorb atorvastatin up taken from the intestinal lumen through OATP1B1 encoded by SLCO1B1. As a result, any variation that modifies OATP1B1 activity affects atorvastatin plasma levels [5]. Statin-associated muscle symptoms (SAMS), despite the fact that there are numerous well-documented advantages of statin for cardiovascular health, still frequently observed clinically by incidence range 10%-29% which represent the most frequent cause of poor adherence and discontinuation of therapy. The causes are complicated, and genetically related factors very certainly contribute. Mitochondrial dysfunction induced by statin considered as a plausible evidence, but the pathophysiology and processes behind it are still poorly understood [6].

AIM

The present study aimed to investigate the distributive characteristic of solute carriers organic anions transporters 1B1 (SLCO1B1) gene polymorphisms and relate it to atorvastatin response and associated myopathy. By detecting the presence and frequency of four registered polymorphisms in SLCO1B1 (rs4149056, rs2306283, rs55901008, and rs729559745) in a sample of patients with dyslipidemia in Iraq.

MATERIALS AND METHODS

The present cross-sectional study, started from April 2021 to August 2022, enrolled 200 patients both males and females of Arabic race, Iraqi nationality, aged between 30-65 years at Kerbala heart disease center. Included are patients with dyslipidemia and using atorvastatin as the primary pharmacologic agent in their treatment plan for at least 6 months. While the excluded patients with chronic liver and renal problems, uncontrolled diabetes mellitus, familial hyperchlestolemia, hypothyroidism or myxedema, those have mental retardation, and patients taking any drugs that have interaction with atorvastatin. The patients were divided into two groups:

Group 1 (Atorvastatin responders and tolerant) were 130 patients, 60 men and 70 women. Those patients (responder) that achieved normal lipid profile after 6 months of atorvastatin monotherapy, and tolerant patients were defined as those treated with atorvastatin daily reporting no myalgia, and their CK-MM level with in the normal range.

Group 2 (Atorvastatin non-responder and intolerant) were 70 patients, 32 men and 38 women. Those patients for whom atorvastatin therapy dose not achieve the normal level of lipid profile after 6 months of atorvastatin monotherapy, and they are atorvastatin intolerant (patients who reporting myalgia as an adverse effects during the atorvastatin treatment, and their CK-MM level higher than normal.

BLOOD SAMPLING

Five milliliters of blood were aspirated from an anti-cubital vein for DNA extraction and biochemical tests for lipid profile (T-cholesterol, LDL, TG, and HDL) by using an in vitro enzymatic quantitative colorimetric method and the muscle enzyme Creatine Kinase (CK-MM) by Eliza technique. From all participants, blood samples were taken following an 8-hour fasting.

GENOMIC STUDY

DNA was extracted from blood specimens using the kit (mini) for genomic DNA extraction (Frozen Blood). Procedure carried out depending on the instructions of the company. Polymerase Chains Reactions (PCR) is a powerful technique in molecular biology to amplify a specific region from a DNA strand across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence. The three main levels in PCR technique involve - annealing, denaturation, and extensions. PCR is suitable in the investigations single-nucleotide polymorphisms SNPs detection [7]. A quick and affordable way to genotype SNPs is using the tetra-primers ARMS-PCR assay. Four primers used in one PCR, then only gels electrophoresis to be performed thereafter. The optimization stage, however, may be time- and labor-intensive. Tetra ARMS-PCR performance may compromise for SNPs detection within regions of DNA rich in guanine and cytosine as well as for samples with unpurified DNA [8].

STATISTICAL ANALYSIS

Data of the present study was represented as mean ± standard deviation (SD). Statistical Package for Social Science (SPSS) version 25 used to perform the statistical analysis. Student T-test and Chi-square tests were used for comparing demographical and categorical parameters between the two groups of dyslipidemia patients also the biochemical parameters between the two groups compared by student T-test. Odds ratio with confidence interval 95% used to evaluate different alleles and the associated risk of poor response to treatment and myopathy.

ETHICAL APPROVAL

The study was conducted after approval of the scientific and ethical committees in the faculty of Medicine, University of Kufa, Iraq, (EC 141/2022).

RESULTS

Demographic (age, bmi, gender) parameters for the dyslipidemia patients: the results of this study show that there is insignificant association ($P \geq 0.05$) between the demographic characteristics of the study population (Tables 1, 2).

The findings (Tables 1, 2) of the present study indicate there is insignificant association ($P \geq 0.05$) between the demographic characteristics of the study population (dyslipidemia patients) for both responders and non-responders groups, regarding (age, weight, height, body mass index, and gender), but the prevalence of dyslipidemia associated with older ages, and higher BMI greater than 30.

The findings of the present study (Table 3) indicates that there is significant different ($P<0.05$) in the biochemical parameters regarding (T-cholesterol, triglycerides, low density lipoproteins, and creatinine kinase-MM) when comparing the two groups, the levels of these parameters is highly elevated in the non-responders group, with exception of (high density lipoprotein) level that show insignificant differences when the two groups are compared.

Odds ratios and confidence intervals 95% for the slco 1b1 gene polymorphisms (rs4149056, rs2306283, rs55901008, and rs72559745); odds ratio with confidence intervals 95%

Table 1. Distribution of gender between groups

Variable		Responders	Non responders	P-value
Gender	Male	80	30	0.13
	Female	54	36	
Total		134	66	

Table 2. Demographic parameters of the study population

Variables	Responders*	Non responders*	P-value
Age	57.73±6.66	58.33±4.3	0.23
Weight	83.07±14.9	80.48±18.75	0.41
Height	1.65±0.09	1.63±0.1	0.66
Body mass index (BMI)	30.65±5.57	30.22±5.83	0.57

**Data expressed as Mean ± SD and compared by independent sample T-test, P-value <0.05 significant*

Table 3. Comparison of the biochemical parameters in the study population

Variables	Responders	Non responders	P-value
T. cholesterol	144.54±28.24	256.18±23.41	0.001
Triglycerides	164.07±53.77	281.7±122.4	0.001
High Density Lipoproteins	36.7±9.04	36.91±9.79	0.91
Low Density Lipoproteins	75.36±20.47	170.4±19.99	0.001
Creatinine Kinase-MM	2.98±0.78	22.81±8.16	0.001

Data expressed as Mean ± SD and compared by independent sample T-test, P-value <0.05 significant

Table 4. Odds ratio and confidence intervals 95% for rs4149056, rs2306283, rs55901008 and rs72559745 in the study population

Variable	OR (95% CI)	P-value
	rs4149056	
TT (Wild Type)	Ref.*	-
CT (Heterozygous)	2.62 (0.51-13.31)	0.243
CC (Homozygous)	4.13 (0.94-18.93)	0.05
	rs2306283	
AA (Wild Type)	Ref.*	-
AG (Heterozygous)	0.83 (0.32-2.15)	0.71
GG (Homozygous)	1.25 (0.54-2.91)	0.59
	rs55901008	
TT (Wild Type)	Ref.*	-
CT (Heterozygous)	0.76 (0.27-2.17)	0.62
CC (Homozygous)	1.47 (0.68-3.16)	0.31
	rs72559745	
AA (Wild Type)	Ref.*	-
AG (Heterozygous)	2.21 (0.79-6.2)	0.13
GG (Homozygous)	2.21 (0.304-16.2)	0.43

** Wild allele for each snp considered the reference for comparisons.*

used to evaluate the risk association to develop myopathy and poor response to atorvastatin therapy in dyslipidemia Iraqi patients (Table 4).

The results of the present study (Table 4) show strong association for the following genotypes (CC) OR 4.13, CI (0.51%-13.31%), and (CT) OR 2.62, CI (0.94%-18.93%) of rs4149056 SNP with the risk to develop poor response to atorvastatin and myopathy, while for rs2306283 SNP (GG) genotype with OR 1.25, CI (0.54-2.91) %have low risk association to develop poor response to atorvastatin and myopathy. Table 4 shows mild association for rs55901008 (CC) genotype OR 1.47, CI (0.27-2.17) %, and insignificant association for (CT) with an OR 0.76, CI (0.27-2.17) % to develop poor response to atorvastatin and myopathy, and moderate association for rs72559745

Table 5. Mean differences of biochemical parameters in dyslipidemia patients groups and different genotypes of rs4149056

Parameters	Genotype Rs4149056	Responder Mean ± SD	Non-Responder Mean ± SD	P value
T-cholesterol	«CC»	141.1±28.6	294±5.66	0.001
	«CT»	152.38±24.4	257.22±26.03	0.001
	«TT»	155±31.67	252.32±20.56	0.001
TG	«CC»	161.02±54.98	311.56±114.86	0.001
	«CT»	177.23±53.7	271.5±129.87	0.001
	«TT»	160±47.55	259.5±91.22	0.001
HDL-C	«CC»	36.71±9.78	34.62±6.45	0.47
	«CT»	35.38±4.05	42.89±14.6	0.059
	«TT»	39.5±11.29	38.5±3.54	0.73
LDL-C	«CC»	74.17±21.59	172.51±22.35	0.001
	«CT»	78±16.67	168.66±19.71	0.001
	«TT»	71.8±11.76	167±0	0.001
CK-MM	«CC»	3.05±0.8	25.75±10.25	0.001
	«CT»	2.83±0.71	21.47±7.87	0.001
	«TT»	2.73±0.85	23.09±8.43	0.001

Data expressed as Mean ± Stander deviation (SD), p< 0.05: statistically significance, studied by the statistical test (independent t – test).

Table 6. Mean differences of biochemical parameters in dyslipidemia patients groups and different genotypes of rs2306283

Parameters	Genotype rs2306283	Responder Mean ± SD	Non-Responder Mean ± SD	P value
T-cholesterol	AA	161±27.81	259.5±24.13	0.001
	GA	144.57±28.1	250±20.28	0.001
	GG	139.34±27.21	257.74±25.08	0.001
TG	AA	176.27±50.85	323±138.96	0.001
	GA	156.29±46.75	277.83±126.32	0.001
	GG	164.91±58.99	265.53±116.84	0.001
HDL-C	AA	39.64±8.63	32.67±7.94	0.37
	GA	36.62±10.6	34±4.66	0.44
	GG	35.83±8.19	39.47±11.3	0.61
LDL-C	AA	81.27±27.57	182.17±21.1	0.001
	GA	69.1±18.37	164.35±23.07	0.001
	GG	77.26±18.77	169.23±17.76	0.001
CK-MM	AA	3.21±0.75	23.17±9.75	0.001
	GA	2.82±0.83	21.91±11.27	0.001
	GG	3.01±0.76	23.07±6.48	0.001

Data expressed as Mean ± Stander deviation (SD), p< 0.05: statistically significance, studied by the statistical test (independent t – test).

genotypes (GG), (AG) with OR 2.21, CI (0.79-6.2 %(to develop poor response to atorvastatin and myopathy.

Effects of treatment with Atorvastatin on biochemical parameters in dyslipidemia patients with different genotypes of SLCO1B1 gene polymorphisms rs4149056 presents table 5.

Effects of treatment with Atorvastatin on biochemical parameters in dyslipidemia patients with different genotypes of SLCO1B1 gene polymorphisms rs2306283 shows table 6

Effects of treatment with Atorvastatin on biochemical parameters in dyslipidemia patients with different genotypes of SLCO1B1 gene polymorphisms rs55901008 shows table 7.

Effects of treatment with Atorvastatin on biochemical parameters in dyslipidemia patients with different genotypes of SLCO1B1 gene polymorphisms rs72559745 shows table 8.

The results in tables 5-8 are comparing the biochemical parameters of different genotypes in the studied population the findings show higher reading in non-responder with (CC) allele of rs4149056, (AA) allele of rs2306283, (CC) allele of rs55901008, and (GG) allele of rs72559745.

DISCUSSION

The findings expressed in table 1 and 2 are compatible with [9] study that confirm BMI is closely related to dyslipidemia. Another study that was done in Saudi Arabia by [10] indicate that high BMI associated with increase in the level LDL cholesterol and decrease in the HDL cholesterol ,in addition to that they show insignificant association between gender and lipid profiles changes [10]. Cho SMJ, et al., [11] study demonstrate that the incidence of dyslipidemia parameters elevation are significantly different with the age of the patients, and the odd ratios (OR) for hyperlipidemia was greater for older than younger patients.

BIOCHEMICAL PARAMETERS FOR THE DYSLIPIDEMIA PATIENTS

There are still concerns about long-term safety, despite the fact that decreasing LDL-C is acknowledged as an important goal in the prevention of CV disease. It is crucial to identify a positive clinical benefit that results from a decrease in CV events and the possibility of adverse clinical events when assessing the long-term effects of statin medication in primary prevention. Myositis is an uncommon adverse effect of statins described as muscular discomfort along with noticeably raised blood Creatine kinase (CK) levels. Muscle discomfort often starts during the first year of treatment, with a median time to commencement of one month, or after a dosage increase or the addition of an interfering medication [12]. Our findings that expressed in table 3 are in agreement with [13] that compare four groups with different treatment duration, and show the mean values of total- cholesterol, triglycerides, and LDL-cholesterol were significantly lower among patients that use statins for 6 months and longer. Also the findings in table (5,6,7,8) are in agreement with [14] explain the possible causes of differences or poor response to statins, when same doses and same statins given to different individuals produce different lipid lowering results which may be due to the polymorphism of gene effect on statins pharmacokinetics and pharmacodynamics that lead to resistance or tolerance. Resistance develop when the patient failed to achieve the intended effectiveness of treatment, while intolerance occur with continued drug administrations , or excesses of side effects that prevents patients from adequate drug use. The adverse effect of statin influencing intolerance is myopathy range from asymptomatic increase in creatinine kinase to sever rahbdomyolysis. Another study [15] reveal the importance of OATP1B1 hepatic transporters mediated uptake of atorvastatin this study focus on the genetic variants of the OATP that lead to inhibition or reduce the function of the transporters which have been associated with greater atorvastatin systemic exposure in clinical studies[15].

ASSOCIATION OF GENOTYPING AND SLCO1B1 GENE POLYMORPHISMS WITH THE RISK OF DYSLIPIDEMIA AND MYOPATHY

rs4149056

Odds ratio with confidence intervals 95% used to evaluate the risk association to develop myopathy and poor response to atorvastatin therapy in dyslipidemia Iraqi patients. Odds ratio (OR)>1 indicate risk association. The findings in table 4 are compatible with many different studies like [16] estimating the clearance of atorvastatin in patients with the mutant allele (CC) for the rs4149056 SNP, the results show that low clearance associated with muscles discomfort (risk for myalgia) and lower efficacy of the drug (lower reduction in LDL-cholesterol) reduction in responsiveness to atorvastatin therapy. Link, et al. [17] clarified that rs4149056 SNP significantly associated with smooth muscle induced myopathy, with an OR 4.5 and 16.9 in heterozygous and homozygous, respectively. These finding are in agreement with ours. Recently [18] study the rs4149056 SNP in diabetic Jordanians patients indicate that frequency of C minor allele was 23%, the risk for development of smooth muscles myopathy associated significantly with homozygous (CC) and heterozygous (CT) genotyping.

rs2306283

The results that showed in table 4 are compatible with Ferrari, et al.[19]investigate the relation between elevated Creatine kinase level and polymorphisms within the genes encoding transporters for statins disposition in Italy show that Europeans Italic patients carry the rs2306283 SNP have significantly lower risk of Creatine kinase elevation in heterozygous genotype for the G allele, with an OR 0.24. Another study [20] clarifies that G allele associates with decrease bioavailability of Rosuvastatin, atorvastatin, & simvastatin, &low risk of statins induce myopathies. Shahrure, et al. [18] study the rs2306283 SNP in diabetic Jordanians patients indicate that the frequency of the minor G allele was 38%, and the risk for development of smooth muscles myopathy associated significantly with homozygous (AA) wild allele genotyping. Another article by [21] study on Emirati diabetic patients show that A allele genotype have strong association with statins associated myopathies, these are in agreement with our results [21].

rs55901008

A limited number of studies available about the rs55901008 one of these is [22] study the importance of OATP transporter in mice by using knockout mice with OATP1b2 null mice and humanized-mice modeling in addition to in vitro transporting studies depending on cells lining, result of the study reveal that numerous polymorphisms for OATP1B1transporter including rs55901008 play an important role with entrance of different statins into the mice liver, and by decreasing the transporting activity the clearance will decrease and the plasma accumulation of statins increased with the associated risk of myopathy. Borobia et al. [23] designed a study that integrate the pharmacokinetic testing into the clinical practice in La Paz hospital in Madrid, the study aimed to individualize the clinical recommendations and make assessment for genotyping in risk population in order to maintain this testing about 180 polymorphisms related with different drugs responding ,and clinical consultations depending on the obtained results, one of studied SNPs was rs55901008 to evaluate the importance of this SNP in treatments plan that involve the statins and anti-diabetic agents. Our noble findings in table 4 show mild association for rs55901008

Table 7. Mean differences of biochemical parameters in dyslipidemia patients groups and different genotypes of rs55901008

Parameters	Genotype rs55901008	Responder Mean ± SD	Non-Responder Mean ± SD	P value
T-Cholesterol	«CC»	143.64±30.74	277.33±14.31	0.001
	«CT»	139.15±25.83	250.75±28.19	0.001
	«TT»	151.53±23.23	251.61±22.2	0.001
TG	«CC»	164.79±59.49	289.57±141.19	0.001
	«CT»	180.62±41.25	278.75±25	0.001
	«TT»	147.87±45.02	253.5±80.85	0.001
HDL-C	«CC»	36.95±9.01	37.57±10.83	0.26
	«CT»	33.62±7.52	32±7.12	0.17
	«TT»	38.73±10.16	37.67±6.68	0.64
LDL-C	«CC»	74.74±23.23	171.67±20.39	0.001
	«CT»	73.38±10.8	171.38±14.19	0.001
	«TT»	78.67±19.88	164.87±23.7	0.001
CK-MM	«CC»	2.88±0.84	31.33±6.61	0.001
	«CT»	2.92±0.72	21±11.97	0.001
	«TT»	3.28±0.64	23.03±9.15	0.001

Data expressed as Mean ± Stander deviation (SD), p< 0.05: statistically significance, studied by the statistical test (independent t – test).

Table 8. Mean differences of biochemical parameters in patients groups and different genotypes of rs72559745

Parameters	Genotype rs72559745	Responder Mean ± SD	Non-Responder Mean ± SD	P value
T-Cholesterol	«AA»	146.51±27.57	254.71±23.09	0.001
	«AG»	125.4±32.9	259± 79.3	0.001
	«GG»	120± 83.28	265.75±30.05	0.001
TG	«AA»	164.89±53.26	268.14±119.08	0.001
	«AG»	170±59.41	298± 93.18	0.001
	«GG»	85± 21.56	372.5±139.16	0.01
HDL-C	«AA»	36.62±9.14	37.04±10.27	0.57
	«AG»	38.2±9.58	38.75±5.32	0.38
	«GG»	34± 2.17	26± 1.45	0.18
LDL-C	«AA»	76.57±20.85	170.33±20.87	0.001
	«AG»	61.8±11.56	166±13.69	0.001
	«GG»	69±28.22	190± 59.24	0.001
CK-MM	«AA»	3.02±0.76	22.6±8.36	0.001
	«AG»	2.48±1.07	22.5±7.94	0.001
	«GG»	3.1± 0.95	30± 11.5	0.001

Data expressed as Mean ± Stander deviation (SD), p< 0.05: statistically significance, studied by the statistical test (independent t – test).

(CC) genotype, and insignificant association for (CT) to develop poor response to atorvastatin and myopathy.

rs72559745

Also limited studies available about rs72559745 one of these is by [24] conducted an extensive analysis of the distribution of different Pharmacogn polymorphisms for 378 SNPs analyzed and studied in 150 Korean subject, which may affect the response and side effects of many drugs, one of the studied SNPs in this research was rs72559745 without any mentioned number for the minor allele frequency, which may be due to the absence of this SNP in Korean subjects. Padula, et al. [25] study the interaction of variant gene such as rs72559745 of biotransformation enzymes and transporters and air pollution exposure and the risk of spinapifida in California population, the results of the study reveal that the frequency of minor allele was <0.01 ,with OR = 2 that show insignificant association with disease development [25]. Our noble results in table 4 showed moderate association for rs72559745 genotypes (GG), (AG) with OR 2.21, CI (0.79-6.2% (to develop poor response to atorvastatin and myopathy,

CONCLUSIONS

The studied polymorphisms have significant associations for the mutant allele's genotypes of rs4149056, rs55901008, and rs72559745, and the wild allele genotype of rs2306283 with the development of poor response to atorvastatin and elevated the level of CK-MM plasma concentration. In addition there is the limited number of global studies and available data for rs55901008 and rs72559745 especially in Arabic countries and Iraqi population.

REFERENCES

1. Hill MF, Bordoni B. Hyperlipidemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; August 8, 2022.
2. Yebyo HG, Aschmann HE, Kaufmann M, et al. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. Am Heart J. 2019;210:18-28. doi:10.1016/j.ahj.2018.12.007.
3. Santos PC, Soares RA, Nascimento RM, et al. SLCO1B1 rs4149056 polymorphism associated with statin-induced myopathy is differently distributed according to ethnicity in the Brazilian general population: Amerindians as a high risk ethnic group. BMC Med Genet. 2011;12:136. doi:10.1186/1471-2350-12-136.
4. Vanwong N, Tipnoppanon S, Na Nakorn C, et al. Association of Drug-Metabolizing Enzyme and Transporter Gene Polymorphisms and Lipid-Lowering Response to Statins in Thai Patients with Dyslipidemia. Pharmgenomics Pers Med. 2022;15:119-130. doi:10.2147/PGPM.S346093.
5. Ingelman-Sundberg M, Mkrtchian S, Zhou Y, et al. Integrating rare genetic variants into pharmacogenetic drug response predictions. Hum Genomics. 2018;12(1):26. doi:10.1186/s40246-018-0157-3.
6. Nikolic D, Banach M, Chianetta R, et al. An overview of statin-induced myopathy and perspectives for the future. Expert Opin Drug Saf. 2020;19(5):601-615. doi:10.1080/14740338.2020.1747431.
7. Undi R, Lim HY, Wang W. Rapid and reliable identification of insulin 2 gene mutation in Akita diabetic mice by a tetra-primer-ARMS-PCR method. Heliyon. 2019;5(1):e01112. doi:10.1016/j.heliyon.2018.e01112.
8. Medrano RF, de Oliveira CA. Guidelines for the tetra-primer ARMS-PCR technique development. Mol Biotechnol. 2014;56(7):599-608. doi:10.1007/s12033-014-9734-4.
9. Xi Y, Niu L, Cao N et al. Prevalence of dyslipidemia and associated risk factors among adults aged ≥35 years in northern China: a cross-sectional study. BMC Public Health. 2020;20(1):1068. doi:10.1186/s12889-020-09172-9.
10. Milyani AA, Al-Agha AE. The effect of body mass index and gender on lipid profile in children and adolescents in Saudi Arabia. Ann Afr Med. 2019;18(1):42-46. doi:10.4103/aam.aam_17_18.
11. Cho SMJ, Lee HJ, Shim JS, Song BM, Kim HC. Associations between age and dyslipidemia are differed by education level: The Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) cohort. Lipids Health Dis. 2020;19(1):12. doi:10.1186/s12944-020-1189-y.
12. Ferri N, Corsini A. Clinical Pharmacology of Statins: an Update. Curr Atheroscler Rep. 2020;22(7):26. doi:10.1007/s11883-020-00844-w.
13. Habte ML, Melka DS, Degef M et al. Comparison of Lipid Profile, Liver Enzymes, Creatine Kinase and Lactate Dehydrogenase Among Type II Diabetes Mellitus Patients on Statin Therapy. Diabetes Metab Syndr Obes. 2020;13:763-773. doi:10.2147/DMSO.S234382.
14. Reiner Z. Resistance and intolerance to statins. Nutr Metab Cardiovasc Dis. 2014;24(10):1057-1066. doi:10.1016/j.numecd.2014.05.009.
15. Vildhede A, Karlgren M, Svedberg EK, et al. Hepatic uptake of atorvastatin: influence of variability in transporter expression on uptake clearance and drug-drug interactions [published correction appears in Drug Metab Dispos. 2015 May;43(5):786-7]. Drug Metab Dispos. 2014;42(7):1210-1218. doi:10.1124/dmd.113.056309.
16. Stillemans G, Paquot A, Muccioli GG et al. Atorvastatin population pharmacokinetics in a real-life setting: Influence of genetic polymorphisms and association with clinical response. Clin Transl Sci. 2022;15(3):667-679. doi:10.1111/cts.13185.
17. SEARCH Collaborative Group, Link E, Parish S et al. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med. 2008;359(8):789-799. doi:10.1056/NEJMoa0801936.
18. Shahrure ZM, Irshaid YM, Mustafa KN et al. SLCO1B1 Gene Polymorphisms (rs2306283 and rs4149056) and Statin-Induced Myopathy in Jordanian Diabetics. Curr Rev Clin Exp Pharmacol. 2021;16(3):281-288. doi:10.2174/1574884715666200827105612.
19. Ferrari M, Guasti L, Maresca A et al. Association between statin-induced creatine kinase elevation and genetic polymorphisms in SLCO1B1, ABCB1 and ABCG2. Eur J Clin Pharmacol. 2014;70(5):539-547. doi:10.1007/s00228-014-1661-6.
20. Nies AT, Niemi M, Burk O et al. Genetics is a major determinant of expression of the human hepatic uptake transporter OATP1B1, but not of OATP1B3 and OATP2B1. Genome Med. 2013;5(1):1. doi:10.1186/gm405.
21. Saber-Ayad M, Manzoor S, El-Serafi A et al. Statin-induced myopathy SLCO1B1 521T > C is associated with prediabetes, high body mass index and normal lipid profile in Emirati population. Diabetes Res Clin Pract. 2018;139:272-277. doi:10.1016/j.diabres.2018.03.014.
22. Choudhuri S, Klaassen CD. Elucidation of OATP1B1 and 1B3 transporter function using transgenic rodent models and commonly known single nucleotide polymorphisms. Toxicol Appl Pharmacol. 2020;399:115039. doi:10.1016/j.taap.2020.115039.
23. Borobia AM, Dapia I, Tong HY et al. Clinical Implementation of Pharmacogenetic Testing in a Hospital of the Spanish National Health System: Strategy and Experience Over 3 Years. Clin Transl Sci. 2018;11(2):189-199. doi:10.1111/cts.12526.
24. Kim JY, Cheong HS, Park TJ et al. Screening for 392 polymorphisms in 141 pharmacogenes. Biomed Rep. 2014;2(4):463-476. doi:10.3892/br.2014.272.
25. Padula AM, Yang W, Schultz K, et al. Genetic variation in biotransformation enzymes, air pollution exposures, and risk of spina bifida. Am J Med Genet A. 2018;176(5):1055-1090. doi:10.1002/ajmg.a.38661.

ORCID AND CONTRIBUTIONSHIP
Noor Dheyaa Aziz: 0000-0001-9795-0579[A-B]
Sameer H. Abbood: 0000-0001-5002-1000[B-D]
Ahmed H. Al-Mayali: 0000-0001-8051-5116[C-E]
Najah Rayish Hadi: 0000-0002-6561-4519[C-E]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 09.05.2023
ACCEPTED: 10.09.2023

ADDRESS FOR CORRESPONDENCE
Noor Dheyaa Aziz
Department of Clinical Pharmacy, College of Pharmacy, University of Kerbala, Kerbala, Iraq
e-mail: noor.dh@uokerbala.edu.iq

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 504-510

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305109

NEEDS AND POSSIBILITIES OF SOCIAL WORK IN IMPLEMENTING SOCIAL INCLUSION WITH THE TOOLS OF ADAPTIVE PHYSICAL ACTIVITY

Liliia Y. Klos[1], Oksana Z. Blavt[1], Oksana Y. Makukh[1], Uliana V. Yatsyshyn[1], Oleksandr P. Kovalchuk[2], Matthias Zimlich[3]

[1]LVIV POLYTECHNIC NATIONAL UNVERSITY, LVIV, UKRAINE
[2]NATIONAL DEFENSE UNIVERSITY OF UKRAINE, KYIV, UKRAINE
[3]UNIVERSITY OF WUERZBURG, WUERZBURG, GERMANY

ABSTRACT

Aim: reveal in social work the possibilities of applying adaptive physical activity in the process of social inclusion of persons with disabilities.

Materials and Methods: To obtain factual information, the survey method (questionnaire) and a complex of mathematical statistics methods were used: methods of descriptive statistics and correlation analysis. Statistical analysis was performed using SPSS Statistics 24.0.0. A total of 102 anonymous respondents took part in the focus groups.

Results: The connection between adaptive physical activity and the increase in the level of social inclusion of persons with disabilities, in particular, former military personnel and war veterans, was investigated. It was determined that social work professionals can use adaptive physical activity tools to promote the social inclusion of persons with disabilities and other low-mobility population groups.

Conclusions: It was established that the ways of using adaptive physical activity tools by social workers for the social inclusion of persons with disabilities are most often socio-psychological, physical, professional rehabilitation, social support, and preventive activities. New opportunities for the implementation of social inclusion by means of adaptive physical activity of persons with disabilities as a result of military operations are opened in connection with the introduction of the position of «helper (assistant) of a veteran in the community», which will be held by a social worker.

KEY WORDS: disabled person, health, social worker

INTRODUCTION

A special place in state target programs in the field of health is emphasized in their comprehensive implementation with the participation of social work specialists [1]. The leading goal of social work in the field of health is to achieve the highest possible level of population health, functioning and adaptation of persons with disabilities, physical and mental pathology, or social disadvantage [2].

The dynamic field of social work is now gaining special importance in Ukraine, where Ukrainian society is in a crisis due to prolonged hostilities. One of the consequences of armed Russian aggression on the territory of Ukraine is an increase in the number of people with disabilities.

According to the Office of the UN High Commissioner for Human Rights, as of June 30, 2023, the number of injured civilians in Ukraine as a result of Russia's full-scale military aggression was 15,997. The figure of the official number of wounded servicemen is not disclosed at this time, but, according to forecasts, at the end of the war, at least 100,000 people are expected to be disabled as a result of hostilities [3]. However, the problem affects the entire world at the same time: one billion people, or about 15% of the global population, live with some form of disability [4].

According to its value system and as a professional activity, social work is aimed at helping people with disabilities and promoting their social inclusion [5]. Currently, social inclusion is part of the framework laws of the EU, which is fully implemented in social work by introducing social inclusion as a mechanism for increasing the degree of participation of all citizens in society [6]. Moreover, social work in the implementation of social inclusion contributes to the maximum involvement of persons with disabilities in social processes by overcoming psychological, social, educational, legal, and other barriers to meet their needs [6].

It is believed [6, 8, 9] that the achievement of defined benchmarks of social work for the implementation of the inclusion of persons with disabilities is largely related to the integration of practical medicine and adaptive physical activity (APA). The experience of social work shows [1, 10] the effectiveness of APA efforts as a social construction that is positioned as a means of inclusion at various levels.

There are ideas [11] that social work is an institution for involving persons with disabilities in systematic APA as a tool for their social inclusion. The scientific interest of researchers from different countries of the world is focused on the possibilities of APA as an cheap and effective means of preserving health, well-being, and social inclusion of persons with disabilities.

From the point of view of social work, APA assistance to persons with disabilities is positioned as a means of improving their quality of life, ensuring their social inclusion and physical rehabilitation [6]. Note that full-fledged physical activity is often the first thing that a person with a disability loses as a result of a serious injury. Such individuals face limitations everywhere and thus, problems with self-esteem and self-realization arise. As a result, a person with a disability seems to be on the sidelines of society. Often - on one's initiative. At the same time, the APA process is generally aimed at adapting persons with disabilities to the physical and social conditions of the environment [8].

Social inclusion of persons with disabilities should be the result of their rehabilitation [12]. However, to date, in the field of social work, the implementation of social inclusion in Ukraine by APA tools has received very little attention and has been used mainly in a declarative nature, which additionally actualizes the stated problem in connection with the long-term hostilities on the territory of Ukraine, and, therefore, the permanent increase in the number of persons with disabilities.

Unfortunately, in Ukraine, there is still a widespread opinion about people with disabilities as carriers of social exclusion. This is reflected in various aspects of their social life and is especially evident in matters of employment, where representatives of this social group may experience an act of discriminatory behavior [15]. Observations allow us to state that persons with disabilities have rather limited opportunities for self-realization, self-affirmation, and establishing social contacts, that is, all components of social inclusion [1, 6].

Therefore, in the context of the study of aspects of social work in the field of health care, we consider it necessary to determine the level of implementation of social inclusion by APA tools in order to understand the opportunities, potentials, and problems of this process.

AIM

is to identify in social work the possibilities of applying APA in the process of social inclusion of persons with disabilities.

MATERIALS AND METHODS

To obtain factual information about the target group, the questionnaire method was used. For the correct processing of empirical data, a complex of mathematical statistics methods was applied: descriptive statistics methods and correlation analysis. Statistical analysis was performed using SPSS Statistics 24.0.0.

Ethical principles of research. The research was planned and carried out in accordance with the principles of ethics of empirical research. In this regard, the requirements of the principles of voluntariness, anonymity, and trust were met. Participants were informed that there were no right or wrong answers, that it was important to reflect on their situation, and that the data obtained will be kept confidential.

The study was planned and carried out following the principles of bioethics set forth by the World Medical Association (WMA-2013) in the Helsinki Declaration «Ethical Principles of Medical Research Involving Humans» and UNESCO in the «General Declaration on Bioethics and Human Rights».

Research organization. Seventeen focus groups were created using Zoom, and participants registered through the created event. A total of 102 anonymous respondents took part in the focus groups and expressed a voluntary desire to answer the proposed questions: women made up 52% of the sample, and the rest - men (48%). Inclusion criteria for survey participants outlined that all those who participated in the focus groups were either professional athletes with disabilities or engaged in APA on their own or in inclusion groups at a university. There were also persons with disabilities - random participants. The questions were provided in a Microsoft forms document, which allowed participants to submit responses in advance to the focus group, which was considered particularly useful for individuals with speech impairments.

The empirical basis of this sociological research and effective data collection was provided with the help of a developed questionnaire with 20 questions regarding the use of APA in social work and the level of social inclusion of respondents. All questionnaire questions were grouped into 2 blocks. The first block concerned personal data - gender, age, term, frequency, and form of classes. The second block -- the state and changes of social contacts, the impact of classes on the level of social activity, and the implementation of social inclusion in the APA process.

RESULTS

The obtained data indicate that the majority of respondents in our analyzed sample are focused on the 2nd year of studies, which corresponds to 49%. The smallest, namely 10.8%, is the first. In general, respondents usually choose 2 classes every week (38 respondents chose this option, which is 40.4% of the choice). The second most preferred option is 3 classes every week (34% of choices). The second option to decrease by preference means 4 classes every week (22.3% of choices). The least good option among respondents included in the data set is only 1 class per week (3.2% of choices).

Most of the respondents of the studied sample who noticed an increase in their social contacts during APA classes, as a rule, have 2 classes every week (42.9%). The majority of respondents who note the stability of social contacts have 3 classes every week (43.9%). Most of the respondents who did not notice any changes in their results also have 2 classes every week (59.4%).

An important question is why exactly APA classes are preferred. The vast majority of respondents (63.6) gave

preference to social communication not in the first year of classes. However, in the future, a tendency for a slight decrease is observed, which is a decrease in the importance of this aspect in classes compared to the beginning of classes, as a result of meeting the need. Regardless of the duration of the classes, in the question of improving the state of social life, the answers «Yes» and «To some extent» have a significant advantage over the answer «No».

Gender and year of study are categorical variables, so we use the cross-tabulation method to analyze the relationship between them (Table 1). There is a relationship between gender and year of study, but it is weak and minimally acceptable (Cramer's V and Phi = 0.176). From further cross-tabulation, we can see that 45.3% of women (most of them) are doing APA for the second year in a row, and 53.1% of men (most of them) are also doing APA for the second year in a row. That is, the majority of the studied sample consists of persons with disabilities in the second year of systematic APA classes (49%). In addition, it can be added that 9.4% of women (at least) do APA in the first year, and 12.2% of men (at least) also do APA in the first year. That is, the smallest part of the sample consists of persons with disabilities in the first year of systematic APA classes (10.8%).

The frequency of training and year of training are categorical variables, so we used the cross-tabulation method to analyze the relationship between them (Table 2). The relationship between frequency and year of classes is moderately strong (Cramer's V = 0.254).

The average time spent by respondents included in the data set in APA classes per week was 6.66 hours at the time of the survey (Table 3, 4; Fig. 1.). The time respondents spend in APA classes differs from this number by an average of

Table 1. What is your gender? How many years have you been doing APA?

Cross Tabulation					
			Term of study (year)?		
			1	4	2
What is your gender?	f	Count	5	5	24
		% within What is your gender?	9,4%	9,4%	45,3%
		% within the term of classes?	45,5%	41,7%	48,0%
	m	Count	6	7	26
		% within What is your gender?	12,2%	14,3%	53,1%
		% within the term of classes?	54,5%	58,3%	52,0%
Total		Count	11	12	50
		% within What is your gender?	10,8%	11,8%	49,0%
		% within the term of classes?	100,0%	100,0%	100,0%

Cross Tabulation				
			Term of study (year)?	Total
			3	
What is your gender?	f	Count	19	53
		% within What is your gender?	35,8%	100,0%
		% within the term of classes?	65,5%	52,0%
	m	Count	10	49
		% within What is your gender?	20,4%	100,0%
		% within the term of classes?	34,5%	48,0%
Total		Count	29	102
		% within What is your gender?	28,4%	100,0%
		% within the term of classes?	100,0%	100,0%

** f – women, m – men*

Table 2. Analysis of symmetry

		Value	Approximate Significance
Nominal by Nominal	Phi	,440	,072
	Cramer's V	,254	,072
N of Valid Cases			

**Phi – numeric φ, Cramer's V – Cramer's coefficient*

Table 3. How many classes per week do you do APA? (statistical analysis)

N	Valid	102
	Missing	0
Mean		6,66
Median		7,00
Mode		8
Std. Deviation		3,039
Variance		9,238
Skewness		,196
Std. Error of Skewness		,239
Kurtosis		-,564
Std. Error of Kurtosis		,474
Minimum		1
Maximum		15
Percentiles	25	4,00
	50	7,00
	75	9,00

Table 4. Analysis of symmetry

		Value	Approximate Significance
Nominal by Nominal	Phi	,176	,370
	Cramer's V	,176	,370
N of Valid Cases		102	

**Phi – numeric φ, Cramer's V – Cramer's coefficient*

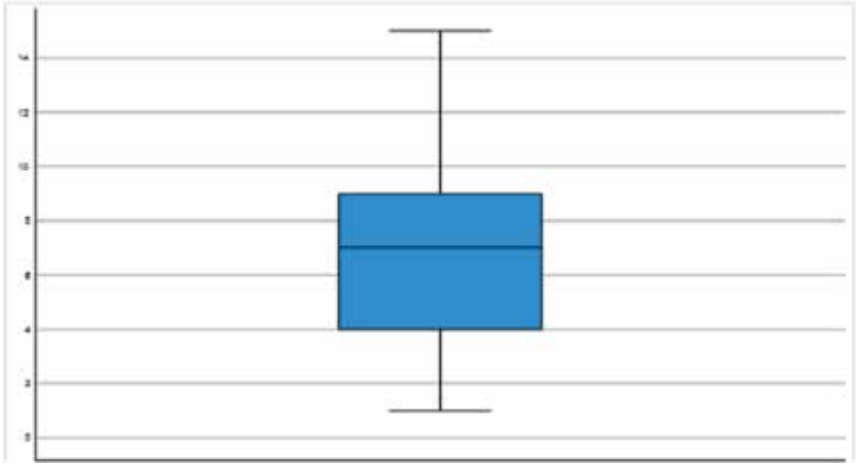


Fig. 1. Boxplot: How much time a week do you do APA?

~3.04 hours. The time spent on APA lessons per week in half of the sample does not exceed 7 hours. 25% of the studied sample spend 9 hours or more in APA classes. The greatest time of APA classes per week among the respondents of the studied sample is 15 hours. The shortest time in the data set is 1 hour. The distribution of time spent on APA classes during the week is positively asymmetric. The distribution of the variable is normal.

The state of social inclusion and the number of classes per week are numeric variables. Therefore, we also use the correlation method to analyze the relationship between them (Table 4). Social inheritance status is a normally distributed variable (skewness = 0.156 and kurtosis = -0.978) that has only a slight deviation from belonging to the range <-1;1>, which is considered the standard of similarity to a normally distributed variable (skewness = -0.269 and

Table 5. Correlations

		How has your social communication changed?	Number of AFA classes
How has your social communication changed?	Pearson Correlation	1	-,480*
	Sig. (2-tailed)		<,001
	N	102	94
Number of AFA classes	Pearson Correlation	-,480*	1
	Sig. (2-tailed)	<,001	
	N	94	94

*Correlation is significant at the 0.01 level (2-tailed).

kurtosis = -1.065). A ratio scale is used to measure both variables. Thus, Pearson's correlation coefficient R will be interpreted as follows: according to our analysis, there is a moderate negative linear relationship between the variables (r = -0.480) (Table 5). Therefore, a decrease in the number of classes will lead to a moderate decrease in the state of social bribery and vice versa.

DISCUSSION

Note that this study aimed to investigate the possibility of social work in the implementation of social inclusion of persons with disabilities using APA tools. According to the processed results, the respondents agree with the thesis about improving the quality of social communication with the help of APA. At the same time, such factors as increasing the circle of acquaintances, communication, and support of others were singled out. Respondents note that APA classes have a positive effect on self-esteem, self-realization, gaining the meaning of life along with improving physical condition. Respondents associate APA classes with improved physical condition, enrichment of motor experience, and increased competence in the field of individual APA strategy.

It is indisputable that some elimination of health disorders due to APA classes directly affect the quality of life of persons with disabilities, promoting mutual assistance. Due to the improvement of their physical condition, and, therefore, somatic health, there is an improvement in well-being, which to a certain extent eliminates their physical limitations.

Among other positive points, respondents note an increase in social activity through participation in mass sports and recreational events, which is, accordingly, a factor in their self-affirmation, a sense of involvement in social life, which is manifested in their relationships, attitude to their place in society, an increase in social activity, acquiring social and personal contacts. This is the result of social inclusion by APA tools. The respondent reported an increase in their social participation through games, especially through the interpersonal relationships that arise in the process of gaming activities.

Regardless of the number of classes per week of APA, the answers regarding the improvement of the state of social communication «Yes» and «I did not pay attention to the relationship of these factors» have a significant advantage over the answer «No». Among those respondents who preferred the «other answer» option, the answer «I did not pay attention to the ratio of these factors» prevails, namely: 47.6% and 62.5%, respectively.

Respondents noted that social integration in the APA process is very important for developing friendships, particularly in social networks, gaining a sense of acceptance and belonging, and for opportunities to participate in the community on the need to create a supportive, non-discriminatory environment for everyone.

Without exception, all respondents expressed their interest and desire to be socially involved in APA. However, it is necessary to state the negative aspects of APA. Among these, we highlight stress, injuries, underdeveloped sports infrastructure, and lack of social support to meet their needs, which limits the participation of persons with disabilities in APA. Certain APA activities may not be accessible to individuals with disabilities because they exceed their current level of physical and social skills. However, it was found that respondents are more optimistic about possible negative consequences of APA than its complete absence.

Particular attention is paid to the results, which allow the way of social work activation to influence the level of social inclusion of persons with disabilities using APA tools. It is about leisure in the context of APA. It is recreational activities as the realization of active leisure time that should be used to establish social bonds through common interests in this aspect of APA.

Our research is based on the ideas [5, 11] that social work in the field of health is currently directed at the implementation of one of the most important goals of social policy - increasing the level of social inclusion through APA. The systematic and continuous implementation of APA is positioned as an effective way to ensure social inclusion [13].

The conducted research is consistent with scientific information [1, 7, 12] that social work in the use of APA opportunities in the process of social inclusion of persons with disabilities involves: the elimination of isolation of any categories of the population, using the potential of the existing strong connection of their physical and social, intellectual, spiritual development, and thus – the possibilities of this process in ensuring full-fledged current and future life activities of persons with disabilities, whose number in Ukraine is growing daily.

Therefore, taking into account the continuation of hostilities on the territory of Ukraine, there is an urgent need for the formation and application of qualitatively new tools of social work in the field of preserving the health of persons with disabilities. We support scientific approaches [9, 10, 14] that the construction of an inclusive model of APA requires in the process of social work effective communications with persons with disabilities, the study of motivational techniques, targeted educational and informational work to form ideas about a healthy lifestyle and highlight international and domestic experience and achievements for the development of the need for physical self-improvement in persons with disabilities, and, therefore, APA classes. At the same time, social work in the field of health, as evidenced by scientific data [15, 16], requires the identification of the most important social factors that have a negative impact on the health of persons with disabilities.

The Ministry of Veterans Affairs of Ukraine in partnership with the United Nations Development Program (UNDP) in Ukraine within the framework of the «EU4Recovery - Community Empowerment in Ukraine» (EU4Recovery) project, with the financial support of the European Union, will begin in July 2023 the training of specialists in intensive educational program «Theory and practice of training specialists for accompanying war veterans and demobilized persons». The results of the implementation of this program will be the creation of a work program for training social workers to work in communities as assistants to veterans. A significant part of the activity of a social worker in helping veterans return to civilian life is related to social inclusion and an important and integral element of it is social rehabilitation using APA tools.

CONCLUSIONS

Social work in the field of health, as a system of measures aimed at ensuring the preservation and development of optimal working capacity and social activity of persons with disabilities and the promotion of a healthy lifestyle, was formed into a self-sufficient system in the context of human resources management. Currently, the state social policy, Ukraine's course towards European integration, regulatory and legal changes - all this should be directed to the formation of a new philosophy in Ukrainian society regarding the social inclusion of persons with disabilities against the background of the spread of ideas of non-discrimination and equality of rights and opportunities in the public consciousness.

The need for social work with persons with disabilities will only grow in the future, given the duration of hostilities on the territory of Ukraine. Since many defenders return from war with injuries, there is a need to solve social problems on a qualitatively new level. Full-scale aggression by Russia destroyed the normal course of social life in Ukraine and led to the urgent need to activate institutions of social work in the field of health to implement the social inclusion of persons with disabilities, to give them the opportunity to develop their competencies, destroying all possible social barriers, to ensure equal opportunities for all conditions, in order to eliminate any feeling of limitation in rights and opportunities. This is the main task of social work in the field of health, both science and practical activity.

Empirically researched the possibilities of implementing social inclusion with APA tools. Implementation of social work in overcoming the social isolation of persons with disabilities by involving them in systematic APA classes has been established. Separate results indicate that APA in their life activities fully ensures overcoming social exclusion, social isolation and provides an opportunity to interact in society as actively as possible.

It was established that APA, including participation in sports competitions, recreational and mass physical education events, contributes to the social adaptation of persons with disabilities, increasing social activity aimed at establishing social ties and contacts, which will lead to an increase in the social significance of APA, and therefore to the formation of the desire for achievements and self-realization, productive life activities, and as a result to the social inclusion of persons with disabilities.

In Ukraine, the formation of professional inclusive competence in the field of APA is currently on the list of the most important areas of social work with persons with disabilities. Numerous expectations in the development of the comprehensive rehabilitation system, particularly of war veterans, prospects for ensuring conditions for comprehensive development of persons with disabilities are connected with this phenomenon. Despite the difficult conditions when the war continues in our country, the implementation of innovative and research-experimental activities in the field of social work in the field of health and the implementation of research results in practice, the combination of theoretical and practical, will undoubtedly contribute to the achievement of the defined standards of social inclusion. Thus, social work in the field of health is an imperative of the times, and Ukrainian society in the course of its next transformation will long feel the acute need for qualified specialists for its widespread, skillful, and effective implementation.

REFERENCES

1. Gehlert S, Browne T. Handbook of Health Social Work (2nd ed.). New Jersey: John Wiley & Sons. 2012, p.769.
2. Spitzer WJ, Davidson KW. Future Trends in Health and Health Care: Implications for Social Work Practice in an Aging Society. Social Work in Health Care. 2013;11:959-986. doi: 10.1080/00981389.2013.834028.
3. United Nations. Office of the High Commissioner for Human Rights (2023). Ukraine: Civilian casualties – 24 February 2022 to 30 June 2023. 07 July 2023. https://www.ohchr.org/en/news/2023/07/ukraine-civilian-casualties-24-february-2022-30-june-2023.

4. Shakespeare T. The social model of disability. London and New York: Routledge. 2006.
5. Skeketee G, Ross AM, Wachman MK. Health outcomes and costs of social work services: A systematic review'. American Journal of Public Health. 2017;107(S3):S256-S266.
6. Merrells J, Buchanan A, Waters R. The experience of social inclusion for people with intellectual disability within community recreational programs: A systematic review. Journal of Intellectual & Developmental Disability. 2018;43(4):381-391. doi: 10.3109/13668250.2017.1283684.
7. Valles M. Técnicas cualitativas de investigación social: Reflexión metodológica y práctica profesional. Madrid: Editorial Síntesis. 2003.
8. Grenier M. Inclusion in Physical Education: From the Medical Model to Social Constructionism. Quest. 2007;59(3):298-310. doi: 10.1080/00336297.2007.10483554.
9. Place K, Hodge SR. Social Inclusion of Students with Physical Disabilities in General Physical Education: A Behavioural Analysis. Adapted Physical Activity Quarterly. 2001;18:389-404.
10. Monforte J, Davis C, Saleem S, Smith B. Moving on From the Delphi Study: The Development of a Physical Activity Training Programme Prototype Through Co-produced Qualitative Research. Qualitative Health Research. 2022;32(13):1952-1964. doi:10.1177/10497323221126535.
11. Williams DJ, William BS. Physical Activity Promotion in Social Work. Social Work. 2006;51(2):180-184.
12. Vislie L. From integration to inclusion: Focusing global trends and changes in the western European societies. European Journal of Special Needs Education. 2010;18(1);17-35. doi:10.1080/088562082000042294.
13. Kiefer M. Disability sport: Integration and inclusion. SCI-Sports Conflict Institute. 2019. https://sportsconflict.org/disability-sport-integration-inclusion/
14. Klos L, Shkoliar M, Stavkova S, et al. Ethics of professional activities of social workers in the field of health: the american experience. Wiad Lek. 2022;75(8pt1):1888-1894. doi: 10.36740/WLek202208112.
15. Klos L, Shkoliar M, Stavkova S, Kokhanova O. Social workers' activities in the field of population' mental health preservation in the XXI century. Wiad Lek. 2021; 74(11cz1): 2823-2828. doi: 10.36740/WLek202111125.
16. Klos L, Nazar N. Integrated social services based on preservation and promotion of community health: an analysis of the state and prospects of development. Mental Health Global Challenges Journal. 2019; 2 (3): 59-69. doi:10.32437/MHGCJ.

The work is a fragment of the research project «Research Initiatives and Practical Implementation of Social and Political Projects to Resolve Social Problems of Modern Ukraine», state registration No. 0118U000886.

ORCID AND CONTRIBUTIONSHIP
Liliia Y. Klos: 0000-0001-9972-7450[A, B,D,E]
Oksana Z. Blavt: 0000-0001-5526-9339[A,B,D,E]
Oksana Y. Makukh: 0000-0001-6461-4448[E, F]
Oleksand P. Kovalchuk: 0000-0002-4571-482X[B,D,F]
Matthias Zimlich: 0009-0005-9565-836X[B,D,F]
Uliana V. Yatsyshyn: 0000-0003-0541-1880[C]

ADDRESS FOR CORRESPONDENCE
Liliia Y. Klos
Lviv Polytechnic National University, Lviv, Ukraine
12 Bandera St., 79013 Lviv Ukraine
e-mail: viktorvus@ukr.net

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 02.07.2023
ACCEPTED: 20.09.2023

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 511-520

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305110

PREVALENCE OF BODY DYSMORPHIC DISORDER AMONG ATTENDANCES SEEKING FACIAL COSMETIC PROCEDURES IN BAGHDAD

Fahem Alwan Bahlol[1], Mushtaq Talip Hashim[2], Maysaa Ali Abdul Khaleq[3], Ahmed Abed Marzook[4]

[1]DEPARTMENT OF PSYCHIATRY, COLLEGE OF MEDICINE, BAALAD HOSPITAL, SALAHADDIN, IRAQ
[2]DEPARTMENT OF PSYCHIATRY, COLLEGE OF MEDICINE, BAGHDAD UNIVERSITY, BAGHDAD, IRAQ
[3]DEPARTMENT OF PHARMACY, AL-MAARIF UNIVERSITY COLLEGE, AL-ANBAR, IRAQ
[4]DEPARTMENT OF DENTISTRY, DIJLAH UNIVERSITY COLLEGE, BAGHDAD, IRAQ

ABSTRACT

Aim: To find out the prevalence of body dysmorphic disorder among patients seeking facial cosmetic procedures, find out association of social demographic (age, gender, occupation, marital status, friends relationship, and dating status) ampatientsient with body dysmorphic disorder.

Materials and Methods: A cross-sectional study was done on a sample of 100 patients from Al-waste Hospital and Ghazy Al-Hariri Hospital for surgical specialties in Baghdad by using a body dysmorphic disorder questionnaire to diagnose a probable case and then a semi-structured questionnaire based on DSM5 criteria to diagnose body dysmorphic disorder during the period extended from beginning of January 2019 to the end of April 2019.

Results: The chi-square test proved the association between female gender and body dysmorphic disorder is significant P=0.026. Significant associations were also noticed between single patients and body dysmorphic disorder 76.8% in comparison with married 37.8, and divorced or widowed 42.9% (P=0.001). It was found that 68.6% of unemployed patients think that they need to correct their body dysmorphic disorder so they attended the hospital while only 40% of employed persons did so P=0.008. The mean age of patients exposed to a second operation was significantly higher than the mean age of other patients P=0.022.

Conclusions: High prevalence of body dysmorphic disorder among patients seeking plastic surgery which is about 60%. Body dysmorphic disorder is more common among single and unemployment and among young adults and gender female. There is no significant association between the mean age of male and female patients of body dysmorphic disorder group.

KEY WORDS: body dysmorphic, facial cosmetic, iraqi patients

INTRODUCTION

Body dysmorphic disorder (BDD) is a DSM5 diagnosis involving distress due to perceived physical anomaly, such as a scar, the shape or size of a body part, or some other personal feature. Individuals with BDD are highly distressed due to defects they perceive in their physical appearance that are not noticeable to others [1]. They have a pervasive feeling of ugliness and are convinced that some part of their body is defective [2]. The most frequent areas of concern are the face and head, and the main worries are related to problems such as acne, wrinkles, scars, the size and shape of the nose or ears, asymmetric or disproportional face, thinning hair, or excessive facial hair. However, there may be a concern regarding any part of the body or with more than one part of the body [3]. Individuals with BDD engage in excessive grooming, skin picking, mirror checking, and camouflaging of their appearance, with the aim of correcting, hiding, or distracting others from perceived defective parts of the body. Focusing on unattractive parts of the body, rumination, mental rituals, or other mental acts are also often reported by individuals with BDD [4]. These preoccupations are very time-consuming and occur, on average, 3-8 hours per day and they are typically difficult to resist or control [5]. BDD is associated with significant distress, disability, unnecessary cosmetic surgery, and suicidal behavior [6]. BDD seems to be a relatively common psychiatric disorder, affecting about 1-2% of the general population. However, BDD is still under-recognized as well as under-studied [7].

HISTORICAL AND CULTURAL PERSPECTIVES OF BODY DYSMORPHIC DISORDER

Body dysmorphic disorder has been described in the literature for over a century. The condition was initially identified by the Italian psychiatrist Enrique Morselli in 1891 and termed dysmorphophobia to describe worries and complaints about an imagined deformity. Dysmorphic is Greek and means 'bad shape' or 'bad body'. Body dysmorphic disorder has also been known as dermatologic non-disease, dermatologic hypochondriasis, beauty hypochondria, and dermatophobia [8]. Ancient Egypt is the earliest historical

period that fully developed the use of cosmetics. A ceremonial palette dating to 3100 BC was used for grinding and mixing cosmetics. It is considered to be the first archaeological finding of Egyptian cosmetics. As for cosmetic equipment, they were so important to the ancient Egyptians, there were carried forth to the afterlife as they were essential parts of their funerary equipment, among this equipment are many toilet accessories: eyeliner applicators, and mirrors [9].

BDD IN THE DIAGNOSTIC AND STATISTICAL MANUAL FOR MENTAL DISORDERS

The Diagnostic and Statistical Manual for Mental Disorders (DSM), published by the American Psychiatric Association, is the most widely accepted nomenclature used by clinicians and researchers for the classification of mental disorders. The DSM is intended to be used in all clinical settings as well as a manual for research in clinical and community settings. Dysmorphophobia was first described in the third edition of the DSM [9] as an example of an 'atypical somatoform disorder' without any diagnostic criteria. Body dysmorphic disorder appeared as a separate disorder in the DSM, 3rd edition, revised [10]. The 'clinical significance criterion', i.e., that the physical appearance preoccupation must be associated with clinically significant distress and/or functional impairment in order to be regarded as a psychiatric disorder, was added in the DSM, 4thedition [11] and the criteria for Body dysmorphic disorder remained unchanged in the DSM, 4thedition, text revision [12, 13]. The latest edition of the DSM has assigned the diagnosis of body dysmorphic disorder, including its delusional form, to a new section of obsessive-compulsive and related disorders. A new criterion was added in the DSM-5, which states that at some point during the course of body dysmorphic disorder, the individual should have performed repetitive behaviors (e.g., mirror checking, excessive grooming, and skin picking) or mental acts (e.g., comparing her or his appearance with that of others) in response to the appearance concerns [1, 14].

ETIOLOGY AND SOCIOCULTURAL CONTEXT

The etiology of body dysmorphic disorder is largely unknown, but research suggests that it is multifactorial, including biological, psychological, and sociocultural factors. Hypothesized risk factors include genetic factors, temperament, childhood adversity such as teasing or bullying, increased aesthetic sensitivity, and a history of dermatological or other physical stigmata [15]. Neurobiological factors in body dysmorphic disorder are not well-established, but there may be abnormal processing of facial and bodily images, and some studies have indicated defects in frontostriatal and temporaparietal regions of the brain. Physical symmetry has been associated with perceived attractiveness and also possibly with physical health across different species, including humans [16]. Therefore, a preference for symmetry may even be a selective adaptation and, thus may have an evolutionary basis. Americans have been reported to place greater value on physical attractiveness than the Japanese and Germans [17]. In a study comparing American and German students, body image concerns and preoccupation with physical appearance were found to be significantly greater in Americans, although the prevalence of self-reported body dysmorphic disorder was similar in the two groups [18]. The anxiety disorder taijin kyofusho in Japan refers to people that are perfectionistic and extremely self-conscious and are concerned about matters such as blushing, or body odor [19]. One subtype of the disorder is defined as the phobia of a deformed body. This self-preoccupation seems to be similar to that in social anxiety disorder (SAD) or indeed body dysmorphic disorder, but individuals with taijin kyofusho are concerned about offending others instead of experiencing anxiousness about being scrutinized by others, as typically seen in Western cultures [14]. Snapchat Dysmorphic is part of Body Dysmorphic, but people often get plastic surgery in order to look like their Snap chat filter. According to the Women's Health Magazine, the 2017 Annual American Academy of Facial Plastic and Reconstructive Surgery Survey, conducted that 55 percent of plastic surgeons reported patients getting surgery done for their selfies. Snapchat filters are bringing new beauty fantasies to reality [15]. WebMD argued that in recent reports, the majority of surgeons saw a major shift in cosmetic or injectable surgery for patients under 30 years old. The doctors also noted that these applications are making up unrealistic expectations of beauty. Plastic surgery isn't the solution for people who suffer from Body Dysmorphic. Patients should seek psychological help and cognitive behavioral therapy [20].

BODY IMAGE DISTURBANCE

Body image can be defined as the mental representation of the body and its organs, or to put it in other words, "the picture we have in our minds of the size, shape, and form of our bodies; and to our feelings concerning these characteristics and our constituent body parts" [20]. Body image, thus, has two components, a perceptual component (how we view our bodies) and an attitudinal component (how we evaluate our bodies). Body image develops early in life as the caregivers touch, caress, and hold the infant, and body image development is of basic importance for self-development [21]. During normal development, the awareness of one´s own body and the perception of others' responses to it are incorporated into one´s self-awareness [22]. Although body image is a complex and multifaceted construct, including perceptual, affective, cognitive, and possibly behavioral aspects of body experience, in Western society the major focus regarding body image has been on the body's appearance, in particular on body shape and weight [23]. Negative body image is common in both men and women and has adverse consequences for individual functioning, including greater psychological stress. Sociocultural factors, such as exposure to media images portraying thin ideals, have been found to contribute to negative perceptions of one's body [24]. Selective attention is an important factor in the maintenance of several emotional disorders, e.g. in patients with panic disorder, who have an increased perception of bodily sensations and have been found able to more accurately estimate their heart rate than controls [25]. Regarding the attitudinal component of body image, body dysmorphic disorder patients may

have a desire for perfection or symmetry in their physical appearance. In one study evaluating physical attractiveness perception using facial photos, body dysmorphic disorder patients n=19 followed similar normative ratings of the attractiveness of others (i.e., rating photos of others as attractive, average, or unattractive) as healthy controls [26]. However, body dysmorphic disorder patients rated their own attractiveness significantly lower than independent evaluators did and they rated photos in the "attractive" group higher than healthy controls did. In the study by Buhlmann et al., [23], body dysmorphic disorder patients also displayed higher levels of perfectionism than healthy controls. High levels of perfectionism have also been found in other disorders, such as depression, eating disorders, and social anxiety disorder, supporting an association between perfectionism and psychopathology [26]. In addition, individuals with body dysmorphic disorder are believed to have an exaggerated sense of the importance of attractiveness to others which contributes to self-esteem that is excessively dependent on physical appearance. Body dysmorphic disorder patients tend to misinterpret imperfections they perceive in their appearance as major flaws in self-worth [27].

ASSESSMENT OF BODY DYSMORPHIC DISORDER

A face-to-face diagnostic interview using the DSM is the gold standard for diagnosing body dysmorphic disorder [3]. The Structured Clinical Interview (SCID) is a semi-structured diagnostic interview intended to be used by clinicians and is considered a state-of-the-art clinical research interview. Body dysmorphic disorder was first introduced in the body dysmorphic disorder for DSM-IV in 2002 [28]. The Body Dysmorphic Disorder Diagnostic Module (BDD Diagnostic Module) is a clinical interview based on the DSM-IV criteria using the body dysmorphic disorder format, which was used as the gold standard for diagnosing body dysmorphic disorder in research settings before body dysmorphic disorder was included in the SCID. In this thesis, semi-structured clinical interviews refer to the diagnosis of body dysmorphic disorder by a clinician using the DSM criteria (including the use of the body dysmorphic disorder and the Body Dysmorphic Disorder Diagnostic Module). The Mini-International Neuropsychiatric Interview-Plus (M.I.N.I.-Plus) is a brief, fully structured diagnostic interview for DSM-IV, which can be used by non-specialized interviewers [29]. The M.I.N.I. has shown good concordance with body dysmorphic disorder for several diagnoses, but the validity properties of the M.I.N.I.-Plus regarding the body dysmorphic disorder diagnoses are not known [30].

DIAGNOSTIC CRITERIA OF BODY DYSMORPHIC DISORDER ACCORDING TO DSM5

Preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others. At some point during the course of the disorder, the individual has performed repetitive behaviors (mirror checking, excessive grooming, skin picking, reassurance seeking) or mental acts (e.g., comparing his or her appearance with that of others) in response to the appearance concerns. The preoccupation causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The appearance preoccupation is not better explained by concern with the body fat or weight in an individual whose symptoms meet the diagnostic criteria for an eating disorder [1], specify if:

- With muscle dysmorphic. The individual is preoccupied with the idea that his or her body build is too small or insufficiently muscular. This specifier is used even if the individual is preoccupied with other body areas, which is often the case. Indicate the degree of insight regarding body dysmorphic disorder beliefs (e.g., I look ugly or I look deformed) [1].
- With good or fair insight. The individual recognizes that the body dysmorphic disorder beliefs are definitely or probably not true or that may or may not be true [1].
- With poor insight. The individual thinks that body dysmorphic disorder beliefs are probably true [1].
- With absent insight/delusional beliefs. The individual is completely convinced that the body dysmorphic disorder beliefs are true [1]. Estimates of prevalence and gender distribution have varied widely via discrepancies in diagnosis and reporting [13].

SIGNS AND SYMPTOMS

Body dysmorphic disorder occasionally still called dysmorphophobia, is a mental disorder characterized by the obsessive idea that some aspect of one's own body part or appearance is severely flawed and therefore warrants exceptional measures to hide or fix one's dysmorphic part on one's figure [13]. In body dysmorphic disorder's delusional variant, the flaw is imagined. If the flaw is actual, its importance is severely exaggerated [31]. Either way, thoughts about dysmorphic are pervasive and intrusive and may occupy several hours a day. The DSM-5 categorizes body dysmorphic disorder in the obsessive-compulsive spectrum and distinguishes it from anorexia nervosa. Body dysmorphic disorder is estimated to affect up to 2.4% of the population [31]. It usually starts during adolescence and affects both men and women [2]. The body dysmorphic disorder subtype of muscle dysmorphic, perceiving the body as too small, affects mostly males [3]. Besides thinking about it, one repetitively checks and compares the perceived flaw, and can adopt unusual routines to avoid social contact that exposes it. Fearing the stigma of vanity, one usually hides the preoccupation. Commonly unsuspected even by psychiatrists, body dysmorphic disorder has been underdiagnosed. Severely impairing quality of life via educational and occupational dysfunction and social isolation, body dysmorphic disorder has high rates of suicidal thoughts and suicide attempts because patients with body dysmorphic disorder are often highly distressed, feel unacceptable to themselves and others, are often highly depressed and socially isolated, and have other risk factors for suicidal thinking and behavior. Whereas vanity involves a quest to aggrandize appearance, body dysmorphic disorder is experienced as a quest to merely normalize appearance [31]. Although delusional in about one of three cases, the appearance concern is usually non-delusional, an overvalued

idea [2]. The bodily area of focus can be nearly any, yet is commonly the face, hair, stomach, thighs, or hips. Some half-dozen areas can be a roughly simultaneous focus. Many seek dermatological treatment or cosmetic surgery, which typically does not resolve the distress. On the other hand, attempts at self-treatment, such as by skin picking, can create lesions where none previously existed [31]. Body dysmorphic disorder shares feature with obsessive-compulsive disorder [32], but involves more depression and social avoidance [13]. Body dysmorphic disorder often associates with social anxiety disorder. Some experience delusions that others are covertly pointing out their flaws [32]. Cognitive testing and neuroimaging suggest both a bias toward detailed visual analysis and a tendency toward emotional hyper-arousal. Most generally, one experiencing body dysmorphic disorder ruminates over the perceived bodily defect several hours daily or longer, uses either social avoidance or camouflaging with cosmetics or apparel, repetitively checks the appearance, compares it to that of other people, and might often seek verbal reassurances [13, 31]. Body dysmorphic disorder's severity can wax and wane, and flare-ups tend to yield absences from school, work, or socializing, sometimes leading to protracted social isolation, with some becoming housebound for extended periods [31]. Poor concentration and motivation impair academic and occupational performance. The distress of body dysmorphic disorder tends to exceed that of either major depressive disorder or type-2 diabetes, and rates of suicidal ideation and attempts are especially high [32].

LIVING WITH BODY DYSMORPHIC DISORDER

Body dysmorphic disorder patients have reported low health-related quality of life, including decreased general mental health, enjoyment, social adjustment, and social functioning. Silver et al., [33] interviewed 11 individuals with body dysmorphic disorder and used photographs combined with narrative analysis to assess the manner in which people with body dysmorphic disorder perceive their own appearance. The most common theme identified by these authors was an exaggerated perception of threat because body dysmorphic disorder patients feared other people's judgments and this resulted in disordered interpersonal relationships. Other themes found were a wish for regularity and symmetry in physical appearance, idealization of the childhood self, the duty to look good, and a focus on specific details rather than on ugliness. In a recent study exploring mirror-gazing in ten individuals with BDD, the participants described mirrors as being controlling and imprisoning, with crippling and paralyzing effects on life [33].

EFFECTIVE TREATMENT

As mentioned above, appearance-enhancing treatments, such as various dermatological treatments or cosmetic surgery, usually do not result in any decrease in body dysmorphic disorder symptom severity. Treatment needs to target the underlying psychiatric pathology and involves psychological and/or pharmacological interventions. Without effective treatment body dysmorphic disorder is usually chronic with a low probability of remission [30, 34].

AIM

The aim of the study is to find out the prevalence of body dysmorphic disorder among patients seeking facial cosmetic procedures and find out the association of social demographic (age, gender, occupation, marital status, friends' relationship, and dating status) among patients with body dysmorphic disorder.

MATERIALS AND METHODS

This cross-sectional study was conducted in Al-Wasti Hospital for plastic and reconstructive surgeries and Ghazy Al-Hariri Hospital for surgical specialties in Baghdad, where one hundred patient was enrolled in this study consulting these two hospitals. This study extended from January 2019 to the end of April 2019, where the rest of the searcher made direct interviews with each patient to fulfill a pretested constructed questionnaire. The used questionnaire included social demographic data like age, gender, job, marital status, types of procedures, and whether the patients need to repeat the same procedures or do new ones in patients already diagnosed with BDD. The Body Dysmorphic Disorder Questionnaire (BDDQ): The Arabic version of BDDQ was translated and adopted by Al-Shuhayb ZS [35]. The sample was taken randomly for five hours a day twice a week (Monday and Wednesday) and every patient who come to the cosmetic department was included in the sample after inclusion and exclusion criteria were applied to them, the information was recorded in pre-designed data collection sheets by an interview with the patient in a calm, soundproof, isolated place and taken about 10 minutes for each patient.

ETHICAL CONSIDERATIONS

The research proposal was fully discussed and approved by the scientific and ethical committee in the Arab Board for psychiatric disease. The agreement of health authorities in the included hospitals was taken before starting the study. Verbal consent was taken from each included patient after full explanations of the aim of this study and ensuring confidentiality of the collected data which will be anonymous and will not be used just for research purposes.

INCLUSION CRITERIA

1. Patients consulted outpatient plastic surgery seeking facial cosmetic surgery in these two hospitals.
2. Both genders.
3. Age from 18 years and above.
4. Patients who performed cosmetic surgery and came for follow-up.

EXCLUSION CRITERIA

1. Patients consulting for reconstruction surgery.
2. Patients seeking cosmetic surgery for other parts of the body.

STATISTICAL ANALYSIS

The collected data were introduced into Microsoft Excel 2016 and after purification and revisions data were loaded into IBM-SPSS 25 statistical software package was used in statistical analysis. Descriptive statistics were displayed

using tables (mean ± SD, frequency, and percentage) and suitable graphs were used accordingly. Inferential statistics were presented using the Chi-square test to find out the significance of statistical associations between related variables. A p-value less than 0.05 was considered a discrimination point for significance.

RESULTS

The results of this cross-sectional study included one hundred patients who attended AL-Wasity and Ghazy Al-Hariri teaching hospitals seeking for aesthetic facial surgery, the mean age was 28.26±8.48 years (Fig.1).

Table 1 shows that 30% of the studied patients were males, 56% of all patients were single, and 37% were married. Regarding occupational status: 30% of patients were employed.

Sixty percent of studied subjects were diagnosed as a probable case of body dysmorphic disorder and considered by the researcher as body dysmorphic disorder cases according to DSM5 criteria, while the remaining 40% were considered without body dysmorphic disorder for the purpose of statistical analysis (Fig. 2).

In structure of interventions rhinoplasty operation sits at the top of the first operation 72% followed by blepharoplasty

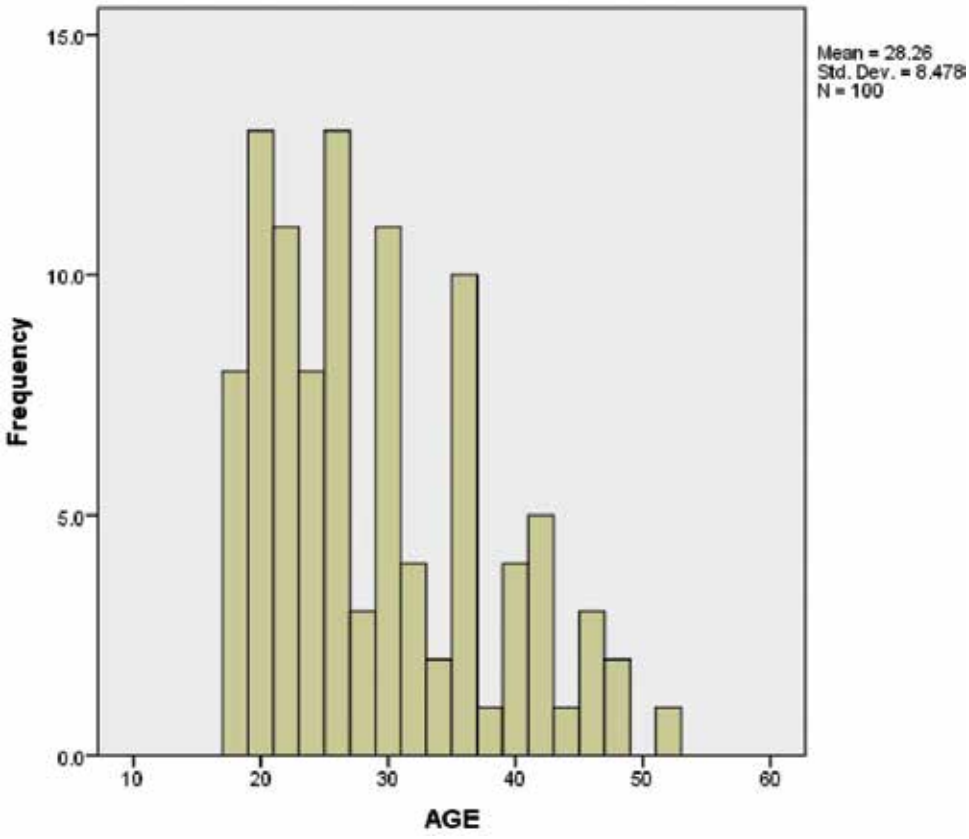


Fig. 1. Age distribution of studied samples.

Table 1. Distribution of patients according to sociodemographic variables

Category		N (abs)	[%]
Age	20-30	65	65
	31-40	21	21
	41-50	10	10
	>50	4	4
Gender	Male	30	30.0
	Female	70	70.0
Social state	Single	56	56.0
	Married	37	37.0
	Other	7	7.0
Occupation	Employed	30	30.0
	Unemployed	70	70.0

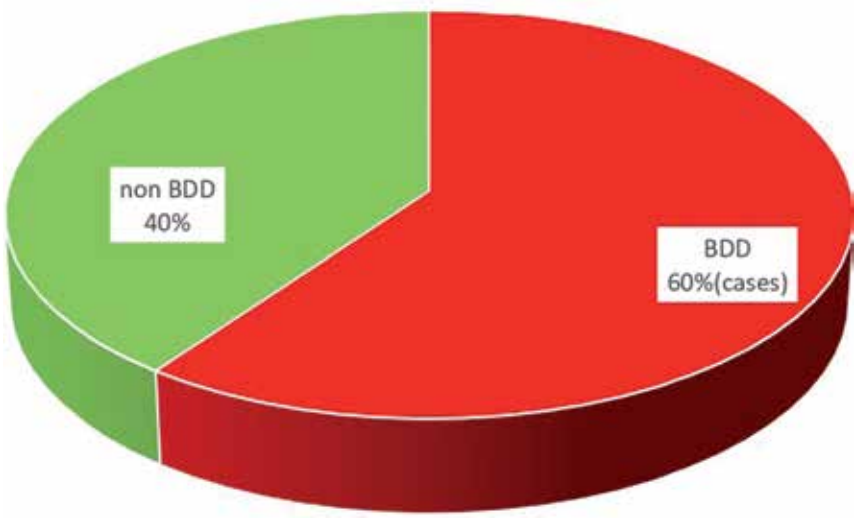


Fig. 2. Distribution of studied patients according presence of BDD.

Table 2. Distribution of studied patients according to the type of first intervention and BDD

Intervention	Total	BDD		Non-BDD		p-value
		N (abs)	[%]	N (abs)	[%]	
Rhinoplasty	72	44	61.1	28.0	38.9	
Blepharoplasty	14	7	50	7	50	
Chin implantation	2	1	50	1	50	
Otoplasty	1	1	100	0	0	
blow lift	2	1	50	1	50	0.695
Botox	3	2	66.7	1.0	33.3	
Mesotherapy	3	2	50	1	50	
Laser	1	1	100	0	0	
Fat injection	2	1	50	1	50	
TOTAL	100	60	60	40	40	

Table 3. Distribution of studied patients according to the type of second intervention

Intervention	N (abs)	[%]
No second intervention	77	77.0
Rhinoplasty	11	11.0
Blepharoplasty	2	2.0
Blow lift	1	1.0
Breast operation	3	3.0
Botox	3	3.0
Mesotherapy	3	3.0
Total	100	100.0

14%, while otoplasty and laser sit at the bottom of the bill 1% for each (Table 2), Chi-square test shows no significant association between type of first intervention and BDD, p-value=0.695.

From chin implantation to fat injection is considered as one group for calculation of the Chi-square test, as shown in table 3, about 22% of patients need a second operation, again rhinoplasty occupied the tip of the bill 11%, while the lowest frequency of second operation was recorded in blepharoplasty and blow lift 1% for each.

Results of research shows that 73.8% of patients belonging to the age group 20-30 years suffered from BDD in comparison with 26.2% of non-BDD in the same age group, while 25% and 75% of patients in the oldest age group got BDD and no BDD respectively (Table 4), Chi-square test shows that younger age patients got more BDD, p-value=0.001.

Table 4. Association between sociodemographic variables and body dysmorphic disorder

Category		BDD		Non-BDD		p-value
		N (60)	%	N (40)	%	
Age	20-30	48	73.8	17	26.2	0.001
	31-40	8	38.1	13	61.9	
	41-50	3	30.0	7	70.0	
	>50	1	25.0	3	75.0	
Gender	Male	13	43.3	17	56.7	0.026
	Female	47	67.1	23	32.9	
Social state	Single	43	76.8	13	23.2	0.001
	Married	14	37.8	23	62.2	
	Other	3	42.9	4	57.1	
Occupation	Employed	12	40.0	18	60.0	0.008
	Unemployed	48	68.6	22	31.4	

Table 5. Association between sociodemographic variables and exposure to the second operation

Category		Yes		No		p-value
		N (100)	Row N [%]	N(100)	Row N [%]	
Age	20-30	8	12.3	57	87.7	0.001
	31-40	7	33.3	14	66.7	
	41-50	5	50.0	5	50	
	>50	3	75.0	1	25	
Gender	Male	3	10.0	27	90.0	0.032
	Female	20	28.6	50	71.4	
Social state	Single	19	33.9	37	66.1	0.006
	Married	2	5.4	35	94.6	
	Other	2	28.6	5	71.4	
Occupation	Employed	4	13.3	26	86.7	0.133
	Unemployed	19	27.1	51	72.9	

About 67.1% of female patients believe that they got body dysmorphic disorder corresponding to 43.3% of male patients, Chi-square test proved the association between female gender and body dysmorphic disorder is significant, p-value=0.026. Significant associations were also noticed between single patients and body dysmorphic disorder 76.8% in comparison with married 37.8, and divorced or widowed 42.9%, p-value=0.001, it was found that 68.6% of unemployed patients think that they need to correct their BDD so they attended the hospital while only 40% of employed people did so p-value=0.008.

The chi-square test shows that the rate of exposure to a second operation among old age patients 75% was significantly higher than young age patients 12.3%, p-value=0.001 (Table 5). The rate of exposure to a second operation among female patients 28.6% was significantly higher than among male patients 10%, p-value=0.032, the rate of exposure to a second operation among single patients 33.9% was significantly higher rate noticed in other marital status groups, p-value=0.006, while no significant association was reported between employment status and seeking for a second operation, p-value=0.133.

DISCUSSION

In the present study, one hundred patients were taken, and the sociodemographic variables were; 70 female (70%), 30 male (30%), the mean age was 28.26±8.48 years, 56% were single, 37% were married, 70% were unemployed and 30% were employed. After applying of body dysmorphic questionnaire, it was found that out of one hundred patients, there was about 60% of patients diagnosed as possible cases of body dysmorphic disorder, and also the same result showed 60% after applying diagnostic criteria of body dysmorphic disorder according to DSM5. In the DSM-III-R and DSM-IV, body dysmorphic disorder was classified as a somatoform disorder, because of the preoccupation with somatic complaints, while its delusional form was classified as a psychotic disorder. Since body dysmorphic disorder has low comorbidity with other somatoform disorders, and instead has presented similarities in symptoms, assessment scores, and treatment approaches with obsessive-compulsive disorder (OCD), researchers have proposed that BDD should be conceptualized as an OCD spectrum disorder [13]. In addition, several studies have indicated that there are many more similarities than differences between individuals with

delusional and non-delusional body dysmorphic disorder, including response to treatment [14]. Studies in different parts of the world that have used semi-structured clinical interviews to assess BDD prevalence have primarily been conducted in psychiatric settings, and have reported BDD prevalence rates of 1.9 to 16% in inpatient samples in Germany, the UK, and the US [7] and 3.2 to 11% in outpatient samples, all in the US. In general settings, a few studies have systematically assessed the occurrence of BDD. Two studies used the SCID to diagnose BDD and found prevalence rates of 6.7% and 8.8% indicating that BDD is common [36]. Body dysmorphic disorder usually develops during early adolescence, although many patients note earlier trauma, abuse, neglect, teasing, or bullying. In many cases, social anxiety earlier in life precedes the development of body dysmorphic disorder. Though twin studies on body dysmorphic disorder are few, one estimated its heritability at 43%. Yet body dysmorphic disorder cause may also involve introversion [15]. Studies using the screening instrument BDDQ-DV found a prevalence of 4.2% in a Turkish sample and about 14% in two US samples. Some studies suggest that BDD may be even more common in cosmetic settings. Studies using semi-structured clinical interviews to diagnose BDD have found prevalence rates ranging between 2.9 and 15% in cosmetic dermatology clinics, and ranging very widely between 6.3 and 53% in cosmetic surgery settings, although the heterogeneity was high and the study quality varied in the latter setting [7]. BDD is more common in females and the number of female patients was higher rate 67.1% in our study this reflected the predominance of the female with body dysmorphic disorder of the total number in our sample, in comparison with other studies at 38-50% [37]. This may have been because the majority of our sample self-referral for doing cosmetic surgery whereas all previous studies have been on the psychiatric population. There has been little research comparing body dysmorphic disorder features across cultures, and the extent to which cultural factors have an impact on the pathogenesis of body dysmorphic disorder is not clear [14]. Community studies of body dysmorphic disorder occurrence have only been carried out in Europe and the US, but studies in cosmetic settings have found the highest prevalence rates in Iran and Brazil [7]. Case reports and case series of body dysmorphic disorder across cultures have shown mostly similarities, including regarding gender ratio, which body areas are disliked, types of compulsive behaviors, and levels of distress and impairment. Nevertheless, cultural differences may influence body dysmorphic disorder symptoms to some degree, for example, eyelid concerns are common in Japan but rare in Western countries [14]. Moreover, which is an expected result because females take more care or pay attention to their faces and are more interested in cosmetic surgery than males. BDD appears to be slightly more common among women, as indicated by a female: male ratio ranging from 1:1 to 3:2 in previous studies [5]. The Body Dysmorphic Disorder Questionnaire (BDDQ) is the most commonly used screening instrument for body dysmorphic disorder across studies [7]; however, prior to the present thesis, it had not been validated in a community setting. The BDDQ dermatology version (BDDQ-DV), a modification of the BDDQ for more continuous scoring, was validated with dermatology patients seeking cosmetic surgical consultation and presented high sensitivity and specificity (100% and 92%; respectively) [38]. The Body Image Disturbance Questionnaire is also modified from the BDDQ for more continuous scoring and the Body Dysmorphic Disorder Examination- Self-Report version (BDDE-SR) is a self-report version of the BDDE clinical interview [39].

All of the population-based studies found slightly higher prevalence rates in women than in men, although the differences were statistically non-significant in most studies. In plastic surgical units, the studies that reported prevalence rates for men and women separately found slightly higher rates in men, although the differences were non-significant. Unemployed patients are considered as most common was 68.6% while 40.0% was for employed patients of our sample. This result may be due to unemployment patients had free time than others exacerbated the preoccupation with a perceived defect in appearance or overemphasis of a slight defect, and might be because the collected sample of our study in government hospitals with low cost in comparison with private hospitals that encouraged them to be made plastic procedure. This study was in accordance with another study in which BDD interferes with functioning and may lead to social isolation, and unemployment, and also was in accordance with another study in which 51.7% of patients with body dysmorphic disorder showed a significant impairment in their academic or job performance because of their symptoms. The mean age for males was 28.33±7.9 and for females was 28.73±8.5. The distribution of age was equal in both males and females because the disease affects the psychological well-being and appearance in the same impact both gender and both need to prepare for marriage and be beautiful in front of others, in addition, maybe the older patient is more likely to develop physical diseases which prevent the patient from doing cosmetic surgery. This study was in accordance with another study which found that there was no statistically significant between males and females patients and distribution of disease is roughly equal between them [37]. According to the results of this study, we see more patients seeking cosmetic surgery have BDD, and from those of BDD patients, about 72% of the patients seek cosmetic clinics for rhinoplastic surgery and 14% for blepharoplasty. After dividing the age of patients with body dysmorphic disorder into groups, we found that there were statistically significant differences between them. It was found that the mean age of body dysmorphic disorder patients was 25.15±6 years the majority. This is because body dysmorphic disorder is more common at this age, as well as people at this age are more interested in cosmetic surgery to be beautiful in front of others or for preparing for marriage. This was in accordance with another study, which found that the common age of onset of the disease is adolescence, and this is associated with increased severity of illness as well as higher levels of co-morbidity with other psychiatric disorders [36]. Our study shows that the number

of previous cosmetic operations of BDD patients is increasing with increasing age, another research found an explanation for such results that after plastic surgery or minimally invasive treatments, some patients switched their preoccupation to another body area. Switching to another body area is not unexpected, because BDD is characterized by distorted body image and tendencies to obsess and excessively worry about nonexistent or minor flaws. Thus, a surface change, such as that accomplished by surgery, is unlikely to treat the underlying disorder [37]. The study also involved the correlation between the history of previous cosmetic operations and marital status and it was found that there is more positive history among single patients than married and this was in accordance with another study that explained such a result as the prevalence of BDD is two times higher in single patients than married and the medical or surgical treatment of them is usually unsatisfactory. Treatments that have been shown to be effective for body dysmorphic disorder are selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT), however, a Cochrane review from 2009 and an updated review from 2016 concluded that there is still a lack of experience and evidence regarding the effective treatment of body dysmorphic disorder, and more research is required to supplement available data [34]. Quantitative studies have demonstrated that body dysmorphic disorder is associated with significant distress and leads to impaired functioning in relationships, socializing, and intimacy as well as to a decreased ability to function at work or in school [3]. In some studies, individuals with body dysmorphic disorder have reported high rates of unemployment and social isolation, and also a high frequency of suicide attempts. Only a few qualitative interview studies have analyzed aspects of body dysmorphic disorder [33]. Another explanation may be because a person after marriage becomes more responsible and cares about his family and has little attention on his appearance from a single in addition to economic causes. In this study, we found that the great negative effects of BDD on friends' status and dating is about 70%, which is similar to findings of another research in a psychiatric setting showed that this might lead to substantial avoidance of everyday activities, social isolation, reduction of quality of life and suicide [36].

CONCLUSIONS

In result of research it was found the high prevalence of body dysmorphic disorder among patients seeking plastic surgery which is about 60%. There is no significant association between the mean age of male and female patients with body dysmorphic disorder. Body dysmorphic disorder is more common among single, unemployed, and females gender and body dysmorphic disorder is more common among young adults.

REFERENCES

1. Conceição Costa DL, Chagas Assunção M, Arzeno Ferrão Y, et al. Body dysmorphic disorder in patients with obsessive-compulsive disorder: prevalence and clinical correlates. Depress Anxiety. 2012;29(11):966-975. doi:10.1002/da.21980.
2. Phillips KA, Kelly MM. Body dysmorphic disorder: clinical overview and relationship to obsessive-compulsive disorder. Focus (Am Psychiatr Publ). 2021;19(4):413-419. doi:10.1176/appi.focus.20210012.
3. Phillips KA, Dufresne RG. Body dysmorphic disorder. A guide for dermatologists and cosmetic surgeons. Am J Clin Dermatol. 2000;1(4):235-243. doi: 10.2165/00128071-200001040-00005.
4. Frías Á, Palma C, Farriols N, et al. Comorbidity between obsessive-compulsive disorder and body dysmorphic disorder: prevalence, explanatory theories, and clinical characterization. Neuropsychiatr Dis Treat. 2015;11:2233-2244. doi:10.2147/NDT.S67636.
5. Wong WW, Rangaprakash D, Moody TD, et al. Dynamic effective connectivity patterns during rapid face stimuli presentation in body dysmorphic disorder. Front Neurosci. 2022; 16:890424. doi:10.3389/fnins.2022.890424.
6. Feusner JD, Kurth F, Luders E, et al. Cytoarchitectonically defined volumes of early Extrastriate visual cortex in unmedicated adults with body dysmorphic disorder [published online ahead of print, 2021 Oct 21]. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021;S2451-9022(21)00283-4. doi:10.1016/j.bpsc.2021.10.008.
7. Chakraborty S, Saetta G, Simon C et al. could brain-computer interface be a new therapeutic approach for body integrity Dysphoria? Front Hum Neurosci. 2021;15:699830. doi:10.3389/fnhum.2021.699830.
8. Shivakumar S, Jafferany M, Sood S, et al. Cosmetic presentations and challenges of body dysmorphic disorder and its collaborative management. J Cutan Aesthet Surg. 2021;14(1):20-25. doi:10.4103/JCAS.JCAS_180_20.
9. Jannini TB, Lorenzo GD, Bianciardi E, et al. Off-label Uses of Selective Serotonin Reuptake Inhibitors (SSRIs). Curr Neuropharmacol. 2022;20(4):693-712. doi: 10.2174/1570159X19666210517150418.
10. Beilharz F, Rossell SL. Treatment modifications and suggestions to address visual abnormalities in body dysmorphic disorder. J Cogn Psychother. 2017;31:272-284. doi:10.1891/0889-8391.31.4.272.
11. Buhlmann U, Glaesmer H, Mewes R, et al. Updates on the prevalence of body dysmorphic disorder: a population-based survey. Psychiatry Res. 2010;178(1):171-175. doi:10.1016/j.psychres.2009.05.002.
12. Deckersbach T, Savage CR, Phillips KA, et al. Characteristics of memory dysfunction in body dysmorphic disorder. J Int Neuropsychol Soc. 2000; 6(6):673-681. doi:10.1017/s1355617700666055.
13. Esteban O, Markiewicz CJ, Blair RW, et al. fMRIPrep: a robust preprocessing pipeline for functional MRI. Nat Methods. 2019; 16(1):111-116. doi: 10.1038/s41592-018-0235-4.
14. Feusner JD, Hembacher E, Moller H et al. Abnormalities of object visual processing in body dysmorphic disorder. Psychol Med. 2011;41(11):2385-2397. doi:10.1017/S0033291711000572.

15. Gauthier B, Eger E, Hesselmann G, et al. Temporal tuning properties along the human ventral visual stream. J Neurosci. 2012; 32(41):14433-14441. doi:10.1523/JNEUROSCI.2467-12.2012.
16. Grace SA, Labuschagne I, Kaplan RA, et al. The neurobiology of body dysmorphic disorder: a systematic review and theoretical model. Neurosci Biobehav Rev. 2017;83:83-96. doi: 10.1016/j.neubiorev.2017.10.003.
17. Jefferies K, Laws KR, Fineberg NA. Superior face recognition in body dysmorphic disorder. J. Obsessive Compuls. Relat. Disord. 2012;1:175-179. doi:10.1016/j.jocrd.2012.03.002.
18. Bohne A, Keuthen NJ, Wilhelm S, et al. Prevalence of symptoms of body dysmorphic disorder and its correlates: a cross-cultural comparison. Psychosomatics. 2002;43(6):486-490. doi:10.1176/appi.psy.43.6.486.
19. Barlow DH. Anxiety and its disorders: The nature and treatment of anxiety and panic. Guilford Press, New York, 2004.
20. Slade PD. What is body image? Behav Res Ther. 1994; 32(5):497-502. doi: 10.1016/0005-7967(94)90136-8.
21. Gupta MA, Gupta AK. Psychodermatology: an update. J Am Acad Dermatol. 1996;34(6):1030-1046. doi:10.1016/s0190-9622(96)90284-4.
22. Allen MS, Walter EE. Personality and body image: A systematic review. Body Image. 2016; 19:79-88. doi:10.1016/j.bodyim.2016.08.012.
23. Buhlmann U, Etcoff NL, Wilhelm S. Facial attractiveness ratings and perfectionism in body dysmorphic disorder and obsessive-compulsive disorder. J Anxiety Disord. 2008;22(3):540-547. doi:10.1016/j.janxdis.2007.05.004.
24. Jerónimo F, Carraça EV. Effects of fitspiration content on body image: a systematic review. 2022; 27(8):3017-3035. doi: 0.1007/s40519-022-01505-4.
25. Barsky AJ, Cleary PD, Sarnie MK, et al. Panic disorder, palpitations, and the awareness of cardiac activity. J Nerv Ment Dis. 1994;182(2):63-71. doi:10.1097/00005053-199402000-00001.
26. Alissa O, James C, Milne-Home J. Repetitive, safe, and automatic: The experience of appearance-related behaviors in body dysmorphic disorder. Australian Psychologist. 2017;52(6):433-441. doi:10.1111/ap.12247.
27. Nagy H, Paul T, Jain E, et al. A Clinical Overview of Anorexia Nervosa and Overcoming Treatment Resistance. Avicenna J Med. 2022;13(1):3-14. doi:10.1055/s-0042-1758859.
28. Murphy ST, Bailey B, Andrew A. Cooper and Daniel R Strunk. Do Clients Learn Specific Skills from Cognitive Versus Behavioral Interventions for Depression? Cognitive Therapy and Research. 2023;47(4):1-7. doi:10.1007/s10608-023-10382-9.
29. Yang HX, Zhang YJ, Hu HX et al. Relationship Between Interoception and Autistic Traits: A Resting-State Functional Connectivity Study [published online ahead of print, 2023 Jul 3]. J Autism Dev Disord. 2023;10.1007/s10803-023-06050-2. doi:10.1007/s10803-023-06050-2.
30. Bernstein EE, Phillips KA, Greenberg JL et al. Mechanisms of cognitive-behavioral therapy effects on symptoms of body dysmorphic disorder: a network intervention analysis. Psychol Med. 2023;53(6):2531-2539. doi:10.1017/S0033291721004451.
31. Hardardottir H, Hauksdottir A, Bjornsson AS. Body dysmorphic disorder: Symptoms, prevalence, assessment and treatment. Laeknabladid. 2019;105(3):125-131. doi:10.17992/lbl.2019.03.222.
32. Eskander N, Limbana T, Khan F. Psychiatric Comorbidities and the Risk of Suicide in Obsessive-Compulsive and Body Dysmorphic Disorder. Cureus. 2020;12(8):e9805. doi:10.7759/cureus.9805.
33. Silver J, Reavey P, Anne Fineberg N. How do people with body dysmorphic disorder view themselves? A thematic analysis. Int J Psychiatry Clin Pract. 2010;14(3):190-197. doi:10.3109/13651501003735492.
34. Al-Shuhayb ZS. Prevalence of body dysmorphic disorder among Saudis seeking facial plastic surgery. Saudi Surg J. 2019;7:83-86. doi:10.4103/ssj.ssj_11_19.
35. Kobusiewicz A, Tomas-Aragones L, Marron SE, Zalewska-Janowska A. Body dysmorphic disorder in patients with acne: treatment challenges. Postepy Dermatol Alergol. 2022;39(1):221-222. doi:10.5114/ada.2022.113616.
36. Phillips KA, Kelly MM. Body Dysmorphic Disorder: Clinical Overview and Relationship to Obsessive-Compulsive Disorder. Focus (Am Psychiatr Publ). 2021;19(4): 413-419, doi:10.1176/appi.focus.20210012.
37. Grant JE, Phillips KA. Recognizing and treating body dysmorphic disorder. Ann Clin Psychiatry. 2005;17(4):205-210. doi:10.1080/10401230500295313.
38. Hostiuc S, Isailă OM, Rusu MC, et al. Ethical Challenges Regarding Cosmetic Surgery in Patients with Body Dysmorphic Disorder. Healthcare (Basel). 2022;10(7):1345. doi:10.3390/healthcare10071345.
39. Kuck N, Cafitz L, Bürkner PC, et al. Body dysmorphic disorder and self-esteem: a meta-analysis. BMC Psychiatry. 2021;21(1):310. doi:10.1186/s12888-021-03185-3.

ORCID AND CONTRIBUTIONSHIP
Fahem Alwan Bahlol: 0000-0003-3548-7835[A-B]
Mushtaq Talip Hashim: 0009-0006-2617-8183[C-D]
Maysaa Ali Abdul Khaleq: 0009-0002-2846-0706[D-E]
Ahmed Abed Marzook: 0000-0002-2179-4773[E-F]

ADDRESS FOR CORRESPONDENCE
Fahem Alwan Bahlol
Department of Psychiatry, College of Medicine,
Baalad Hospital, Salahaddin
e-mail: LYANLYAN2014@yahoo.com

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 17.05.2023
ACCEPTED: 15.09.2023

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 521-526

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305111

PHYSICAL HEALTH OF FEMALES FROM THE MOUNTAIN DISTRICTS OF ZAKARPATTIA ACCORDING TO THE METABOLIC LEVEL OF AEROBIC AND ANAEROBIC ENERGY SUPPLY DEPENDING ON THE COMPONENT BODY COMPOSITION

Olena A. Dulo [1], Yurii M. Furman [2], Lidiia G. Dotsiuk [3], Mariia Yu. Shcherba[1]

[1]UZHHOROD NATIONAL UNIVERSITY, UZHHOROD, UKRAINE
[2]ZHYTOMYR IVAN FRANKO STATE UNIVERSITY, ZHYTOMYR, UKRAINE
[3]YURIY FEDCOVYCH CHERNIVTSI NATIONAL UNIVERSITY, CHERNIVTSI, UKRAINE

ABSTRACT

Aim: To determine the aerobic and anaerobic productivity of females from the mountain districts of Zakarpattia region, depending on the component composition of body weight.

Materials and Methods: A comparative analysis of physical health status of females in the post-pubertal period of ontogenesis, was carried out. Physical health status was assessed by indicators of aerobic and anaerobic productivity depending on the component composition of the body, which was determined by impedance measurement.

Results: Physical health of females from the mountain districts depends on the component composition of the body, namely: an excellent level of aerobic productivity is observed in females who have a insufficient body weight with a normal relative fat content and a high relative content of skeletal muscles, $VO_{2\ max\ rel} > 38\ ml \cdot min^{-1} \cdot kg^{-1}$; as a result, their physical health exceeds the "critical level" according to H.L. Apanasenko and corresponds to "excellent" according to Ya.P. Pyarnat's criteria. Females from the mountain districts with normal body weight, high relative fat and normal relative skeletal muscle have average level of aerobic performance., i.e., $VO_{2\ max\ rel.}$ is within 28-33 $ml \cdot min^{-1} \cdot kg^{-1}$. As a result, their physical health is below the "critical level".

Conclusions: "Excellent" and "good" level of aerobic productivity of females from the mountain districts of the Zakarpattia region guarantees "safe health level". Females from mountain districts with a high content of fat component have an "average" level of aerobic performance, which does not provide a "safe health level".

KEY WORDS: body mass, fat, skeletal muscles, post-pubertal age

INTRODUCTION

According to existing concepts about physical health [1], its level is determined by a person's ability to adapt to the influence of various factors, that is, to maintain normal life activities in inadequate situations [2]. Moreover, the individualization of a person's adaptive capacity is determined by a number of factors, namely: age, gender, constitutional characteristics of body composition, functional state of the body, etc. [3]. It should be noted that the ability to effectively perform physical work in aerobic and anaerobic (alactic and lactic) modes of energy supply can serve as an indicator of the level of adaptive capacity [4]. Because there is scientific information about the dependence of the level of physical health on the efficiency of aerobic and anaerobic metabolic processes that ensure physical activity [5].

A whole series of scientific works testify that a person's ability to adapt to aerobic and anaerobic physical work depends on the somatotype [6-8]. Recently, scientists have also focused their attention on the dependence of the individual's capacity to adapt to work in aerobic and anaerobic modes of energy supply on the component composition of body weight, namely on the ratio of fat and muscle components [9].

The physical health of certain population groups is formed as a result of many years of living in a certain territory due to the influence of exogenous (meteogeographic) factors on the human genetic apparatus [10, 11].

AIM

The aim is to determine the aerobic and anaerobic productivity of females from the mountain districts

of Zakarpattia region, depending on the component composition of body weight.

MATERIALS AND METHODS

A comparative analysis of physical health status of 102 post-puberty females aged 16 to 20, residents of the mountain districts of Zakarpattia region, was carried out. Physical health status was assessed by indicators of the aerobic productivity of the body, namely, the maximum oxygen consumption was measured ($VO_{2\ max}$) using the bicycle ergometry method. To evaluate the level of aerobic productivity, the Ya.P. Pyarnat's rating scale was used [12]. Indicators of anaerobic productivity of the body were studied by: measuring the power of anaerobic alactic energy supply processes by the Peak Power Output in 10 s ($WAnT_{10}$); the power of anaerobic lactic energy supply processes by the Peak Power Output in 30 s ($WAnT_{30}$), using the Wingate anaerobic test described by Yu.M. Furman et al [13]. The anaerobic lactic productivity of the organism was measured by the Peak Power Output (PPO) in 1 min using A. Shogy and G. Cherebetin's method [14]. The component body mass composition was determined using the impedance method with the application of Omron BF511 Body Composition Monitor to estimate the percentage of fat mass (subcutaneous and visceral fat) and the percentage of skeletal muscle [15]. The statistical processing of the material was carried out in Excel 7.0 and SPSS version 10.0 using Student's t-test to find out the reliability of the difference between the average values.

RESULTS

As a result of determining the component composition of body weight, the females studied were divided into three groups depending on the relative content of fat and into three groups depending on the relative content of skeletal muscles. The number of females with a normal relative fat content (21.0-32.9%) was the largest – 52 individuals (51.0%), while the number of females with a high relative fat content (33.0 -38.9%) was the smallest – 11 (10.8%). There were no individuals with a very high relative fat content (> 39.0%) among those studied. The representatives of the mountain districts were almost equally distributed regarding relative content of skeletal muscles, namely: there were 59 females (57.8%) with normal and 40 females (39.2%) with high relative content of skeletal muscles. We also recorded 3 individuals (3%) with a very high relative content of skeletal muscles (>35.3%). There were no females with a low relative content of skeletal muscles (<24.3%) among the studied individuals (Table 1).

The value of the absolute $VO_{2\ max}$ index in females with low relative fat content is 14.0% significantly lower than the value in females with normal relative fat content. The average value of $VO_{2\ max\ rel.}$ in females with a high relative fat content is 33.8±1.76 $ml \cdot min^{-1} \cdot kg^{-1}$, which is1.23 times lower than the average value in females with a normal relative fat content ($p<0.05$) and does not reach the "safe health level". The average value of the relative indicator of maximal oxygen consumption in females from the mountain districts with a normal relative fat content exceeds the "safe health level" by 18.9%. The results of the study of the power of anaerobic lactic energy supply processes according to the relative value of $WAnT_{10\ rel.}$ in females from the mountain districts, show a significant prevalence of this indicator in females with a normal relative content of the fat component compared to persons with a high content by 9.1%. Peculiarities of the manifestation of anaerobic productivity in representatives of the mountain districts with different component composition of body weight were also revealed when determining the relative power of anaerobic lactic energy supply processes. It should be noted that the lowest average values of $WAnT_{30\ rel.}$ are observed in representatives of the mountain districts with both high and low relative fat content, while in females with normal relative fat content, the average value of the absolute indicator of the capacity of anaerobic lactic energy supply processes is higher compared to representatives of the mountain districts with low and high relative fat the content of the fat component by 17.8% and 18%, respectively. However, females from the mountain districts with different relative fat content probably do not differ from each other in terms of the

Table 1. Distribution of females from the mountain districts of Zakarpattia by component composition of body weight, n=102

Relative fat content (%)							
< 21,0 (-) low		21,0 – 32,9 (0) normal		33,0 – 38,9 (+) high		>39,0 (++) very high	
number of persons	%	number of persons	%	number of persons	%	number of persons	%
39	38,2	52	51,0	11	10,8	-	-
Relative content of skeletal muscles (%)							
< 24,3 (-) low		24,3 – 30,3 (0) normal		30,4 – 35,3 (+) high		> 35,3 (++) very high	
number of persons	%	number of persons	%	number of persons	%	number of persons	%
-	-	59	57,8	40	39,2	3	3,0

Table 2. Average values of indicators of aerobic and anaerobic productivity of the body (M±m) of females from the mountain districts of Zakarpattia, depending on the relative fat content, n=102

Indicators	Aerobic productivity				Anaerobic productivity			
	Maximum oxygen consumption		power of alactic energy supply processes		power of lactic energy supply processes		capacity of lactic energy supply processes	
Relative fat content (%)	$VO_{2\,max}$ $ml \cdot min^{-1}$	$VO_{2\,max\,rel.}$ $ml \cdot min^{-1} \cdot kg^{-1}$	$WAnT_{10'}$ $kgm \cdot min^{-1}$	$WAnT_{10\,rel}$•, $kgm \cdot min^{-1} \cdot kg^{-1}$	$WAnT_{30.}$ $kgm \cdot min^{-1}$	$WAnT_{30\,rel}$•, $kgm \cdot min^{-1} \cdot kg^{-1}$	PPO, $kgm \cdot min^{-1}$	$PPO_{rel.}$, $kgm \cdot min^{-1} \cdot kg^{-1}$
< 21,0 (-) low (n=39)	2032,6 ± 53,4 ·	38,5 ± 1,67	2063,0 ±59,2	39,3 ± 0,9	1983,4 ± 56,5 "	37,2 ± 0,68 ·	1121,6 ± 31,3 ·	20,6 ± 0,7
21,0 – 32,9 (0) normal (n= 52)	2364,8 ± 64,6	41,6 ± 1,93	2202,1 ± 62,7	42,1 ±1,18	2128,3 ± 62,4	40,5 ± 1,07	1286,2 ± 40,8	21,2 ± 0,9
33,0 – 38,9 (+) high (n=11)	2101,4 ± 58,6 ·	33,8 ± 1,76 ·	2122,4 ± 61,1	38,6 ± 0,8	2218,4 ± 61,3	36,8 ± 0,66 *	1206,3 ± 40,4	19,9 ± 0,8

Note: the probability of a difference in mean values (p<0.05):
** - relatively low fat content;*
• - relatively normal fat content;
" - relatively high fat content.

relative value of the capacity of anaerobic lactic energy supply processes (p>0, 05) (Table 2).

The dependence of the level of aerobic productivity on the content of the muscle component of body weight was established. The value of the absolute $VO_{2\,max}$ index in females with normal and high relative content of skeletal muscles is significantly lower than the value in females with very high relative content of skeletal muscles (p<0.05) by 19.9% and 13.2%, respectively. The average value of the relative indicator of maximum oxygen consumption $VO_{2\,max\,rel}$• in females from the mountain districts with normal, high, and very high relative skeletal muscle mass is significantly higher than the "safe health level" and corresponds to an excellent level of aerobic performance. The results of studies of the power of anaerobic lactic energy supply processes of the body in terms of the absolute value of $WAnT_{10}$ in females from the mountain districts revealed a significant prevalence of this indicator in females with a very high relative content of skeletal muscles by 23.7% compared to individuals with a normal relative content of this body mass component. Peculiarities of anaerobic productivity manifestation in representatives of the mountain districts with different component composition of body weight were also revealed when determining the absolute value of the power of anaerobic lactic energy supply processes. However, the lowest absolute average values of $WAnT_{30}$ are observed in females from the mountain districts with normal and high relative content of skeletal muscles. In females with a normal relative content of skeletal muscles, the average value of the absolute indicator of the capacity of anaerobic lactic energy supply processes is reliably the lowest by 19.1% and 21.7% compared to representatives of the mountain districts with high and very high relative content of skeletal muscles, respectively (p<0.05). At the same time, according to the relative indicator of the capacity of anaerobic lactic energy supply processes, females from the mountain districts with different relative content of skeletal muscles probably do not differ among themselves, p>0,05 (Table 3).

Thus, according to the results of the research of aerobic and anaerobic processes of energy supply in females from mountain districts, we came to the conclusion that females with a normal relative fat content (21.0-32.9%) and a high relative content of skeletal muscles (30.4-35.3%) with insufficient body weight (BMI<18.5 kg/m^2) have an excellent level of aerobic productivity, i.e. VO_2 max rel. > 38 $ml \cdot min^{-1} \cdot kg^{-1}$. Females with a normal relative fat content and a normal relative skeletal muscle content (24.3-30.3%) with normal body weight (18.5 ≤ BMI < 25 kg/m^2) have a good level of aerobic productivity, i.e. VO_2 max rel. > 34 to 38 $ml \cdot min^{-1} \cdot kg^{-1}$. Females with a high relative fat content and a normal relative skeletal muscle content with normal body weight have an intermediate level of aerobic productivity, i.e. VO_2 max rel. 28-33 $ml \cdot min^{-1} \cdot kg^{-1}$. At the same time, all the individuals studied have a normal level of visceral fat, in the range from 1 to 9% (Fig.1).

DISCUSSION

The issues of physique are in the field of interests of both theoretical and clinical medicine. Traditional anthropometric approaches are now successfully complemented by high-tech and effective research methods (bioimpedancemetry, etc.), which provide an objective assessment of the component composition of the human body and other morphological features. The expediency of conducting such studies with a clinical purpose is determined by the repeatedly proven fact of constitutional predisposition to the development of a number of diseases, as well as by the fact that belonging to a certain constitutional type can be considered as a factor of well-being, indicating the optimal adaptation potential and low probability of the development of certain nosological forms. This allows for individualization of approaches to disease prevention, selection of treatment tactics, and prediction of treatment

Table 3. Average values of indicators of aerobic and anaerobic body productivity (M±m) of girls from the mountain districts of Zakarpattia depending on the relative content of skeletal muscles, n=102

Indicators	Aerobic productivity				Anaerobic productivity			
	Maximum oxygen consumption		power of alactic energy supply processes		power of lactic energy supply processes		capacity of lactic energy supply processes	
Relative skeletal muscle content (%)	$VO_{2\ max}$ $ml \cdot min^{-1}$	$VO_{2\ max\ rel.}$ $ml \cdot min^{-1} \cdot kg^{-1}$	$WAnT_{10'}$ $kgm \cdot min^{-1}$	$WAnT_{10\ rel'}$ $kgm \cdot min^{-1} \cdot kg^{-1}$	$WAnT_{30.}$ $kgm \cdot min^{-1}$	$WAnT_{30\ rel'}$ $kgm \cdot min^{-1} \cdot kg^{-1}$	PPO, $kgm \cdot min^{-1}$	$PPO_{rel.'}$ $kgm \cdot min^{-1} \cdot kg^{-1}$
24,3 – 30,3 (0) normal (n=59)	2098,3 ± 48,6"	43,7 ± 0,61	2006,8 ± 54,5"	41,7 ± 1,04	2014,7 ± 67,8"	41,8 ± 2,01	1208,4 ± 28,3"'	25,1 ± 1,02
30,4 – 35,3 (+) high (n=40)	2273,4 ± 63,8"	40,5 ± 0,48*	2311,4 ± 70,4	40,0 ± 1,7	2291,1 ± 43,2	40,4 ± 1,92	1494,6 ± 31,2	26,3 ± 0,9
> 35,3 (++) very high (n=3)	2618,3 ± 59,66	41,69 ± 0,46	2482,7 ± 62,7	40,17 ± 1,4	2447,7 ± 50,4	40,2 ± 1,68	1543,7 ± 40,1	25,3 ± 1,4

Note: the probability of a difference in mean values ($p<0.05$):
** - relatively low fat content;*
" - relatively normal fat content;
' - relatively high fat content.

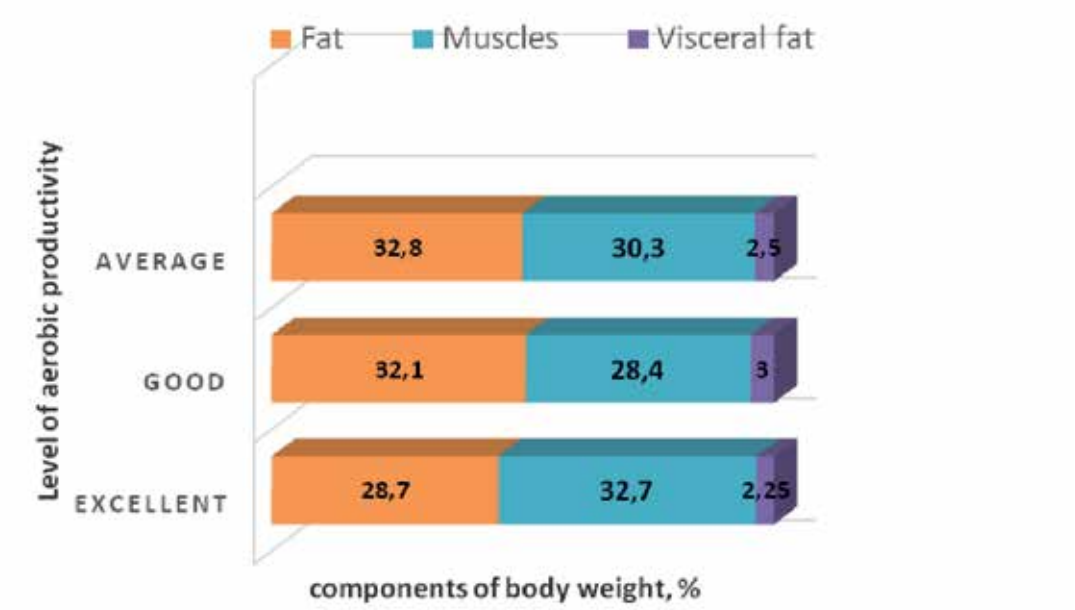


Fig. 1. Graphic representation of the dependence of the level of aerobic productivity of females from the mountain districts of Zakarpattia on the ratio of the component composition of body weight (n=102).

effectiveness [16]. M. I. Nemesh's study of the relationship between indicators of the component composition of the body and central hemodynamics in females with excessive body weight, proves that an increase in body weight due to adipose tissue, first of all, serves as a load for the heart muscle, which leads to increase the minute blood volume. Another mechanism that occurs in parallel is characterized by the production of hormones by visceral fat: tumor necrosis factor-α, resistin, visphantin reduce the production of nitric oxide by the vascular endothelium, which negatively affects the vasodilatation of peripheral arteries and leads to hardening of the arterial walls, and eventually to the appearance of arterial hypertension [17-19]. However, with physical exertion, training of the skeletal muscles increases, and this will correct the indicators of central hemodynamics.

A. S. Shklyar's research shows the importance of studying the component composition of the body at various stages of postnatal ontogenesis, which makes it possible to explain age and gender differences in the frequency of formation of functional disorders, pre-nosological, as well as nosologically defined pathological conditions as manifestations of the general process of growth and development in postnatal ontogeny. After all, the fat component of a person's body weight is one of the indicators of a person's physique and of their nutritional (alimentary) status. It can change dynamically under the influence of various factors [20]. The muscle component of a person's body weight is one

of the indicators of body structure and an indicator of its structural and functional state at various stages of ontogenesis. Changes in the muscle component of body weight can be transitory or permanent, which is determined by the state of metabolic processes in the corresponding period of ontogenesis, the nutritional support of nutrient homeostasis, the mode of motor activity and the state of the person's somatic health [21].

Yu.I. Huminskiy et al. conducted a longitudinal study for the first time on the territory of Ukraine. The study determined changes in the component composition of the body mass of young cadets of the 1st, 2nd, and 3rd years of study in the academic setting as an exogenous factor, which, together with the daily regime, way of eating, motor activity and emotional load affect the body. It was found that the indicators of the muscle and bone components of the body weight of the cadets increased during training, while the indicator of the fat component reduced. Significant differences were found when comparing annual changes in muscle and fat components of body weight. In addition, annual changes in the fat component were more significant in the second year of study than in the first, while indicators of the muscle and bone components prevailed in the first year of study [22]. Identifying patterns of individual typological variability of the body structure and its parts is ideal for monitoring health and physical status, and can be used in personalized approaches of clinical and preventive medicine.

CONCLUSIONS

In females from the mountain districts with a high fat content, the average value of the power of anaerobic lactic energy supply processes based on the relative value of $WAnT_{10}$ and the power of lactic processes based on the relative value of $WAnT_{30}$ is probably lower than that of peers with a normal content of the fat component by 9.1% and 18.0%, correspondingly. The capacity of anaerobic lactic processes of energy supply in females with a high fat content in terms of the relative value of PPO in 1 min is probably 11.5% lower than in females with a normal fat content. "Excellent" and "good" level of aerobic productivity in females from the mountain districts of Zakarpattia region guarantees "safe health level". Females from the mountain districts with a high content of fat component have an "average" level of aerobic performance, which does not provide "safe health level".

REFERENCES

1. Shakhlina LYAH, Kohan BH, Tereshchenko TO et al. Sportyvna medytsyna [Sports medicine]. Kyyiv: Natsional'nyy universytet fizychnoho vykhovannya i sportu Ukrayiny. 2019, p.424. (Ukrainian)
2. Kostyukevych V, Mel'nychuk A, Chkhan' A. Analiz metodiv doslidzhennya problemy shchodo formuvannya modeley zdorovoho sposobu zhyttya students'koyi molodi [Analysis of methods of research on the problem of forming healthy lifestyle models of student youth]. Aktual'ni problemy fizychnoho vykhovannya ta metodyky sportyvnoho trenuvannya. 2021; 1:31-48. (Ukrainian)
3. Larry Kenney W, Wilmore JH, Costill DL. Physiology of Sport and Exercise. Human Kinetics. 2021, p.611.
4. Dulo O, Furman Y, Hema-Bahyna N. Gender and Somatotypological Peculiarities of Indicators of Aerobic and Anaerobic Productivity of Energy Supply of the Body in the Post-Pubertal Period of Ontogenesis in the Residents of the Zakarpattia Region. Wiad Lek. 2022; 75(10):2359-2365.
5. Zimnitskaya R, Paramonova N, Jakubovskii D. Comparative analysis of functional state and working capacity on veloergometer of average training level women of age. Sporto Mokslas. 2017; 1(87):32-37. doi:10.15823/sm.2017.5.
6. Furman YM, Miroshnichenko VM, Bohuslavska VYu et al. Modeling of functional preparedness of women 25-35 years of different somatotypes. Pedagogy of Physical Culture and Sports. 2022; 26(2):118-125. doi:10.15561/26649837.2022.0206.
7. Gaul CA, Docherty D, Cicchini R. Differences in anaerobic performance between boys and men. Int. J. Obes Relat. Metab. Disord. 2000; 24:7841-7848.
8. Ryan-Stewart H, Faulkner J, Jobson S. The influence of somatotype on anaerobic performance. PLoS ONE. 2018;13(5):e0197761. doi:10.1371/journal.pone.0197761.
9. Dulo O, Furman Yu, Maltseva O et al. Physical Health of Females from the Lowland Districts of Zakarpattia According to the Metabolic Level of Aerobic and Anaerobic Energy Supply Depending on the Component Body Composition. Wiad Lek. 2023; 76(3):568-574.
10. Furman YuM, Miroshnichenko VM, Brezdeniuk OYu et al. Otsinka aerobnoyi ta anaerobnoyi produktyvnosti orhanizmu molodi 17-19 rokiv Podil's'koho rehionu [An estimation of aerobic and anaerobic productivity of an organism of youth aged 17-19 years old of Podilsk region]. Pedagogics, Psychology, Medical-Biological Problems of Physical Training and Sports. 2018; 22(3):136-141. doi:10.15561/18189172.2018.0304. (Ukrainian)
11. Nesterova SYu. Adaptatsiya orhanizmu molodi 18-20 rokiv do fizychnykh navantazhen' aerobnoho ta anaerobnoho spryamuvannya v umovakh riznoyi meteosytuatsiyi [Adaptation of the body of youth aged 18-20 to aerobic and anaerobic physical exertion in different weather conditions]. Moloda sportyvna nauka Ukrayiny: zbirnyk naukovykh prats'. 2007; 11(4):196-200. (Ukrainian)
12. Pyarnat YAP. Vozrastno-polovyye standarty (10-50 let) aerobnoy sposobnosti cheloveka [Age-sex standards (10-50 years) of human aerobic capacity]: avtoref. dis. dokt. med. nauk: 03.00.13. M.1983, p.44. (Russian)
13. Furman YuM et al. Funktsional'na pidhotovlenist' [Functional readiness]. Promising models of physical culture and health technologies in physical education of students of higher educational institutions. Kyiv: Olympic literature. 2013, p. 24-42. (Ukrainian)
14. Shögy A, Cherebetin G. Minutentest auf dem Fanradergometer zur Bestimmung der Annaeroben Kapazität. J. Appl. Physiol. 1974; 33:171-176.
15. Dovgiy YuI. Impedansometriya yak metod monitorynhu komponentnoho skladu masy tila studentiv [Impedancemetry as a method of monitoring the component composition of students' body mass]. Prospects, problems and existing achievements of the development of physical culture and sports in Ukraine IV All-Ukrainian Internet Conference «Color of Science». 2021, p.299-302. (Ukrainian)

16. Nikolenko VN, Nikityuk DB, Chava SV. Otechestvennaya konstitutsional'naya anatomiya v aspekte personifitsirovannoy meditsiny. [Native constitutional anatomy in the aspect of the personificative medicine]. Sechenovskiy vestnik. 2013; 4(14):9-17. (Russian)
17. Kovaleva YuV. Gormony zhirovoy tkani i ikh rol' v formirovanii gormonal'nogo statusa i patogeneze metabolicheskikh narusheniy u zhenshchin [Hormones of adipose tissue and their role in the formation of hormonal status and the pathogenesis of metabolic disorders in women]. Arterial'naya gipertenziya. 2015; 21(4):356-370. doi:10.18705/1607-419X-2015-21-4-356-370. (Russian)
18. Karstoft K, Pedersen BK. Skeletal muscle as a gene regulatory endocrine organ. Current opinion in clinical nutrition and metabolic care. 2016; 19(4):270-275.
19. Nemesh MI. Vzayemozv'yazok pokaznykiv komponentnoho skladu tila z tsentral'noyu hemodynamikoyu u zhinok z nadmirnoyu vahoyu [The relationship between indicators of body composition and central hemodynamics in overweight women]. Multidisziplinäre Forschung: Perspektiven, Probleme und Muster der Sammlung wissenschaftlicher Arbeiten «ΛΌΓΟΣ» zu den Materialien der II internationalen wissenschaftlich-praktischen Konferenz, 2021, p.97-98. (Ukrainian)
20. Shklyar AS. M'yazova komponenta masy tila lyudyny: antropometrychna otsinka na etapakh postnatal'noho ontohenezu (Metodolohichni, innovatsiyni ta prykladni aspekty) [The muscle component of human body weight: anthropometric assessment at the stages of postnatal ontogenesis (Methodological, innovative and applied aspects)]. Zbirnyk naukovykh prats': Problemy ekolohichnoyi ta medychnoyi henetyky i klinichnoyi imunolohiyi. 2013; 5(119):44-52. (Ukrainian)
21. Shklyar AS. Zhyrova komponenta masy tila lyudyny: antropometrychna otsinka na etapakh postnatal'noho ontohenezu (Metodolohichni, innovatsiyni ta prykladni aspekty) [The fat component of human body weight: anthropometric assessment at the stages of postnatal ontogenesis (Methodological, innovative and applied aspects)]. Zbirnyk naukovykh prats': Problemy ekolohichnoyi ta medychnoyi henetyky i klinichnoyi imunolohiyi. 2014; 1(121):34-44. (Ukrainian)
22. Humins'kyy YuY, Bashyns'ka OL, Andriychuk VM et al. Osoblyvosti zmin pokaznykiv komponentnoho skladu masy tila y unakiv-kursantiv v umovakh navchal'no-vykhovnoho protsesu [Peculiarities of changes in indicators of the component composition of the body weight of young cadets in the conditions of the educational process]. VII mizhnarodnyy konhres z intehratyvnoyi antropolohiyi, Zhovten' 17-18,.2013: 49-50. (Ukrainian)

ORCID AND CONTRIBUTIONSHIP
Olena A. Dulo: 0000-0003-0473-5605[A, B, D, F]
Yurii M. Furman: 0000-0002-5206-7712[A, C, E, F]
Lidiia G. Dotsiuk: 0000-0002-1298-4428[A, E]
Mariia Yu. Shcherba: 0009-0004-0216-2393[B, E]

ADDRESS FOR CORRESPONDENCE
Olena A. Dulo
Uzhhorod National University
3 Narodna Square, 88000 Uzhhorod, Ukraine
e-mail: olena.dulo@uzhnu.edu.ua

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 22.04.2023
ACCEPTED: 03.09.2023

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 527-532

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305112

IN SILICO STUDY OF NOVEL SULFONAMIDE DERIVATIVES BEARING A 1, 2, 4-TRIAZOLE MOIETY ACT AS CARBONIC ANHYDRASE INHIBITORS WITH PROMISING ANTI-CANCER ACTIVITY

Zainab Kifah Abbas[1], Noor H. Naser[2], Rana Neama Atiya[1]

[1]PHARMACEUTICAL CHEMISTRY DEPARTMENT, FACULTY OF PHARMACY, KUFA UNIVERSITY, NAJAF, IRAQ

[2]PHARMACEUTICAL CHEMISTRY DEPARTMENT, COLLEGE OF PHARMACY, AL-ZAHRAA UNIVERSITY FOR WOMEN, KARBALA, IRAQ

ABSTRACT

Aim: To evaluate the theoretical binding affinities of four synthetic compounds that target the carbonic anhydrase IX enzyme in solid tumors.

Materials and Methods: To accurately depict the molecular structure, we utilized the Chem Draw Professional 12.0 program. We downloaded the carbonic anhydrase IX enzyme (29.25 KDa) (PDB code: 4YWP) from the Protein Data Bank into the Molecular Operating Environment software. Then, the S-score and rmsd were calculated for the proposed compounds.

Results: The theoretically synthesized compounds demonstrated good binding affinities with the receptor active pockets Sa, Sb, and Sd, with S-scores of -7.6491, -8.3789, and -8.3218, respectively. Substitutions improve compound orientation. The substituted triazoles ring increases flexibility and receptor interaction. In addition, the benzyl chloride derivatives play an important role in the interaction, with varying effects dependent on the groups substituted at position 4 of the benzene ring.

Conclusions: The synthesized compounds Sb with para Br substitution (S-score = -8.37) and Sd with para Cl substitution (S-score = -8.32) are considered the best ones as they exhibit a high affinity for the receptor.

KEY WORDS: *in silico*, triazoles moiety, carbonic anhydrase inhibitor

INTRODUCTION

When considering causes of death in the United States, cancer comes just behind cardiovascular illnesses [1, 2]. Treatment choices are limited if cancer has metastasized, leaving chemotherapy as the only viable alternative [3, 4]. The main reasons for chemotherapy failure are the inability of anticancer treatment to reach the malignancy cell, requiring a dosage increase, and the lack of selectivity of these medications, resulting in considerable severe cell damage [4]. Existing chemotherapeutic drugs have problems with high toxicity, drug resistance, and a lack of selectivity, necessitating the development of new therapies [5]. In humans, 15 different α-class Carbonic Anhydrase (CA) isoforms are expressed. Catalytically active (CA) isoforms in humans include 12 of the 15 α-class isoforms. These CA isoforms are responsible for catalyzing the reversible hydration of CO_2 into HCO_3. Each of these isoforms has multiple physiological roles and diverse expression patterns [6-8]. It has been discovered that carbonic anhydrase IX and carbonic anhydrase XII have significant links to the development of cancer [9]. On the other hand, studies have shown that carbonic anhydrase IX, rather than carbonic anhydrase XII, is more commonly found in solid tumors [10, 11]. Sulfonamides have many different types of biological activity, and members of this class of pharmacological substances are commonly employed in clinical settings as antibacterial, hypoglycemic, diuretic, antihypertensive, and antiviral medications, amongst other uses. Recent studies have shown that a variety of structurally unique sulfonamide derivatives exhibit significant anticancer activity *in vitro* and/or *in vivo* [12, 13]. Sulfonamide derivatives share a common aromatic/heterocyclic molecular motif, and based on the substitution on the aromatic ring (tail or linker moiety), specific interactions may be established within the typical enzyme bipolar structure, either in the center of the site of activity or on its edge [14, 15]. Heterocyclic compounds are of interest to medicinal chemists due to their distinct chemical characteristics and varied biological activities [16]. It has been studied for the possibility of being used as a therapy for the treatment of a large variety of diseases, one of which is cancer. because of the presence of heterocyclic core rings in the structure of naturally occurring biological components in our bodies, such as DNA, RNA, and vitamins, advancements in the field of medicine that involve heterocyclic compounds have become increasingly significant [17]. Triazoles is a significant nitrogen heterocyclic structure composed of three nitrogen and two carbon atoms [18]. Triazoles-containing compounds have been shown to have considerable industrial applications in a variety of fields [19]. There are already a number of commercially

available compounds that utilize this nucleus [20]. The 1, 2, 4-triazole nucleus shows promise for enhancing solubility and bimolecular binding because of its resistance to metabolic degradation and dual role as H-bond donor and acceptor at the active region of a receptor [21]. Depending on this background, novel sulfonamide derivatives bearing a 1, 2, 4-triazole ring linked to benzyl chloride with different para substitutions were designed and synthesized to act as CAIs.

AIM

To evaluate the theoretical binding affinities of four synthetic compounds that target the carbonic anhydrase IX enzyme in solid tumors.

MATERIALS AND METHODS

CHEMICAL SYNTHESIS

The following scheme shows the synthesis pathway for compounds (Sa-Sd) derived from sulfanilamide. Compound (A) was synthesized according to Mina et al., [22], and compound (B) synthesized according to Li, et al. [23]. Compound (1) is synthesized by the reaction of compound A with compound B, according to the method described by Park H-S, et al., [24]. Synthesized compound (2) is by the reaction of compound (1) with $NH_2NH_2 \cdot H_2O$ (99%), according to Jubie, et al. [25]. Compound (3) was synthesized according to Husain et al. [26]. Compound (4) was synthesized according to Jubie et al. [25]. Synthesized into different final products, according to Park, et al., (Sa-Sd) [24] (Fig.1).

THE SYSTEM AND SOFTWARE OF THE COMPUTER

The present evaluation made use of a Huawei computer system with the following standard properties: CPU @ 2.10 GHz, Intel(R) Core(TM) i3-10110U, 8 GB RAM. MOE 2015

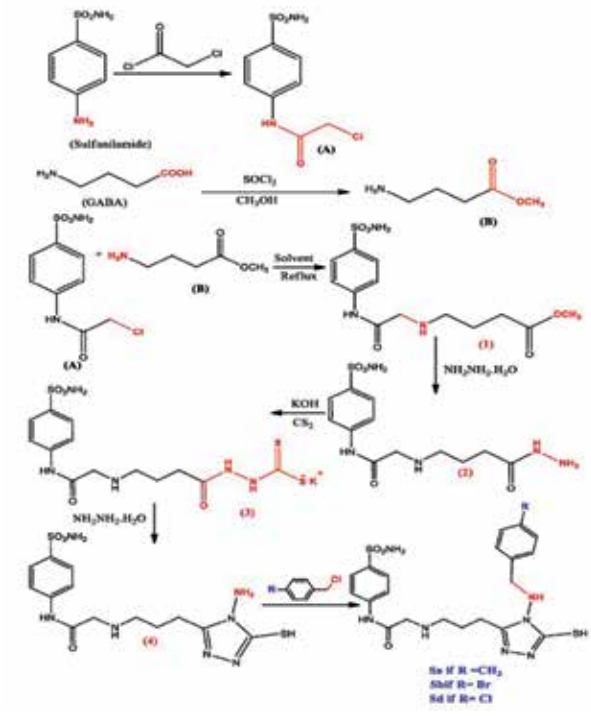


Fig. 1. Synthesis of the final compounds and their intermediates.

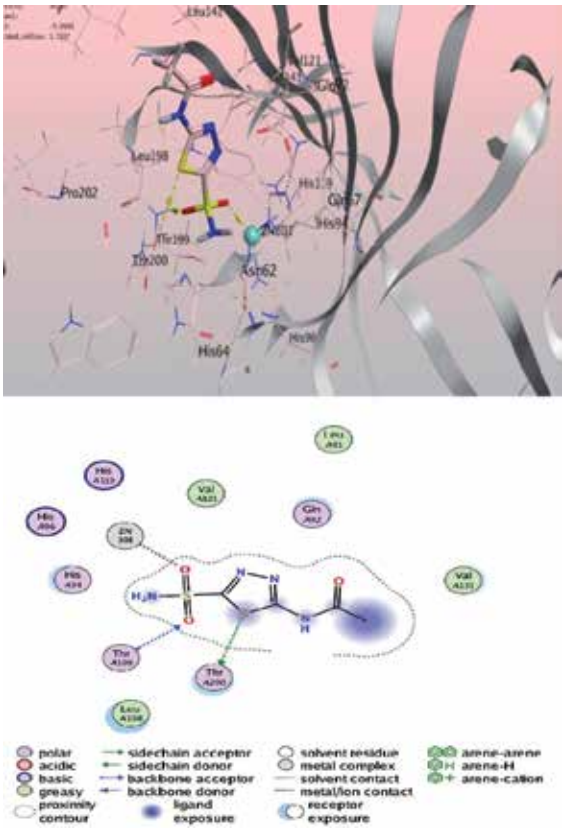


Fig. 2. Acetazolamide compound with carbonic anhydrase IX (PDB code: 4ywp).

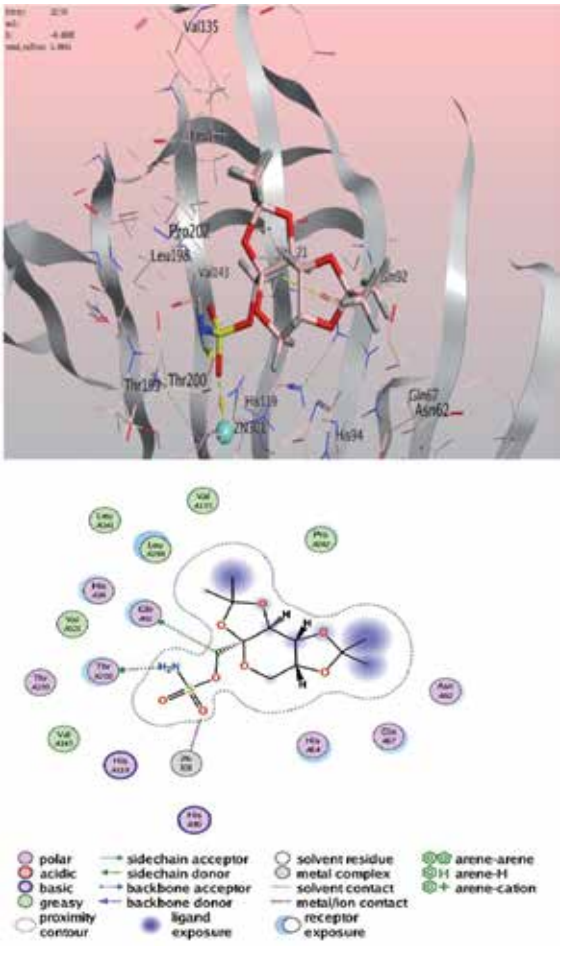


Fig. 3. Topiramate compound with carbonic anhydrase IX (PDB code: 4ywp).

and Chem Draw Professional Software Pro 12.0 were both downloaded and set up.

PREPARATIONS OF LIGAND/RECEPTOR AND PROTOCOL OF MOLECULAR DOCKING

The ligand molecular structures were drawn accurately in Chem Draw Professional 12.0, after that, protonating the ligand in 3D shape, partial charge addition, energy minimization, and finally saving the results. Using the PDB website, we download the receptor into the Molecular Operational Environment (MOE), which is the crystal structure of genetically engineered carbonic anhydrase IX (29.25 kDa) (PDB code: 4YWP).

The target protein is prepared through the following steps: The chain sequences that participate in the protein action were only selected; the remaining chains were deleted. The small molecules were deleted. Water molecules were removed also. Adding hydrogen hides bonds; after that, fix the potential of the protein atoms and identify its active site. At the end, the previously prepared ligand is loaded into MOE from saved data, followed by the docking process.

RESULTS AND DISCUSSION

DOCKING OF MOLECULAR AND VIRTUAL SCREENING

The optimum way for a ligand to connect to a target's active site is explored using the simulation technique known as molecular docking, the Molecular Operating Environment (MOE), which aids in the visualization, characterization, and evaluation of protein interactions with ligands, was used in this study because it provides an excellent graphical representation of results by displaying the positions and interactions of ligand with receptor-binding residues [27]. Because carbonic anhydrase IX is a transmembrane protein, it has been challenging for purify, yield, and crystallize it for use in SBDD. However, the similar cytoplasmic-soluble carbonic anhydrase II isoform can be easily produced and crystallized [28]. The molecular operating environment showed that binding selectivity of designed compounds to the carbonic anhydrase IX enzyme in the same main active site as acetazolamide and topiramate. Topiramate (also known as TPM) has been documented as having an anti-tumorigenic effect in a

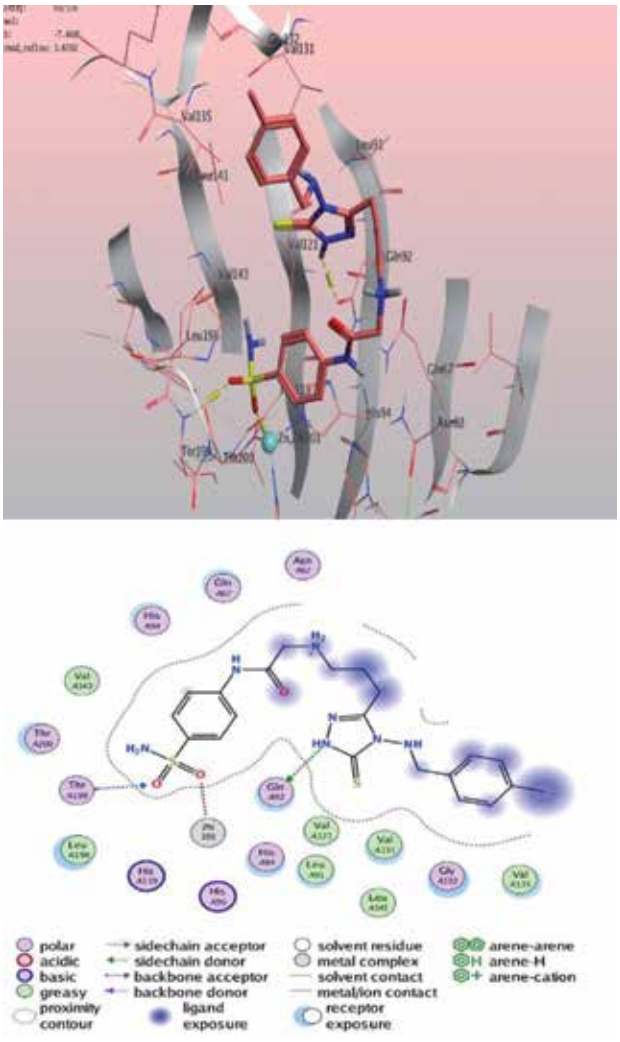


Fig. 4. Sa final compound with carbonic anhydrase IX (PDB code: 4ywp).

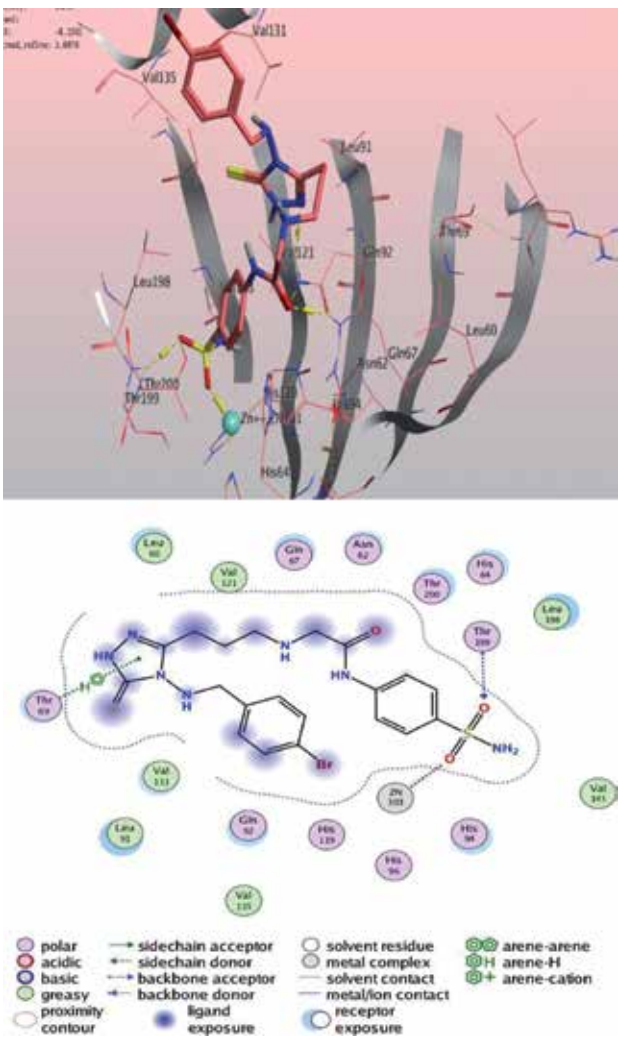


Fig. 5. Sb final compound with carbonic anhydrase IX (PDB code: 4ywp). IX (PDB code: 4ywp).

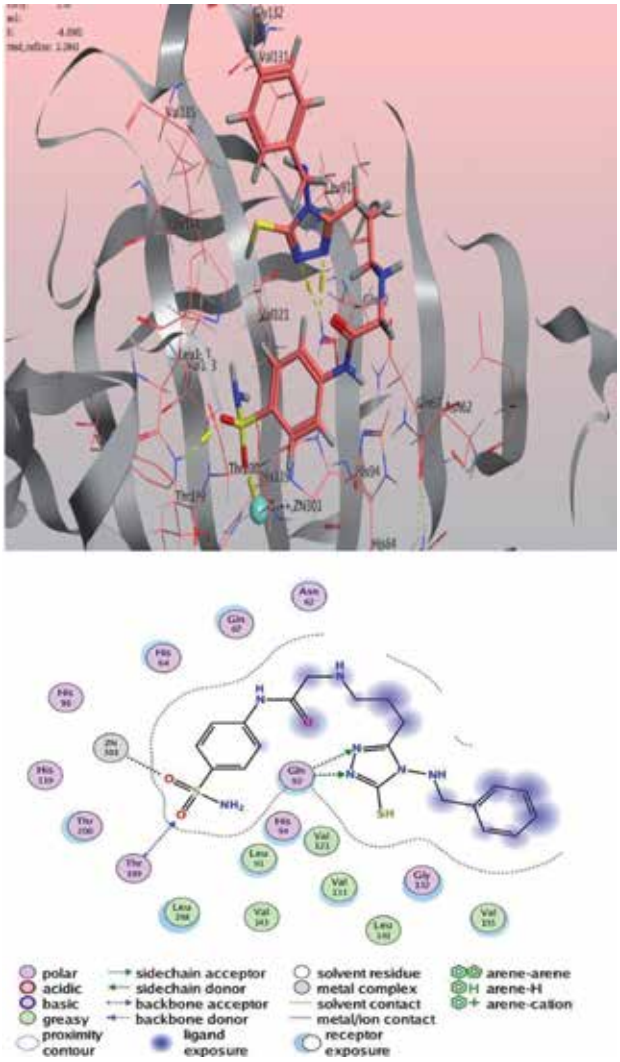


Fig. 6. Sc final compound with carbonic anhydrase IX (PDB code: 4ywp).

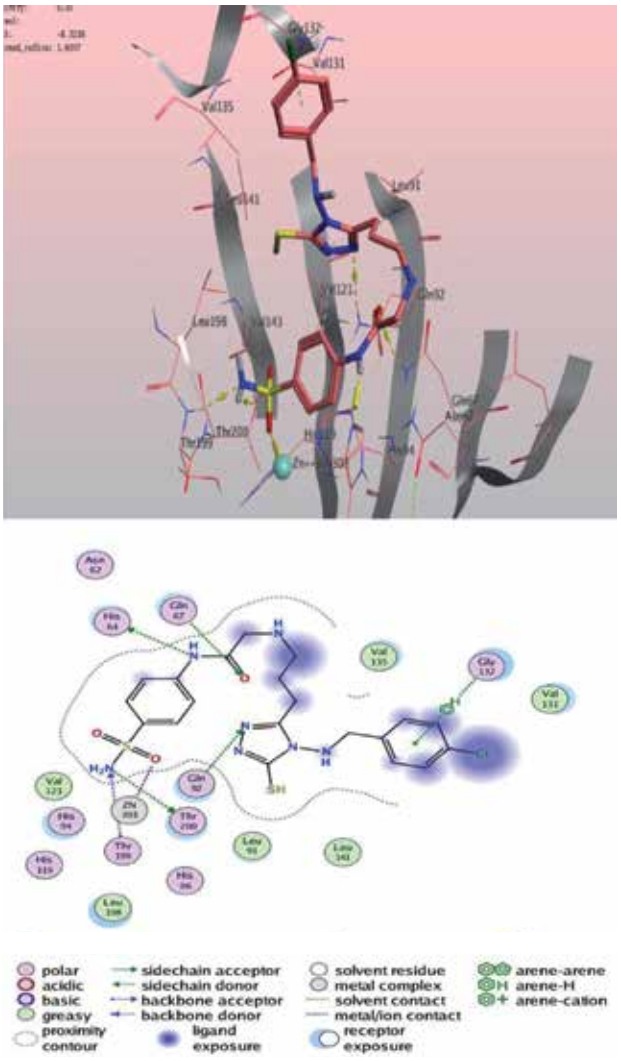


Fig. 7. Sd final compound with carbonic anhydrase IX (PDB code: 4ywp).

Table 1. S-score, rmsd, and the primary amino acids participated in the interaction of the final products of the reaction

Compound	R group	S-score	rmsd	No. of binding site	Binding amino acids
Acetazolamide (Fig. 2)	-------	-5.06	1.7	1	Zn_{301}Thr199,Thr200.
Topiramate (Fig. 3)	-------	-6.69	1.9	3	Gln92,Thr200,Zn301.
Sa (Fig. 4)	CH_3	-7.64	1.6	3	Thr199, Zn301, Gln A92.
Sb (Fig. 5)	Br	-8.37	1.8	3	Zn,Thr199,Thr69.
Sc (Fig. 6)	H	-8.09	2.2	3	Thr199,Zn,Gln.
Sd (Fig. 7)	Cl	-8.32	1.6	7	Thr199, Zn, Th200, His, Gln Gly.

number of malignancies due to its potent inhibition of the carbonic anhydrase enzyme, in particular carbonic anhydrase IX [29]. S-score and rmsd (root-mean-square deviation) values, which represent the average distance between the atoms of the posed ligand and the ligand for the site of the anti-cancer that was tested, were used to evaluate the inhibitory effects of created compounds, and the similarity between the amino acids that interact on the same active site. This data was utilized to evaluate the efficacy of the compounds. Acetazolamide interacts with its interaction site, which is composed of Zn301, Thr199, and Thr200. Topiramate interacts with its interaction site, which is composed of Gln92, Thr200, and Zn301. Table 1 demonstrates the S-score, rmsd, and the primary amino acids that participated in the interaction of the final products of the reaction. All final products Sa, Sb,

and Sd showed better binding affinity with target proteins when compared to acetazolamide and topiramate with S-score (-7.6491, -8.3789, and -8.3218, respectively) and rmsd (1.6792, 1.8982, and 1.6307).

The highest S-score-8.37 was found for compound Sb, suggesting that the Br substitution improves the orientation of the proposed ligand in the receptor pocket. On the other hand, the Sd derivative with Cl substitution made more H-bonds with several important amino acid residues in the protein, with S-score -8.32 resulting in a more stable orientation and a tighter binding affinity than other compounds, in compound Sa with para methyl substitution, the S-score is less -7.46, but good rmsd. In contrast, the inhibitor with para H substitution shows a high rmsd and a lower S-score compared with other substituted inhibitors.

CONCLUSIONS

The synthesized compounds Sb with para Br substitution (S-score = -8.37) and Sd with para Cl substitution (S-score = -8.32) are considered the best ones as they exhibit a high affinity for the receptor. These substitutions have a positive effect on the compound's orientation. Providing evidence for the role of the substituted triazoles ring in increasing flexibility and enhancing the chances of interaction with the receptor. Additionally, the benzyl chloride derivatives play a significant role in the interaction, with variations depending on the groups substituted at position 4 on the benzene ring.

REFERENCES

1. iegel RL, Miller KD, Jemal A. CA: a cancer journal for clinicians. Cancer statistics. 2018;68(1):7-30. doi:10.3322/caac.21442.
2. Zaorsky NG, Churilla TM, Egleston BL, et al. Causes of death among cancer patients. Ann Oncol. 2017;28(2):400-407. doi:10.1093/annonc/mdw604.
3. Ganesh K, Massagué J. Targeting metastatic cancer. Nat Med. 2021;27(1):34-44. doi:10.1038/s41591-020-01195-4.
4. Horn SR, Stoltzfus KC, Mackley HB, et al. Long-term causes of death among pediatric patients with cancer. Cancer. 2020;126(13):3102-3113. doi:10.1002/cncr.32885.
5. Tuğrak M, Gül Hİ, Sakagami H et al. Synthesis and biological evaluation of new pyrazolebenzene-sulphonamides as potential anticancer agents and hCA I and II inhibitors. Turk J Chem. 2021;45(3):528-539. doi:10.3906/kim-2009-37.
6. Frost SC. Physiological functions of the alpha class of carbonic anhydrases. Subcell Biochem. 2014;75:9-30. doi:10.1007/978-94-007-7359-2_2.
7. Párraga-Ros E, Latorre-Reviriego R, Aparicio-González M, et al. The immunolocalization of HIF-2α, GLUT1 and CAIX in porcine oviduct during the estrous cycle. Anat Rec (Hoboken). 2023;306(1):176-186. doi:10.1002/ar.25014.
8. Balandis B, Šimkūnas T, Paketurytė-Latvė V, et al. Beta and Gamma Amino Acid-Substituted Benzenesulfonamides as Inhibitors of Human Carbonic Anhydrases. Pharmaceuticals (Basel). 2022;15(4):477. doi:10.3390/ph15040477.
9. Venugopal DC, Ravindran S, Shyamsundar V, et al. Integrated Proteomics Based on 2D Gel Electrophoresis and Mass Spectrometry with Validations: Identification of a Biomarker Compendium for Oral Submucous Fibrosis-An Indian Study. J Pers Med. 2022;12(2):208. doi:10.3390/jpm12020208.
10. Riemann A, Güttler A, Haupt V, et al. Inhibition of Carbonic Anhydrase IX by Ureidosulfonamide Inhibitor U104 Reduces Prostate Cancer Cell Growth, But Does Not Modulate Daunorubicin or Cisplatin Cytotoxicity. Oncol Res. 2018;26(2):191-200. doi:10.3727/096504017X14965111926391.
11. Kalinin S, Malkova A, Sharonova T, et al. Carbonic Anhydrase IX Inhibitors as Candidates for Combination Therapy of Solid Tumors. Int J Mol Sci. 2021;22(24):13405. doi:10.3390/ijms222413405.
12. Mondal UK, Doroba K, Shabana AM, et al. PEG Linker Length Strongly Affects Tumor Cell Killing by PEGylated Carbonic Anhydrase Inhibitors in Hypoxic Carcinomas Expressing Carbonic Anhydrase IX. Int J Mol Sci. 2021;22(3):1120. doi:10.3390/ijms22031120.
13. Janoniene A, Petrikaite V. In Search of Advanced Tumor Diagnostics and Treatment: Achievements and Perspectives of Carbonic Anhydrase IX Targeted Delivery. Mol Pharm. 2020;17(6):1800-1815. doi:10.1021/acs.molpharmaceut.0c00180.
14. Supuran CT. Carbonic anhydrase inhibitors as emerging agents for the treatment and imaging of hypoxic tumors. Expert Opin Investig Drugs. 2018;27(12):963-970. doi:10.1080/13543784.2018.1548608.
15. Shaldam MA, Almahli H, Angeli A, et al. Discovery of sulfonamide-tethered isatin derivatives as novel anticancer agents and VEGFR-2 inhibitors. J Enzyme Inhib Med Chem. 2023;38(1):2203389. doi:10.1080/14756366.2023.2203389.
16. El-Hazek RMM, Zaher NH, Emam HES, et al. Pyrazole-sulfonamide scaffold featuring dual-tail strategy as apoptosis inducers in colon cancer. Sci Rep. 2023;13(1):5782. doi:10.1038/s41598-023-32820-0.
17. Denner TC, Heise N, Zacharias J, et al. Small Structural Differences Govern the Carbonic Anhydrase II Inhibition Activity of Cytotoxic Triterpene Acetazolamide Conjugates. Molecules. 2023;28(3):1009. doi:10.3390/molecules28031009.
18. Moskalik MY. Sulfonamides with Heterocyclic Periphery as Antiviral Agents. Molecules. 2022;28(1):51. doi:10.3390/molecules28010051.
19. Vasan N, Baselga J, Hyman DM. A view on drug resistance in cancer. Nature. 2019;575(7782):299-309. doi:10.1038/s41586-019-1730-1.
20. Mansoori B, Mohammadi A, Davudian S, et al. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. Adv Pharm Bull. 2017;7(3):339-348. doi:10.15171/apb.2017.041.
21. Roma-Rodrigues C, Mendes R, Baptista PV et al. Targeting Tumor Microenvironment for Cancer Therapy. Int J Mol Sci. 2019;20(4):840. doi:10.3390/ijms20040840.
22. Wojtkowiak JW, Verduzco D, Schramm KJ, Gillies RJ. Drug resistance and cellular adaptation to tumor acidic pH microenvironment. Mol Pharm. 2011;8(6):2032-2038. doi:10.1021/mp200292c.
23. Pillai SR, Damaghi M, Marunaka Y et al. Causes, consequences, and therapy of tumors acidosis. Cancer Metastasis Rev. 2019;38(1-2):205-222. doi:10.1007/s10555-019-09792-7.

24. Luo Y, Zhou LQ, Yang F, et al. Construction and analysis of a conjunctive diagnostic model of HNSCC with random forest and artificial neural network. Sci Rep. 2023;13(1):6736. doi:10.1038/s41598-023-32620-6.
25. Wen H, Ji T, Lin L, et al. High Expression of Ten Eleven Translocation 1 Is Associated with Poor Prognosis in Hepatocellular Carcinoma. Mediators Inflamm. 2023;2023:2664370. doi:10.1155/2023/2664370.
26. Liu X, Feng M, Hao X, et al. m6A methylation regulates hypoxia-induced pancreatic cancer glycolytic metabolism through ALKBH5-HDAC4-HIF1α positive feedback loop. Oncogene. 2023;42(25):2047-2060. doi:10.1038/s41388-023-02704-8.
27. Nan X, Liu Y, Gao Y, et al. Multiple epigenetic modification profiles reveal the tumor immune microenvironment and clinical outcomes of uveal melanoma. Front Genet. 2023;14:1155199. doi:10.3389/fgene.2023.1155199.
28. Manduca N, Maccafeo E, De Maria R, et al. 3D cancer models: One step closer to in vitro human studies. Front Immunol. 2023;14:1175503. doi:10.3389/fimmu.2023.1175503.
29. Gonzalez-Avila G, Sommer B, García-Hernández AA, et al. Matrix Metalloproteinases' Role in Tumor Microenvironment. Adv Exp Med Biol. 2020;1245:97-131. doi:10.1007/978-3-030-40146-7_5.

ORCID AND CONTRIBUTIONSHIP
Zainab Kifah Abbas: 0009-0003-5022-4184[B,C,D]
Noor H. Naser: 0000-0001-6148-3040[A,E]
Rana Neama Atiya: 0000-0002-5556-8424[A,E-F]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 26.05.2023
ACCEPTED: 11.09.2023

ADDRESS FOR CORRESPONDENCE
Zainab Kifah Abbas
Pharmaceutical Chemistry Department,
Faculty of Pharmacy, Kufa University, Najaf, Iraq
e-mail: z_k_abdulhadi@yahoo.com

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 533-541

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305113

EFFECTS OF PROFESSIONAL ORAL HYGIENE AND TEETH WHITENING ON THE MICROELEMENT COMPOSITION OF ENAMEL

Anna V. Dvornyk, Yaroslav Y. Vodoriz, Oleg A. Pysarenko, Iryna Y. Marchenko, Iryna M. Tkachenko

POLTAVA STATE MEDICAL UNIVERSITY, POLTAVA, UKRAINE

ABSTRACT

Aim: The objective of this study is to investigate the impact of professional teeth cleaning and the substances used in modern dentistry for whitening on the microelement composition of tooth enamel.

Materials and Methods: To study the morphology and microelement composition of the enamel, scanning electron microscopy was performed using the MiraLM microscope equipped with a Schottky field emission electron gun from Tescan.

Results: A comparative analysis between the areas subjected to mechanical cleaning and those where it was not applied revealed a significant difference in the research results, particularly in carbon, which changed from 25.16±1.04 to 32.02±1.8. An analysis of the enamel's chemical composition before and after whitening revealed a decrease in carbon from 45.91±1.20 to 42.46±1.74. The change in phosphorus content was determined to be from 9.77±0.39 to 9.56±0.75. A decrease in calcium from 15.96±0.64 to 15.21±1.22 and magnesium from 0.07±0.01 to 0.01±0.01 was also observed.

Conclusions: Professional dental hygiene does not have a direct impact on the microelement composition of enamel, such as the levels of calcium, phosphorus, fluoride, and other microelements. However, it can have an indirect and temporary influence due to the use of abrasive materials that affect dental deposits, pellicle, and the surface layer of enamel. Teeth whitening can affect the microelement composition of enamel, but these changes are mostly temporary and associated with processes of demineralization/remineralization and oxygenation.

KEY WORDS: tooth bleaching, teeth whitening, carbamide peroxide, hydrogen peroxide, electron scanning microscopy

INTRODUCTION

Oral health and dental care play a crucial role in overall well-being [1]. One key aspect is the regular cleaning of teeth, which includes not only daily brushing at home but also professional cleaning performed by dentists. Professional teeth cleaning is an important procedure aimed at removing plaque, tartar, and other deposits that accumulate on the tooth surfaces [2].

Recently, an increasing number of studies have focused on investigating the impact of professional teeth cleaning on the microelement composition of tooth enamel. Tooth enamel, which is the hardest tissue in the human body, consists of various microelements such as calcium, phosphorus, fluoride, and various trace elements. These microelements play a vital role in dental health by strengthening the enamel and preventing the occurrence of cavities and other dental problems [3].

Moreover, while being a popular procedure teeth whitening can have an impact on the microelement composition of enamel. The majority of whitening methods are based on the use of carbamide peroxide or hydrogen peroxide, which can penetrate the enamel and break down pigments, resulting in a change in tooth color. However, these substances can also affect the microelement composition of tooth enamel, which may lead to potential negative consequences in the future.

Significant attention is being given to studying the changes that occur in the microelement composition of tooth enamel after professional cleaning. However, further research is needed for a deeper understanding of the impact of professional cleaning on the microelement composition of enamel.

In this article, we will examine the impact of professional teeth cleaning and whitening on the microelement composition of tooth enamel, as well as explore the potential consequences of these procedures for dental health [4,5].

AIM

The objective of this study is to investigate the impact of professional teeth cleaning and the substances used in modern dentistry for whitening on the microelement composition of tooth enamel. Understanding these changes can be of significant importance for improving methods of prevention and treatment of dental diseases.

MATERIALS AND METHODS

To achieve the objective, 60 previously extracted anterior teeth were investigated. To prevent dehydration of the hard tissues, all samples were stored in a physiological solution under normal conditions [6].

All specimens were divided into three groups:

Group I included extracted teeth that underwent a professional hygiene procedure (10 samples).

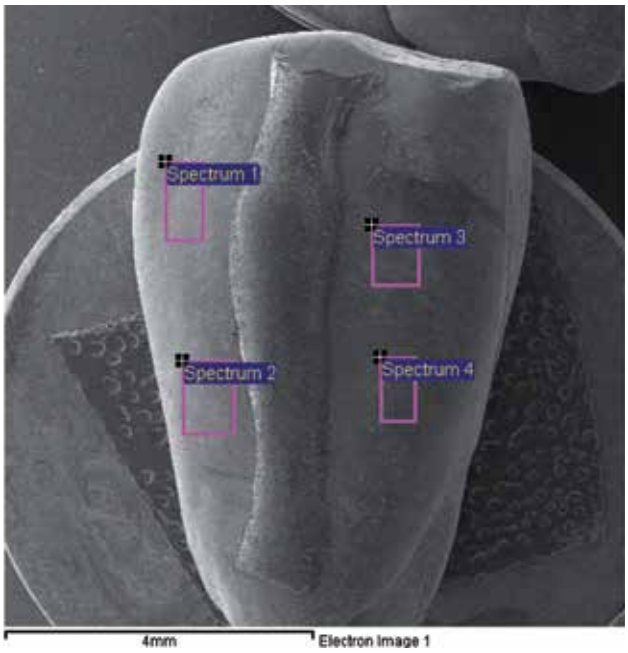


Fig. 1. Enamel surface of tooth 21 obtained by SEM with marked areas for surface elemental composition analysis.

Group II consisted of extracted teeth that underwent a prior professional hygiene procedure and were whitened using photoactivation with a 35% hydrogen peroxide (27 samples).

Group III included extracted teeth that underwent professional hygiene and were whitened using photoactivation with a 44% carbamide peroxide (23 samples).

The preparation process of the specimens involved the following steps:

1. Removal of hard and soft dental deposits was performed using an ultrasonic tip.
2. Enamel polishing was conducted using a medium--hardness nylon brush and Cleanic polishing paste (Kerr), with an RDA value of 27.
3 The professional whitening procedure was performed using a cold light lamp to activate the gel with either a 35% hydrogen peroxide concentration or a 44% carbamide peroxide concentration.

After the cleaning and whitening procedures, specific areas for microelement analysis of the enamel were determined (Fig. 1). In the examination of the microelement composition of the enamel, the studied tooth surfaces were divided into zones. The left half (Spectrum 1,2) served as the control zone, while the right half (Spectrum 3,4) served as the experimental zone. The boundary was established using liquid rubber dam.

For a detailed understanding of the changes in enamel morphology resulting from mechanical cleaning, a series of images were taken of the right and left sides of the tooth at various magnifications before and after the professional hygiene procedure (Fig. 2, 3).

After evaluating the morphological changes the determination of the microelement composition was

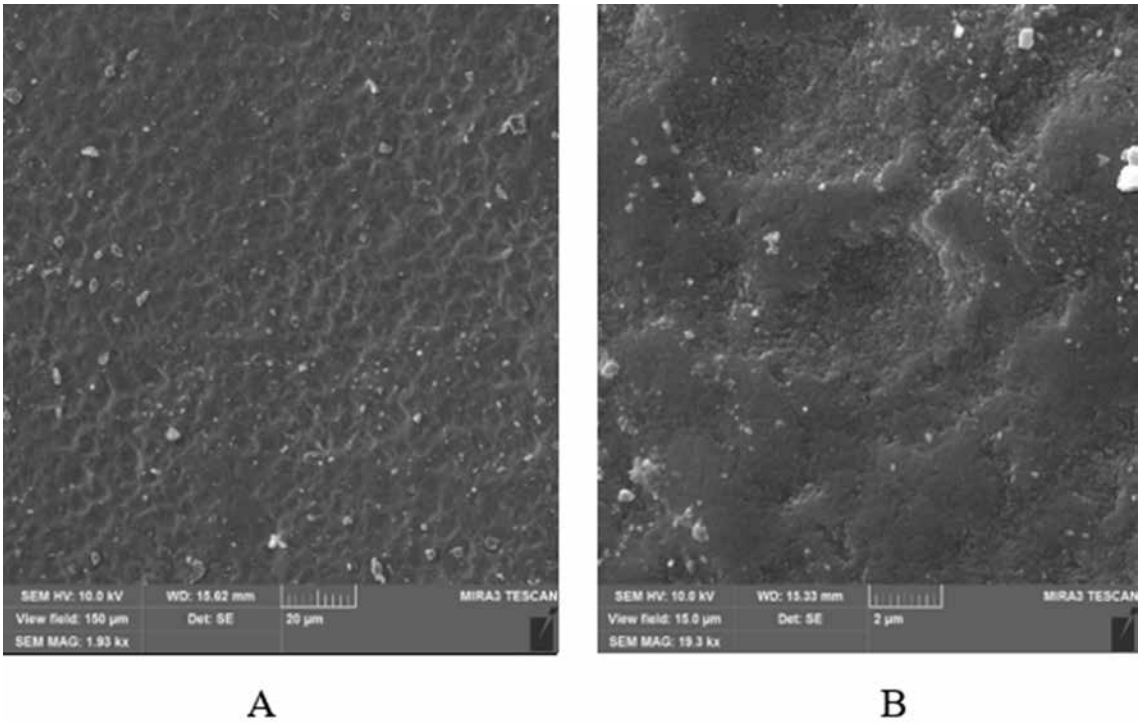


Fig. 2. Enamel surface of tooth 21 obtained by SEM (left side, before the mechanical cleaning procedure): A – 150 µm view field; B – field of view 150 µm view field.

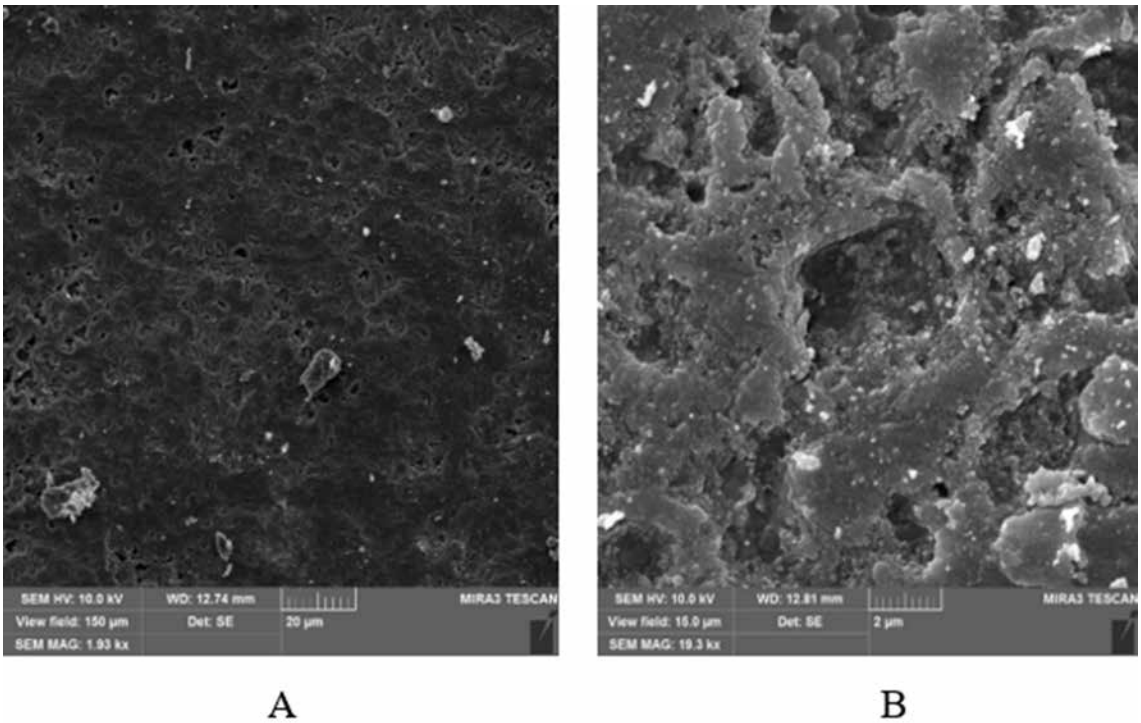


Fig. 3. Enamel surface of tooth 21 obtained by SEM (right side, after the mechanical cleaning procedure): A – 150 µm view field; B – field of view 150 µm view field.

carried out in selected areas on the right and left sides (Spectrum 1, 2, 3, 4) (Fig. 1).

To study the morphology and microelement composition of the enamel, scanning electron microscopy was performed using the MiraLM microscope equipped with a Schottky field emission electron gun from Tescan. The areas for microanalysis in the enamel zone were analyzed using the energy-dispersive spectrometer «X-max 80mm2» (Oxford Instruments, UK), which was integrated into the microscope.

After obtaining the results, they were subjected to statistical analysis using the analysis of variance (ANOVA) method. The data were recorded in the «Microsoft Excel 2010» program, and statistical calculations were performed using «IBM SPSS Statistics V22».

RESULTS

A comparative analysis between the areas subjected to mechanical cleaning and those where it was not applied revealed a significant difference in the research results, particularly in carbon, which changed from 25.16±1.04 to 32.02±1.8. This suggests surface changes in the enamel resulting from mechanical treatment without affecting the crystalline lattice of calcium hydroxyapatite but leading to the formation of free carbon ions that can further participate in chemical reactions. A significant difference was also found in the oxygen level, with initial values of 31.87±0.75 changing to 36.44±0.68, indicating a disturbance in the crystalline lattice of hydroxyapatite and increased activity towards interaction and substitution of certain microelements. This may have implications for the course and activity of chemical reactions with chemical whitening agents that have different compositions and activities, while the oxygen activity, as indicated, increases (Table 1).

For other chemical elements, certain changes in the indicators were observed. There was a slight increase in the amount of phosphorus, aluminum, and gold from 14.4 to 14.54, from 0 to 0.05, and from 0 to 1.37, respectively. Additionally, there was a slight decrease in the amount of chlorine, nitrogen, and magnesium from 0.86 to 0.79, from 0.25 to 0, and from 0.02 to 0, respectively. However, these changes were not statistically significant (Tab. 1, Fig. 3).

Analyzing the obtained data regarding the comparison of groups II and III (Fig. 4, 5), where different bleaching systems were used, the following changes in morphology and elemental indicators can be noted.

When comparing the indicators related to the chemical composition of the enamel before the whitening procedure and after the use of whitening agents such as 35% hydrogen peroxide, an evaluation of the obtained indicators regarding changes in the chemical composition was conducted. An analysis of the enamel's chemical composition before and after whitening revealed a decrease in carbon from 45.91±1.20 to 42.46±1.74. The change in phosphorus content was determined to be from 9.77±0.39 to 9.56±0.75. A decrease in calcium from 15.96±0.64 to 15.21±1.22 and magnesium from 0.07±0.01 to 0.01±0.01 was also observed. On the other hand, an increase was observed in the following elements: oxygen from 23.03 to 26.18, sodium from 0.38 to 0.57, silicon from 0.37 to 0.68, and nitrogen from 2.89 to 4.35.

When examining the statistical differences between the investigated trace elements, no significant differences

Table 1. Comparison of the average elemental composition in the studied group of teeth with mechanical cleaning

Researched trace elements	Native enamel,N = 10	Enamel after mechanical cleaning, N = 10	p
C	25,16±1,04	32,02±1,8	0,001
O	31,87±0,75	36,44±0,68	0,000
Na	0,49±0,04	0,49±0,02	0,998
P	14,40±0,48	14,54±0,31	0,805
Cl	0,86±0,07	0,79±0,06	0,458
Ca	23,75±0,88	23,67±0,52	0,941
Si	0,00±0,00	0,05±0,04	0,212
N	0,25±0,25	0,00±0,00	0,309
Mg	0,02±0,013	0,00±0,00	0,152
Al	0,00±0,00	0,01±0,01	0,168
Au	0,00±0,00	1,37±0,66	0,047

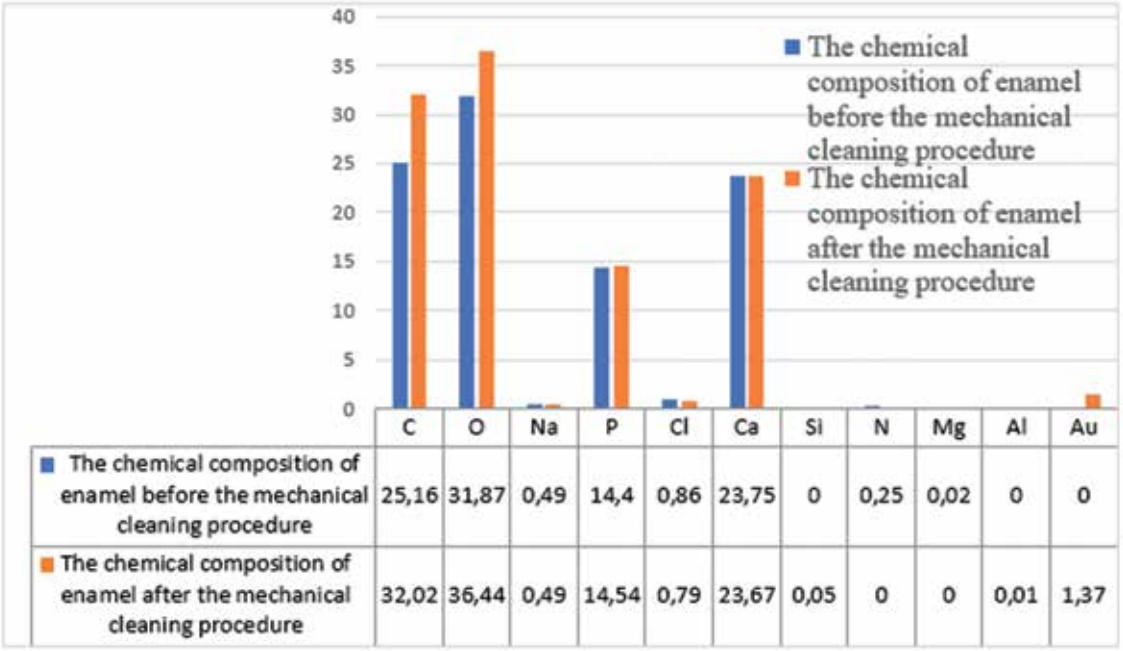


Fig. 4. Changes in the chemical composition of enamel before and after the mechanical cleaning procedure.

were found for the carbon indicators, which may indicate that carbon enters into a chemical reaction already after mechanical cleaning and the application of hydrogen peroxide as the main component of the whitening system, binding with active trace elements. Differences between the indicators relate to oxygen as one of the most active trace elements (p=0.007), sodium (p=0.06), which is responsible for retaining oxygen and hydrogen, as well as Mg, F, and Ba.

After conducting research using 35% hydrogen peroxide and 44% carbamide peroxide, differences in trace element indicators were observed before the whitening procedure and after its completion. The reliability of changes in trace element indicators and their list varied for the applied components of the whitening systems.

In Figure 6, we present a sample of enamel surface examination after professional tooth cleaning and the application of 44% carbamide peroxide.

We also observed differences in the morphological characteristics of enamel in the experimental teeth when using different types of whitening systems. The difference was evident when comparing images obtained after tooth whitening. Figures 7 (A and B) and 8 (A and B) present images of teeth treated with 38% hydrogen peroxide and 44% carbamide peroxide as whitening agents, respectively.

The electron micrographs provided show the same magnification but reveal different structures in terms of the distribution of the whitening agent on the enamel

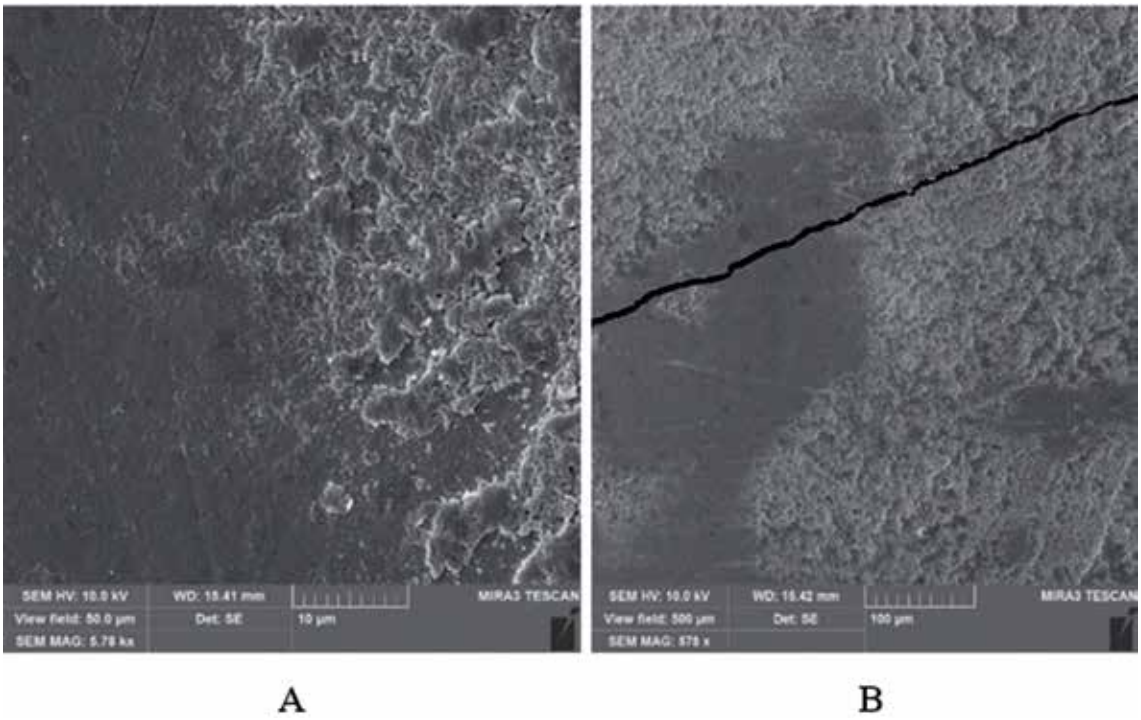


Fig. 5. Enamel surface of tooth 11 obtained by SEM (control zone): A – field of view 50 µm; B – field of view 500 µm.

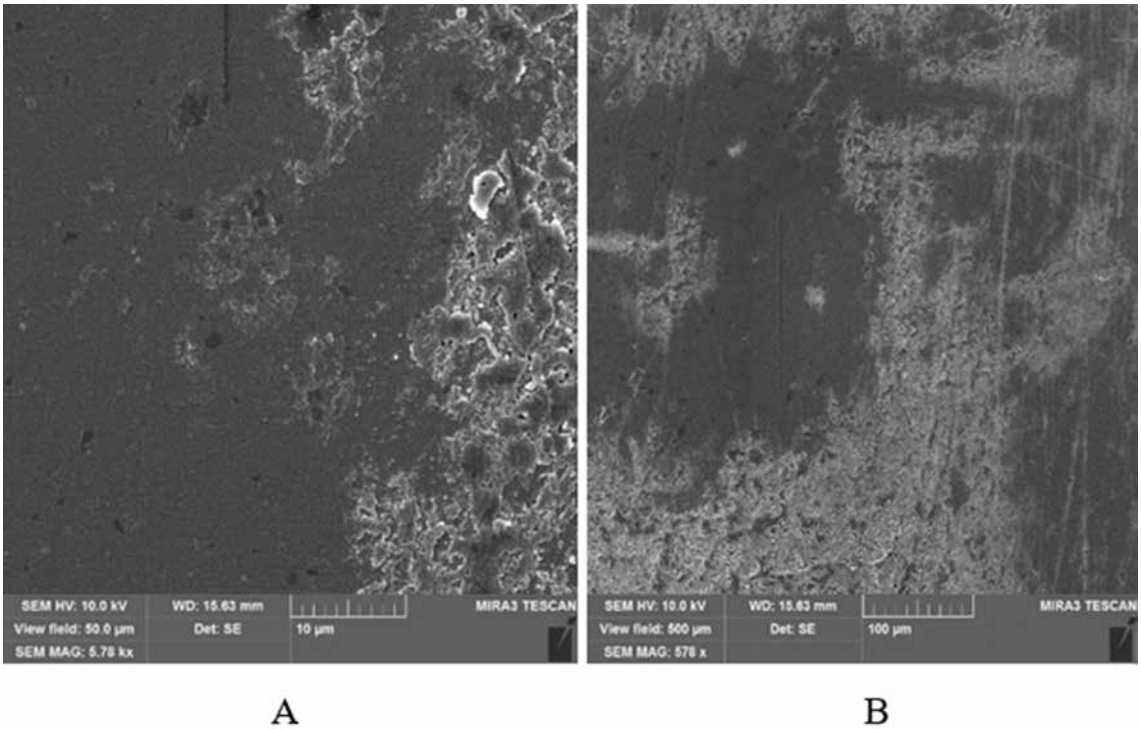


Fig. 6. Enamel surface of tooth 11, obtained by the SEM method (after professional cleaning and hydrogen peroxide application): A – field of view 50 µm; B – field of view 500 µm.

surface, which will subsequently lead to differences in the quantity of microelements on the enamel surface.

Table 2 presents a comparison of the enamel's chemical composition indicators in normal conditions and when using whitening agents with 44% carbamide peroxide and 35% hydrogen peroxide.

The study revealed a significant decrease in the levels of carbon, oxygen, sodium, chlorine, magnesium, and aluminum ($p \leq 0.05$). There was also a slight decrease in the level of nitrogen from 2.17±0.25 to 1.54±0.47 and an increase in the level of magnesium from 0.04±0.01 to 0.1±0.03. The alteration of these indicators will significantly impact

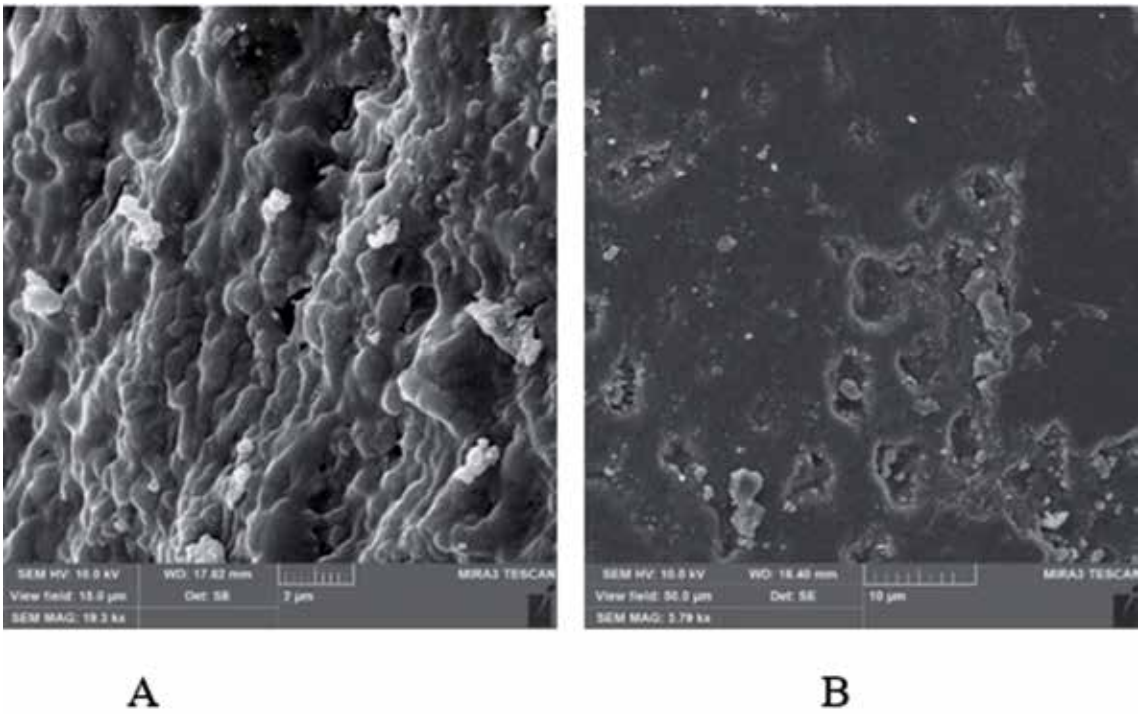


Fig. 7. Enamel surface of tooth 21 enamel obtained by the SEM method after professional cleaning and application of 44% carbamide peroxide: A – field of view 15 μm; B – field of view 50 μm.

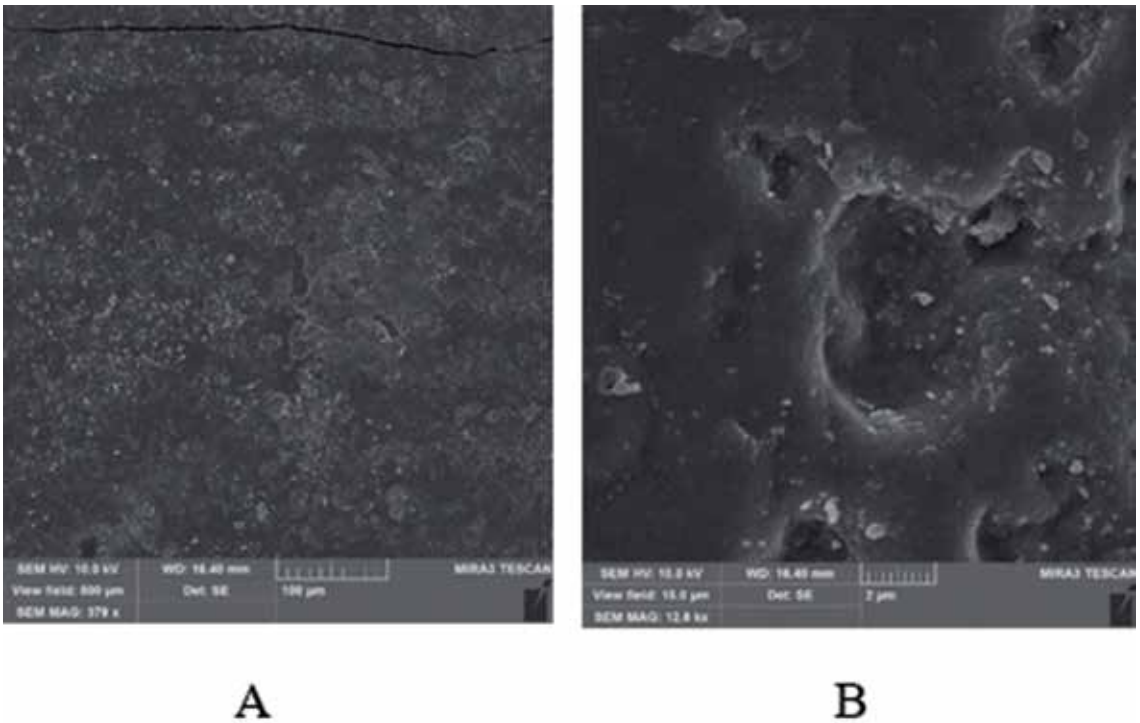


Fig. 8. Enamel surface of tooth 11 obtained by the SEM method, the research protocol, the area after professional cleaning and application of carbamide peroxide: A – field of view 500 μm; B – field of view of 15 μm

the clinical indicators and manifestations, depending on the characteristics of enamel's functional and structural resistance.

Additionally, the calcium content increased in Group III (18.81±0.48) compared to the experimental samples in Group II (15.21±1.22). As for nitrogen levels, a significant difference was observed: the level for Group II was 4.35±0.76, while for Group III, it was 1.54±0.47.

Through the analysis of microelements in the experimental groups using different whitening systems, statistically significant differences in carbon levels were found: from 42.46±1.74 when using hydrogen peroxide to 44.92±1.90 when using

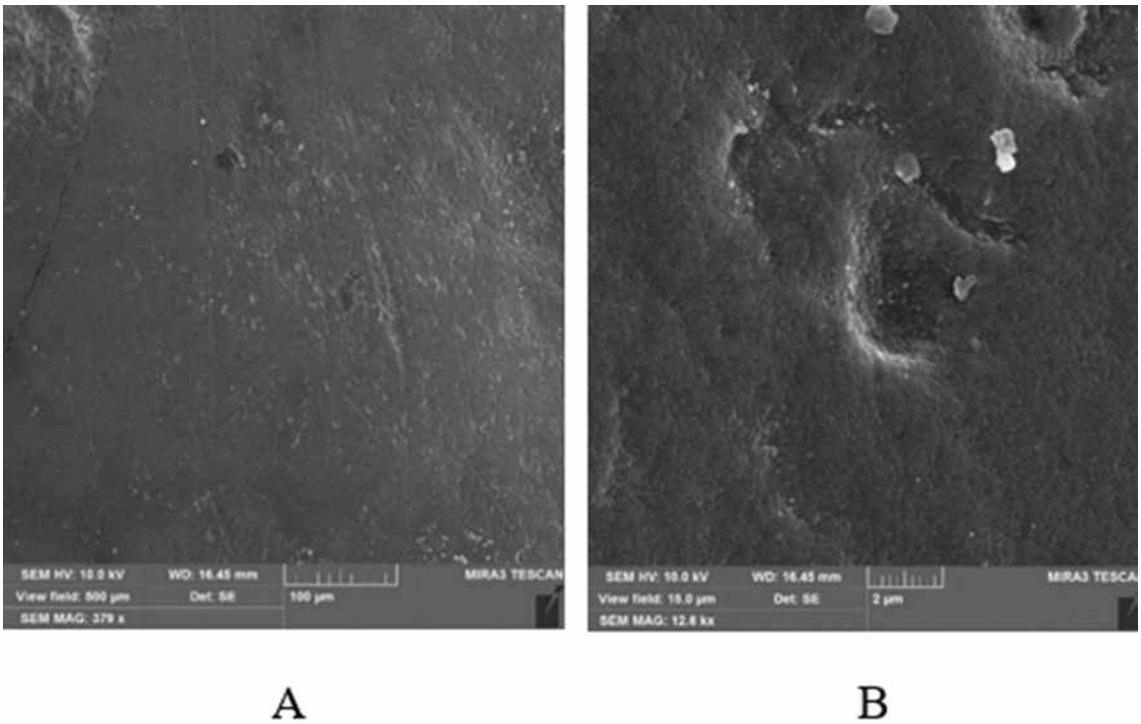


Fig. 9. Enamel surface of tooth 21 obtained by SEM, zone after professional cleaning and application of carbamide peroxide: A – field of view 500 µm; B – field of view of 15 µm

Table 2. Comparison of the average elemental composition of tooth enamel in normal conditions and after the application of bleaching agents with hydrogen peroxide 35% and carbamide peroxide 44% between the study indicators (M±m), (data are given in weight %)

Researched trace elements	Microelement composition of enamel before the whitening procedure (N =50)	Microelement composition of enamel after hydrogen peroxide application (N=27)	Microelement composition of enamel after carbamide peroxide application (N=23)	p
C	45,91±1,20	42,46±1,74	44,92±1,90	0,008
O	23,03±0,63	26,18±0,81	20,74±1,01	0,007
Na	0,38±0,03	0,57±0,05	0,224±0,03	0,006
P	9,77±0,39	9,56±0,75	12,11±0,51	0,792
Cl	0,14±0,03	0,16±0,53	0,19±0,06	0,654
Ca	15,96±0,64	15,21±1,22	18,81±0,48	0,570
Si	0,37±0,10	0,68±0,30	0,16±0,098	0,213
N	2,89±0,40	4,35±0,76	1,54±0,47	0,075
Mg	0,07±0,01	0,01±0,01	0,01±0,03	0,034
Al	0,06±0,02	0,09±0,04	0,01±0,00	0,475
Au	0,37±0,56	0,00±0,00	0,37±0,66	0,143
F	0,00±0,00	0,02±0,01	0,05±0,03	0,004
Ba	0,00±0,00	0,45±0,25	0,38±0,00	0,004

whiteners based on 44% carbamide peroxide at p=0.008. Changes in oxygen levels were also observed, from 26.18±0.81 to 20.74±1.01, with a significance difference of 0.007. The sodium content changed from 0.57±0.05 to 0.224±0.03 at p=0.006, and the fluoride quantity changed from 0.02±0.01 to 0.05±0.03 with a significance difference of 0.004.

Evaluating the obtained indicators when comparing Groups II and III where different whitening systems were used we can mention changes in the indicators for phosphorus: 9.56±0.75 for Group II and 12.11±0.51 for Group III. There was an increase in the level of calcium in Group III: 18.81±0.48 compared to 15.21±1.22 in the experimental samples of

Group II. A significant difference in nitrogen levels can be observed: the level for Group II was 4.35±0.76, while for Group III, it was 1.54±0.47.

By analyzing the microelement indicators in the experimental groups using different whitening systems, statistically significant differences were obtained for carbon levels, ranging from 42.46±1.74 when using hydrogen peroxide to 44.92±1.90 when using whiteners based on 44% carbamide peroxide (p=0.008). There were changes in oxygen levels, from 26.18±0.81 to 20.74±1.01, with a significance difference of 0.007. The sodium content changed from 0.57±0.05 to 0.224±0.03 at p=0.006 and the fluoride quantity changed from 0.02±0.01 to 0.05±0.03 with a significance difference of 0.004.

These changes in the indicators will significantly impact the alteration of clinical indicators and clinical manifestations.

DISCUSSIONS

The observed significant differences in carbon and oxygen levels may indicate surface changes in the enamel that are likely not associated with changes in the microelement composition of tooth enamel but rather with the breakdown of dental plaque (pellicle) and mineralized dental deposits on its surface, as evidenced by electron micrographs (Fig. 1, 2) [7].

After professional teeth cleaning, the temporary increase in the quantity of free carbon and oxygen ions on the tooth enamel should be associated with the process of oxygenation, i.e., improved oxygen access to the tooth enamel. This phenomenon may have a beneficial effect on the condition of the tooth enamel [8]. Free carbon ions can contribute to the neutralization of acidic substances and reduce the risk of developing caries, while oxygen ions can have antimicrobial effects and promote gum healing and overall oral health [9]. Cleaning the enamel surface also improves the access of whitening agents, adhesive systems, and conditioning solutions to the enamel, thereby increasing their effectiveness [10].

Regarding the change in the microelement composition of enamel after whitening, it should be noted that as a result of the chemical reactions of bleaching agents with organic substances in the enamel, the breakdown of carbonates and the removal of carbon from the enamel structure may occur. This leads to a decrease in carbon content in the enamel after whitening [3,11].

During the interaction of hydrogen peroxide with enamel, its molecules decompose, releasing oxygen (O_2) molecules. This oxygen can penetrate the structure of tooth enamel, increasing the amount of oxygen present in the enamel. This process occurs through the oxidation of organic compounds contained in the enamel and the alteration of their chemical structure. When carbamide peroxide interacts with enamel and stains on the tooth surface, it breaks down into carbamide molecules and oxides. The oxides can be released in the reaction process, leading to the removal of stains and pigments on the teeth. The formed oxides may contain oxygen, which can result in a decrease in the amount of oxygen in the enamel [3,11].

Tooth whitening with carbamide peroxide may cause a decrease in sodium content in tooth enamel because when carbamide peroxide interacts with enamel and stains on the tooth surface, it breaks down into carbamide molecules and oxides. These oxides can interact with enamel minerals, including sodium, and contribute to their removal from the enamel. This can lead to a reduction in the amount of sodium in the enamel after whitening [12].

CONCLUSIONS

Professional dental hygiene does not have a direct impact on the microelement composition of enamel, such as the levels of calcium, phosphorus, fluoride, and other microelements. However, it can have an indirect and temporary influence due to the use of abrasive materials that affect dental deposits, pellicle, and the surface layer of enamel.

Mechanical cleaning and teeth whitening with various systems can affect the microelement composition of tooth enamel. The use of hydrogen peroxide during teeth whitening can increase the amount of oxygen in dental enamel. This may be related to the oxidizing properties of hydrogen peroxide, which promote changes in the chemical structure of enamel. The use of carbamide peroxide during teeth whitening can decrease the amount of oxygen in dental enamel. The reasons for this effect may be related to the peculiarities of the chemical reaction that occurs during the interaction of carbamide peroxide with enamel.

For discolorations, both external and internal, mechanical cleaning methods and chemical agents can be used. In our study, a comparison of the chemical composition of the tooth enamel surface was performed when using professional hygiene and the application of carbamide peroxide and hydrogen peroxide as chemical components of the system for influencing tooth enamel.

After conducting experimental research and establishing discrepancies regarding the main elements, we may be able to choose whitening agents in a dental clinic based on clinical and laboratory research data, with appropriate prescription of remineralizing agents with a specified quantity of chemical elements depending on the choice of the whitening component.

Overall, it may be concluded that teeth whitening can affect the microelement composition of enamel, but these changes are mostly temporary and associated with processes of demineralization/remineralization and oxygenation.

REFERENCES

1. Vodoriz Y, Lemeshko A, Marchenko I, Shyndryk M, Tkachenko I, Kov. Assessment of quality of life in patients who require treatment in anterior dentition. Visnyk problem biolohiyi i medytsyny. 2019;4(1):296-300.
2. Bali C, Gurdet C, Hauer G, Handler I, Fischer R. Evaluation of the effect of professional dental cleaning and education in dental hygiene in type 1 diabetic patients. Acta Med Austriac. 1999;26(5):159-62.

3. Dvornyk A V, Tkachenko IM, Pysarenko OA, Vodoriz YY, Dvornyk VM, Brailko NM. Experimental study of changes in the chemical composition of tooth enamel when using hydrogen peroxide as the main chemical component in professional bleaching. Wiad Lek. 2022;75(7):1683-7.
4. Reitznerová E, Amarasiriwardena D, Kopčáková M, Barnes RM. Determination of some trace elements in human tooth enamel. Fresenius J Anal Chem. 2000;367(8):748–54. doi:10.1007/s002160000461.
5. Teutle-Coyotecatl B, Contreras-Bulnes R, Rodríguez-Vilchis LE, Scougall-Vilchis RJ, Velazquez-Enriquez U, Almaguer-Flores A, et al. Effect of Surface Roughness of Deciduous and Permanent Tooth Enamel on Bacterial Adhesion. Microorganisms. 2022;10(9).
6. Flores MT, Malmgren B, Andersson L, Andreasen JO, Bakland LK, Barnett F, et al. Guidelines for the management of traumatic dental injuries. III. Primary teeth. Dent Traumatol. 2007;23(4):196-202.
7. Fischer NG, Aparicio C. The salivary pellicle on dental biomaterials. Colloids Surfaces B Biointerfaces. 2021;200:111570.
8. Sundfeld D, Pavani CC, Pavesi Pini NI, Machado LS, Schott TC, Bertoz AP de M, et al. Esthetic recovery of teeth presenting fluorotic enamel stains using enamel microabrasion and home-monitored dental bleaching. Vol. 22, Journal of conservative dentistry : JCD. India; 2019. p. 401-5.
9. Chen H, Gu L, Liao B, Zhou X, Cheng L, Ren B. Advances of Anti-Caries Nanomaterials. Molecules. 2020;25(21):5047. doi: 10.3390/molecules25215047.
10. Mushashe A-M, Coelho B-S, Garcia P-P, Rechia B-CN, da Cunha L-F, Correr G-M, et al. Effect of different bleaching protocols on whitening efficiency and enamel superficial microhardness. J Clin Exp Dent. 2018 Aug;10(8):e772-5.
11. Mayer-Santos E, Maravic T, Comba A, Freitas PM, Marinho GB, Mazzitelli C, et al. The Influence of Different Bleaching Protocols on Dentinal Enzymatic Activity: An In Vitro Study. Molecules. 2022 Mar;27(5).
12. Dvornyk A V., Dvornyk VM, Vodoriz YY, Skripnykov PM, Tkachenko IM. Clinical Features of Influence of Different Groups of Bleaching Agents in the Oral Cavity At Different Periods After the End of the Treatment. World Med Biol. 2022;18(80):56.

ORCID AND CONTRIBUTIONSHIP
Anna V. Dvornyk: 0000-0002-3660-3239[A,B]
Yaroslav Y. Vodoriz: 0000-0001-9388-1270[C,D]
Oleg A. Pysarenko: 0000-0002-6104-6745[E,C]
Iryna Y. Marchenko: 0000-0001-7092-1786[A,E]
Iryna M. Tkachenko: 0000-0001-8243-8644[A,E,F]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 27.04.2023
ACCEPTED: 03.09.2023

ADDRESS FOR CORRESPONDENCE
Iryna M. Tkachenko
Poltava State Medical University
23 Shevchenko St., 36011 Poltava, Ukraine
e-mail: tkachenkoirmix@gmail.com

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 542-547

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305114

CONSIDERATION OF THE PECULIARITIES OF A PERSON WITH POST-TRAUMATIC STRESS DISORDER IN MEDIATOR`S PROFESSIONAL ACTIVITY

Vitalii M. Pashkov[1], Olha V. Hubanova[2], Svitlana M. Buzhynska[2]

[1]POLTAVA LAW INSTITUTE OF YAROSLAV MUDRIY NATIONAL LAW UNIVERSITY, POLTAVA, UKRAINE

[2]MUNICIPAL ESTABLISHMENT «KHARKIV HUMANITARIAN-PEDAGOGICAL ACADEMY» OF THE KHARKIV REGIONAL COUNCIL, KHARKIV, UKRAINE

ABSTRACT

Aim: To study and take into account the behavioral characteristics of a person with post-traumatic stress disorder (PTSD) during the mediation procedure and to experimentally test the peculiarities of PTSD in young adults and to study the causal relationship between PTSD and personality resilience.

Materials and Methods: The diagnosis was carried out using the methods of diagnosing resilience (S. Muddy in the adaptation of D. Leontiev) and the Mississippi Scale for Combat-Related PTSD. Statistical analysis was performed using the statistical software package STATISTICA 10. The analysis of the study results included the distribution of the results of the arithmetic mean and the identification of correlations using Pearson's correlation coefficient. The obtained empirical data were processed qualitatively and quantitatively.

Results: In the course of the study we found that mediation is the best alternative way to resolve legal disputes with a person with PTSD, as the mediator creates a safe space, an atmosphere of trust, helps to cope with emotions, and, through questioning and other techniques, forms a conscious attitude towards their own needs and interests. Such interaction is empathetic and non-traumatic for a person with PTSD who is a party to mediation. It has been established that the level of PTSD manifestation in young adults affects their level of resilience.

Conclusions: mediator's work with a person with PTSD requires more activity on the part of the mediator, empathic communication, and possession of skills in dealing with psychotrauma. All decisions made as a result of mediation will be aimed at satisfying the basic need for safety of such a person.

KEY WORDS: traumatic event, post-traumatic stress disorder, mediation, resilience, psychotherapy

INTRODUCTION

The war in Ukraine has caused and continues to cause massive psychological trauma to the civilian and military population of the country. Since the beginning of hostilities, a huge number of Ukrainians have been left homeless and have suffered physical and mental trauma. According to the report of the Ministry of Reintegration of the Temporarily Occupied Territories of Ukraine [1], 4,867,106 internally displaced persons (IDPs) are officially registered in Ukraine today, and international estimates put the number of internally displaced persons at over 7 million. Another 4 million people have registered for temporary protection in Europe. Such a high level of stress on the adaptive mechanisms of the psyche during the war has already caused and is likely to cause the development of stress disorders in Ukraine in the post-war years, which will manifest itself through social maladjustment, an increase in the number of offenses, and the development of psychosomatic disorders, in particular, manifestations of post-traumatic stress disorder (hereinafter referred to as PTSD). The symptoms of PTSD significantly affect a person's behavior in everyday life, can be unexpected and unpredictable in the system of social relations, and as a result, can become a prerequisite for conflicts.

One of the forms of conflict is a legal dispute, and mediation is an effective alternative way to resolve legal disputes. European countries, such as Poland, France, Germany, Italy, Lithuania, and Latvia, which actively accept IDPs from Ukraine, have long been using mediation as an alternative way to resolve legal disputes (conflicts). Ukraine, which adopted the Law of Ukraine "On Mediation" on November 16, 2021 [2], is no exception, as its development has been slowed down by the current socio-political situation, on the one hand, and posed challenges to mediators due to the peculiarities of working in wartime, on the other. Therefore, combining these two different phenomena (the presence of a significant number of people with PTSD and mediation), we note that it is important to study the peculiarities of a mediator's work with parties, one or both of whom are people with PTSD. At the same time, it is important to clarify both the possibility of conducting a mediation procedure and, if the answer is yes, the specifics of the mediator's role in it.

The analysis of scientific research has made it possible to assert that the problem of the peculiarities of mediator's work with parties, one or both of whom are persons with PTSD, is relevant in modern psychological science, but insufficiently studied.

AIM

The purpose of the article is to theoretically substantiate the peculiarities of a mediator's interaction with a person with PTSD; to empirically study the level of PTSD manifestation and resilience in young adults; to test the means of non-violent communication in mediation with a person who has experienced a traumatic event**.**

MATERIALS AND METHODS

The experimental study was conducted on the basis of the Municipal Institution "Kharkiv Humanitarian and Pedagogical Academy" of the Kharkiv Regional Council and the Poltava Law Institute of the Yaroslav Mudryi National Law University of Ukraine during the academic year 2022-2023. The experimental sample included 60 students aged 20 to 40 years, studying in different faculties.

The diagnostics were performed using the methods of diagnosing resilience (S. Muddy in the adaptation of D. Leontiev), which is an adaptation of the Hardiness Survey developed by S. Muddy. Resilience characterizes the degree of a person's ability to withstand psychological stress during a stressful situation without reducing the effectiveness of their activities and maintaining internal balance. The resilience test contains 45 questions, the answers to which are interpreted on a four-point Likert scale. The scoring system used was from 0 to 3.

The Mississippi Scale for Combat-Related PTSD was developed by N.M. Kean, J.M. Caddell, and K.L. Taylor, is based on the MMPI and has 39 questions and three main scales that correlate with the manifestations of PTSD: the questions of the first scale describe the symptoms of the "invasion" group, the questions of the second – the symptoms of the "avoidance" group, the questions of the third – the symptoms of "excitability", 5 questions describe symptoms related to guilt and suicidal tendencies. Respondents are asked to indicate how much they agree or disagree with the statements from "1" to "5". The sum of the scores allows us to identify those with PTSD and those without.

Statistical analysis was performed using the statistical software package STATISTICA 10. The analysis of the study results included the distribution of the results of the arithmetic mean and the identification of correlations using Pearson's correlation coefficient.

The theoretical basis of the psychodiagnostic work was the scientific works of foreign scientists (A. Shalev, R. Bryant, D. Delahanty, M. Olff, S. Seedat, T. de Roon-Cassini, R. Kessler, V. Laroson); works by G. Selye, M. Horowitz, J. Mitchell, R. Yanof-Burman, L. Kitaeva-Smyk, R. Lazarus; studies of domestic scientists (I. Malkina-Pikh, O. Morozov, V. Omelyanovych, N. Tarabrin, O. Timchenko, S. Yakovenko).

RESULTS

An event in which a person believes that there was a clear threat to his/her life/health or the life/health of a loved one, or a person was sure or thought that it was a clear threat, is called a traumatic event [3]. For most people who have experienced a traumatic event symptoms subside over time, the psyche recovers and stabilizes, but for some people who have experienced a traumatic event, symptoms persist and worsen, indicating a transition to more severe conditions, including PTSD.

According to the ICD-10 Research Diagnostic Criteria (WHO, 1992), post-traumatic stress disorder (F43.1) is a delayed or prolonged reaction to a stressful event or situation of an exceptionally threatening or catastrophic nature that can cause distress in almost anyone. This mental disorder develops in some people after traumatic events such as natural and man-made disasters, shelling, bombing and other threats to life during war, sexual or physical abuse, traffic accidents, torture, etc., that have caused intense fear, helplessness or terror. Other emotional reactions include guilt, shame, anger, or emotional numbness [4].

In May 2013, the DSM-V was published with significant changes to the criteria for diagnosing PTSD. A fifth cluster of symptoms was added to the four previously edited symptom clusters, which includes negative changes in cognition and emotions. Given that it was American psychiatrists who, after their experience with the consequences of the Vietnam War, first officially introduced the term post-traumatic disorder into the DSM in 1980, as well as the large number of studies they have already conducted, the vast majority of psycho-diagnostic methods developed are based on this classification, compared to the ICD-10 developed by the WHO.

In the context of the current socio-political situation in Ukraine we can state that the risk group for the development of PTSD is internally displaced persons and refugees; military personnel and their families; civilians in the combat zone; victims of sexual and/or physical violence; prisoners and victims of torture; witnesses of terrorist attacks; rescue workers, etc.

In Ukraine, the issue of working with patients with PTSD is regulated by the Unified Clinical Protocol for Primary, Secondary (Specialized) and Tertiary (Highly Specialized) Medical Care (hereinafter – UCPMC), which was developed on the basis of the adapted clinical guideline "Posttraumatic Stress Disorder" and focuses on the organization of medical care for patients in accordance with international clinical guidelines: 1. Australian Guidelines for the Treatment of Adults with Acute Stress Disorder and Posttraumatic Stress Disorder, 2013, developed in accordance with NICE CG26 "Post-traumatic stress disorder. The management of PTSD in adults and children in primary and secondary care" (2005) 2. VA/DoD Clinical Practice Guideline for the Management of Post-Traumatic Stress, 2010 4. Inter-Agency Standing Committee Guidelines (2007); European Network for Traumatic Stress Guidelines (TENTS, 2008); The Disaster Mental Health Subcommittee (2009) [5]. In the section of the UCPMC "Response to severe stress and adjustment disorders. Posttraumatic Stress Disorder", PTSD is defined similarly to the above-mentioned ICD-10 Research Diagnostic Criteria (WHO, 1992).

PTSD is experienced by individuals in different ways. Some people involuntarily relive aspects of the traumatic event in a very vivid way that causes them distress (flashbacks, nightmares, disturbing intrusive images). Others try to push memories of the event, especially the worst moments, out of their minds. Some people with PTSD complain of symptoms of emotional numbness (lack of ability to feel emotions, detachment from other people, loss of memory of the event). PTSD is also manifested by excessive agitation, difficulty concentrating, and sleep problems [4, p. 13-14]. Recent studies demonstrate that PTSD manifestations are masked by eating disorders (bulimia, anorexia), when distress and negative cognitions contribute to either overeating or, conversely, refusal to eat [6; 7].

Summarizing the symptoms of PTSD, we can distinguish the following basic symptoms: repeated experiences, avoidance and emotional numbness, and excessive arousal [5]. S. Suliman divided these symptoms into two categories: those that "make noise" and those that demonstrate "withdrawal and silence". The first group includes movement, excitement, explosive anger, violence, nightmares, and terror (hyperarousal symptoms); the second is associated with sadness, isolation, loss of concentration and memory, difficulty thinking, and crying (avoidance and obsessive symptoms). [8].

PTSD is diagnosed no earlier than one month after the traumatic event, but people with PTSD may not seek help for several months or even years after the onset of symptoms, despite the significant distress they experience [4].

Taking into account the above-mentioned contingent of persons who are at risk for developing PTSD, symptoms and related changes in behavioral reactions, we understand that the range of legal disputes in which a person with PTSD may become a subject is quite wide: from family, labor, civil and other private law disputes to administrative and criminal disputes. In view of the above, we can hypothesize that mediation is the best alternative way to resolve legal disputes (conflicts) with a person with PTSD, because the mediator creates a safe space for discussing the disputed issue, an atmosphere of trust, helps to cope with emotions, and forms a conscious attitude to one's own needs and interests through questioning techniques and other techniques. Such interaction is empathetic and not traumatic for a person with PTSD who is a party to the mediation.

DISCUSSION

The UCPMC indicates that the main method of treatment of PTSD is psychotherapy, which should be used in the complex treatment and rehabilitation of such patients [5, p.11]. Therefore, in our opinion it is necessary to analyze certain scientific studies on trauma work in order to understand the peculiarities of the behavior of a person with PTSD, as well as the purpose of psychotherapeutic work with him or her.

Gestalt trauma therapy is based on the idea that psychological trauma is a consequence of the loss or blocking of the process of experience, which is accompanied by a complex of mental phenomena, so the psychotherapeutic strategy is aimed at the client's contact with the environment (therapist and the client's social environment) [9].

The behavioral approach focuses on the client's stimuli and phobias [10], they are offered to deal with unpleasant situations by teaching them to relax [9].

In Viktor Frankl's logotherapy, trauma psychotherapy is about finding the life meaning lost during traumatization. The method is based on the concepts of the meaning of life, free will, will to meaning, fear, existential emptiness, self-transcendence, conscience, and the method of paradoxical intention. [11].

In the existential psychotherapy of work with trauma (L. Biswanger and R. May), there are three modes of the world: 1) the external world (the real world, including instincts, biological needs, and aspirations); 2) the world shared with others (the social world of relationships and communication); 3) the internal world (the subjective world of a person). This type of therapy focuses on long-term work and takes place in a group setting [12].

Client-centered therapy by C. Rogers focuses on empathy, congruence, psychological climate, and self. One of the important methods is reflective techniques [10].

Body-oriented approaches are actively used in somatic therapy for mental trauma. Its task is to identify energy that blocked in the body and create conditions for its unblocking. That is, a person changes their attitude, which affects the quality of their life and development [13].

Cognitive psychotherapy is based on helping the client learn to think correctly, analyzing objectivity, focusing on specific problems and relationships [13]. The main task of psychotherapy is to teach the client to identify maladaptive signs and automatically correct them [14]. For example, to redefine hot spots during an oral story ("Now I know that..."), or to do it mentally imagining that the wounds have healed and the offender is in prison [14].

Israeli trauma specialists use the method of salutogenesis, which is based on mental health and access to human resources. The therapeutic process is aimed at finding activity, i.e., the specialist creates conditions for maintaining not only mental but also physical health [15].

Another psychotherapeutic method of dealing with trauma is integrative community therapy, which is based on the mutual exchange of life experience between participants, with a key role played by a mediator. This method provides a safe space, a sense of community, and social support, as a result of which people realize their resources and, accordingly, their resilience to the problem increases, which has a positive impact on both their psychological and emotional state and health [16].

Based on the above, we can state that each theoretical paradigm has its own understanding of the essence of trauma and possible strategies for dealing with it. Therefore, it is important to clearly understand the specifics and psychological essence of a traumatized person, his or her personal characteristics, and the essential features of psychotherapeutic relationships. It is also necessary to note the influence of personal self-actualization on the choice of ways of responding in stressful life situations: the higher

Table 1. Distribution of diagnostic results according to the S. Muddy resilience method in young adults

Levels	Sub-scales			
	Involvement	Control	Acceptance of risk	Resilience
Low	17%	14%	–	16%
Medium	21%	31%	57%	44%
High	62%	55%	43%	40%

the level of personal development, the more successfully they overcome difficulties. That is, styles of response in psychologically stressful situations are related to attitudes toward other people and oneself, experiences, attitudes, life experience, emotional, behavioral, and cognitive levels of the psyche structure.

After diagnosing the level of personality resilience according to S. Muddy's methodology in the adaptation of D. Leontiev, the following results were obtained (Table 1).

Analyzing the results presented in Table 1, we note that no one showed a low level on the Risk Acceptance subscale, while there were more respondents with a low level on other scales. The majority of respondents showed an average level on the same subscale of Risk Acceptance. Only the Involvement subscale revealed a high level. The data obtained are evidence of a dynamic balance between positive and negative processes aimed at maintaining the integrity and positive development of self-attitude and self-concept. It is obvious that positive social experiences stimulate the emergence of positive individual experiences (attitude towards oneself), increase the degree of differentiation of personal identity, helping to maintain its adequacy and integrity. At the same time, negative social experiences play an equally important role in the development of destabilizing processes of the self-concept, which may be associated with the displacement of negative ideas about oneself.

The results of the Mississippi PTSD Scale diagnosis in young adults are shown in Fig. 1.

Analyzing the results shown in Fig. 1 it can be argued that most of the respondents among young adults have a low potential level of PTSD manifestation, 40% demonstrated an average level and, unfortunately, 15% demonstrated a high level of PTSD manifestation.

Analyzing the relationship between the scales of resilience of young adults and the level of PTSD manifestation, the following results were obtained (Table 2).

Analyzing Table 2, we can see that there is a significant correlation between the level of PTSD manifestation and the "control" scale ($r = 0.3637$; $p<0.05$), and a strong correlation between the level of PTSD manifestation and "resilience" ($r = 0.4796$; $p<0.01$). The obtained results show that there is a direct correlation between the psychological phenomenon of resilience and PTSD manifestations in young adults, proven at a statistically significant level.

Thus, it has been established that the level of PTSD manifestation in young adults affects their level of resilience. That is, provided that the specifics and psychological essence of the traumatized person, his or her personal characteristics, and the essential features of psychotherapeutic relationships when working with a traumatized person are understood, a shift towards reducing the level of PTSD manifestation in young adults and thus stabilizing the client's emotional state is possible, which confirms the purpose of our study.

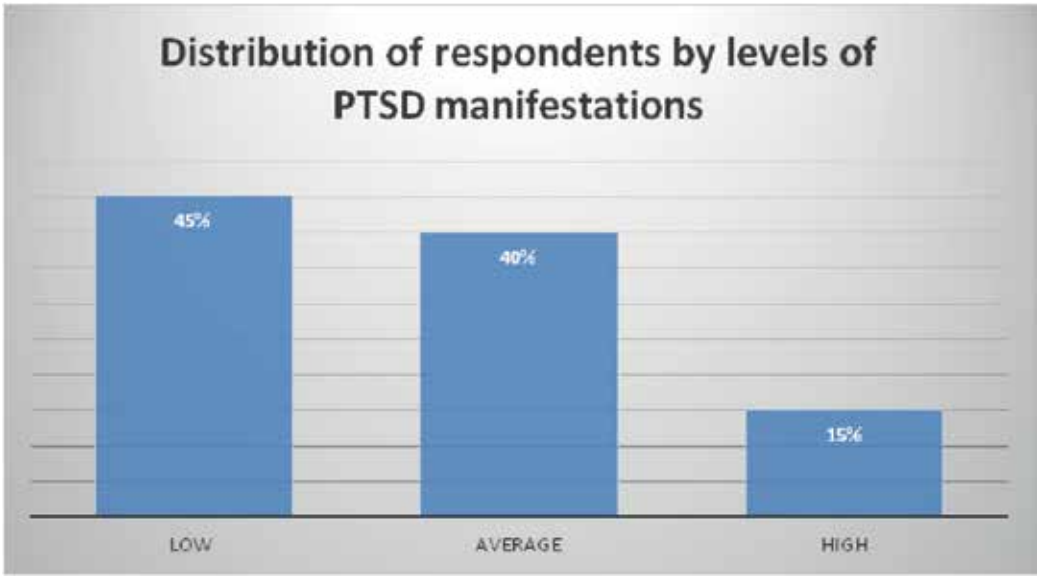


Fig. 1. Distribution of diagnostic results by levels of PTSD manifestations in young adults.

Table 2. Analysis of the relationship between resilience scales and PTSD manifestations in young adults

Resilience scales	Manifestations of PTSD
Resilience	0,4796 **
Involvement	-0,8364
Control	0,3637*
Acceptance of risk	-0,7453

** – $p < 0,05$ at $r \leq 0,31$; ** – $p < 0,01$ at $r \leq 0,40$;*

Based on this, mediation with a person with PTSD, in our opinion, requires more activity on the part of the mediator, especially when the mediating party shows symptoms of avoidance and numbness.

It is clear that traumatization primarily affects the need for security, thereby creating a set of psychological problems related to the person's sense of control over their own life, inviolability of personal boundaries, and a sense of trust in others. Psychologically, such a person needs support, understanding, and attentive attitude from the immediate environment. In this regard, the mediator must understand that in the process of mediation, it is the satisfaction of the need for safety of a person with PTSD (its external manifestation through the emergence of trust in the mediator, the creation of a safe environment for mediation by the mediator) that will become the basis for its conduct. Particular attention should be paid to satisfying this need at the stage of discussion and decision-making on the results of mediation.

When conducting mediation with a person who has experienced a traumatic event it is advisable for the mediator to use the "Careful Interview" technique to obtain information about the experience of the traumatic event and its impact on the psychological state. It is suggested to use simple questions in communication, such as: "Were you (or your loved ones) participants or observers of the traumatic event? When did it happen? What kind of event happened? What changes do you observe in your behavior? In your emotions? In your body? In your health? In your communication with others? Are there people in your environment who support you?" During the interview the mediator should focus on the conversation not expressing his or her opinion about the event, not giving assessments. Symptoms and the time period that has passed since the traumatic event make it possible to understand at what stage a person is reliving the traumatic event and whether they may have PTSD [3, p. 12]. If there are affirmative answers, it is advisable for the mediator to decide on further mediation, having previously asked the question: "Are you ready to continue the mediation procedure?" Additional training of the mediator in the skills and techniques used by psychologists in dealing with trauma (to stabilize the emotional state of the parties) will also be advisable.

In addition, in the work of a mediator with a person with PTSD, "shuttle" mediation is effective as it allows the mediator to use all the techniques he or she has developed in order to understand and realize the needs of such a person, his or her interests and values through personal communication. This will also help to avoid additional traumatization of a person with PTSD during joint meetings of the parties to the conflict. The mediator should also understand that a person with PTSD may have some difficulty making a decision, and therefore should not speed up the stages of this procedure and, if necessary, refer the person with PTSD for a consultation with a general practitioner or a specialist in dealing with psychotrauma (psychologist, psychotherapist, psychiatrist).

CONCLUSIONS

The theoretical analysis of the study proved that mastering transformation skills plays an important role in working with trauma, which contribute to the achievement of internal integration and integrity of the individual's self, a state of psychological balance, personality harmony, and productive relationships with the outside world. An important resource in working with trauma is a person's social experience, psychological competence, level of psychological education, and level of emotional intelligence (mental abilities involved in recognizing and understanding one's own emotions and the emotions of others).

It has been empirically proven that the level of PTSD manifestation in young adults affects their level of resilience. That is, awareness of the specifics and psychological nature of a traumatized person, his or her personal characteristics, and the essential features of psychotherapeutic relationships when working with a traumatized person can lead to a shift in the direction of reducing the level of PTSD in young adults, and thus stabilizing the client's emotional state.

It has been established that the interaction of a mediator with a person with PTSD requires empathic communication, creating an atmosphere of trust and safe communication, using shuttle mediation to avoid additional trauma, and applying the "Careful Interview" technique. In addition, if necessary, a mediator may recommend that a person with PTSD seek advice from a general practitioner or a specialist in dealing with psychotrauma (psychologist, psychotherapist, psychiatrist).

REFERENCES

1. Ministry of Reintegration of the Temporarily Occupied Territories of Ukraine: Results of 2022. https://www.minre.gov.ua/news/minreintegraciyi-zvituye-pro-robotu-u-2022-roci
2. On mediation: Law of Ukraine of November 16, 2021, No. 1875-IX. Holos Ukrayiny. 2021. № 236. (Ukrainian)
3. Neseniuk N, Chudaieva N, Murashkevych O. Travmatychni podii: psykholohichna pidtrymka ta samodopomoha. Dovidnyk dlia fakhivtsiv i fakhivchyn dopomizhnykh profesii sotsialnoi sfery, yaki pratsiuiut z vnutrishno peremishchenymy osobamy ta postrazhdalym naselenniam. Rada Yevropy. 2022. p. 1-92. https://rm.coe.int/te-print-version/1680a7943e (Ukrainian)
4. Bisson D, Elers A, Pillinh S. et al. Protokol z diahnostyky ta terapii PTSR Natsionalnoho instytutu klinichnoi maisternosti Velykobrytanii (NICE). Onlain-vydannia. Lviv, 2015, p. 1-64. https://ipz.org.ua/wp-content/uploads/2017/12/nice_2.pdf (Ukrainian)
5. A unified clinical protocol for primary, secondary (specialized) and tertiary (highly specialized) medical care. Reaction to severe stress and adaptation disorders. Post-traumatic stress disorder: Order of the Ministry of Health of Ukraine dated 3.02.2016 p., № 121. https://dec.gov.ua/wp-content/uploads/images/dodatki/2016_121_PTSR/2016_121_YKPMD_PTSR.pdf?fbclid=IwAR067yDcA17RTxg67qO3m5jk6gnQmaS5HAe49cy0WzBggEciVhmhD_hTg7k (Ukrainian)
6. Jones DE, Cusack K, Forneris CA, Wilkins TM, Sonis J, Middleton JC, et al. Psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Apr. Report No.: 13-EHC011-EF. https://pubmed.ncbi.nlm.nih.gov/23658937/
7. Nader K, Schafe G. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Doux JE.Nature. 2016; 406: 722-726.
8. Suliman S, Mkabile SG, Fincham DS, Ahmed R, Stein DJ, Seedat S. Cumulative effect of multiple trauma on symptoms of posttraumatic stress disorder, anxiety, and depression in adolescents. Compr Psychiatry. 2009;50(2):121-127.
9. Brady KT, Killeen TK, Brewerton T, Lucerini S. Comorbidity of psychiatric disorders and posttraumatic stress disorder. Journal of Clinical Psychiatry. 2000;61:22-32.
10. Sories F, Maier C, Beer A, Thomas V. Addressing the Needs of Military Children Through Family-Based Play Therapy. Contemporary Family Therapy: An International Journal. 2015;37(3):209-220. doi: 10.1007/s10591-015-9342-x.
11. Horowitz MJ, Solomon GF. A prediction of delayed stress response syndromes in Vietnam veterans. J of social issues: soldiers in and aftes Vietnam. 1975;31(4):67-80.
12. Van Etten ML, Taylor S. Comparative efficacy of treatments for posttraumatic stress disorder: A meta-analysis. Clinical Psychology and Psychotherapy. 1998;5:126-144.
13. Sposoby pidvyshchennia sotsialno-adaptyvnykh mozhlyvostei liudyny v umovakh perezhyvannia naslidkiv travmatychnykh podii: metodychni rekomendatsii. Natsionalna akademiia pedahohichnykh nauk Ukrainy, Instytut sotsialnoi ta politychnoi psykholohii / za nauk. red. T. M. Tytarenko. Kropyvnytskyi: Imeks LTD, 2017, p. 80. (Ukrainian)
14. Osnovy reabilitatsiinoi psykholohii: podolannia naslidkiv kryzy. Navchalnyi posibnyk. Tom 1,2,3. Kyiv, 2018. 240 p. (Ukrainian)
15. Hershanov O. Osnovy roboty z travmoiu. Robochi materialy uchasnykiv treninhiv «Robota z travmoiu ta vtratoiu. Osnovy supervizii». https://rm.coe.int/osnovu-raboty-z-travmoi-ukr/1680a035d8 (Ukrainian)
16. Hroiter S. Intehratyvna terapiia spilnot: Robochyi posibnyk moderatora. Ternopil, 2023. 35 p. (Ukrainian)

ORCID AND CONTRIBUTIONSHIP

Vitalii M. Pashkov: 0000-0001-9489-7768[A, B, D, E, F]
Olha V. Hubanova: 0000-0003-1984-146X[A, B, C, D, E]
Svitlana M. Buzhynska: 0000-0002-5103-0053[A, B, C, D, E]

CONFLICT OF INTEREST

The Authors declare no conflict of interest

RECEIVED: 12.06.2023
ACCEPTED: 17.09.2023

ADDRESS FOR CORRESPONDENCE

Vitalii M. Pashkov
Poltava Law Institute of Yaroslav Mudriy
National Law University
Pershotravnevy Avenue, 5, 36011, Poltava, Ukraine
e-mail: poltava_inst@nulau.edu.ua

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 548-557

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305115

COMPARATIVE ANALYSIS OF EFFECTIVENESS OF OBESITY TREATMENT IN PRIMARY CARE USING PATIENT-ORIENTED APPROACH WITH MOTIVATIONAL COUNSELING FOR LIFESTYLE CORRECTION AND ITS COMBINATION WITH ARMODAFINIL THERAPY IN PATIENTS WITH CONCOMITANT SHIFT WORK SLEEP DISORDER

Victoria I. Tkachenko[1], Taisiia O. Bagro[1,2]

[1]FAMILY MEDICINE DEPARTMENT, SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE
[2]FAMILY AND INTERNAL MEDICINE DEPARTMENT, MUNICIPAL NON-COMMERCIAL ENTERPRISE OF THE KYIV REGIONAL COUNCIL «KYIV REGIONAL CLINICAL HOSPITAL», KYIV, UKRAINE

ABSTRACT

Aim: Conduct a comparative analysis of effectiveness of obesity treatment in primary care using patient-oriented approach with motivational counseling for lifestyle correction and its combination with armodafinil therapy in patients with concomitant shift work sleep disorder.

Materials and Methods: 75 patients with obesity were studied, 38 patients had shift work disorder. Patients were divided into 2 groups: I (37 patients with obesity treated with motivational counseling) and II (38 patients with obesity and shift work disorder treated additionally with armodafinil 150 mg daily). The examination was at baseline, after 1st, 3th and 6th months. Statistical analysis was provided.

Results: After 1 month of treatment, there were improvement of eating behavior, level of anxiety and depression, prognosis of diabetes development. At 3rd month, more pronounced changes were observed in 2nd group: 10% body weight loss, changes in eating behavior, sleep quality, anxiety level ($p<0.05$). After 6 months, examined indicators in both groups normalized, but dynamics in 2nd group was more significant; armodafinil-treated group had significantly better results in body weight loss, BMI, WC, HC, ConI, AVI, BPs, HOMA index, serotonin, leptin, levels of anxiety and depression, eating behavior, daytime dysfunction, level of sleepiness, quality of life and risk of developing diabetes.

Conclusions: The use of armofafinil in addition to patientoriented motivational counseling in lifestyle correction ("5 As" and "5R") in patients with obesity connected with shift work disorder and excessive daytime sleepiness allows to reduce body weight by more than 16,52%, in contrast to isolated use of the same technique of motivational counseling in obese patients without sleep disorder (only 5,51%).

KEY WORDS: obesity, shift work sleep disorder, motivational counseling, armodafinil, primary care, patient-oriented approach

INTRODUCTION

Every year in the world there is a rapid increase in the number of patients with the phenomena of anxiety and depression, progress in digital technologies increasingly leads to the phenomena of hypodynamia in the working population, which collectively contributes to the progression of obesity and, as a consequence, the increase in the number of non-infectious diseases and the increase in the risk of mortality from them. A significant number of recommendations first indicate the need to correct the lifestyle of patients, reduce the amount of carbohydrate food in the diet and increase physical activity in patients, however, such a goal is quite difficult to achieve, the patient requires a multidisciplinary approach, since the problem includes not only physical, but also psychological aspects [1-8]. The "Obesity Canada" recommends the use of the "5 A^s" system motivational counseling, which can be used by primary care physicians to help the patient change [1-3, 9-13]. Quite often, when it is impossible to achieve goals using motivational interviewing, the use of pharmacotherapy is recommended. Among all suggested drugs (sibutramine, liraglutide, semaglutide, naltrexone/bupropion, phentermine, phentermine/topiramate, lorcaserin, orlistat) [1-8, 13-15] we see that the most effective are drugs

with central mechanisms of action, where the process of changing eating behavior directly or indirectly affects serotonergic pathways.

Often, obese patients have psychosocial problems, excessive sleepiness during the day, sleep disturbances, which can affect the course of obesity due to the activation of neurotransmitters (serotonin, dopamine) and peptides (orexin A, B) of the hypothalamus, in particular the centers of hunger and satiety, so these aspects must be taken into account in complex patient-oriented treatment. Sleep disorders are often associated with a nighttime work schedule and disruption of circadian rhythms. According to the International Classification of Sleep Disorders (ICSD-3), this type of disorder called shift work disorder this type of disorder is called shift work disorder and causes depletion of the dopaminergic, orexin, and serotonergic systems [16-18]. The FDA recommends armodafinil for treatment and emphasizes that melatonin is not effective [19].

Therefore, given the selective effect of armodafinil on the transmission of catecholamine signals to the hypothalamus through dopaminergic, serotonergic and noradrenaline receptors, its ability to stimulate the secretion of hypocretin (Orexin A and Orexin B), which in turn stimulates the release of dopamine and noradrenaline, which promote wakefulness and regulation of eating behavior. We decided to analyse its effectiveness in complex patient-oriented treatment of obesity concomitant with sleep disorders and compare such approach with isolated patient-oriented motivational counseling for lifestyle correction in obese patients without sleep disorder [20-22].

AIM

Aim is to conduct a comparative analysis of effectiveness of obesity treatment in primary care using patient-oriented approach in motivational counseling for lifestyle correction and its combination with armodafinil therapy in patients with concomitant Circadian Rhymth Sleep-Wake Disorders.

MATERIALS AND METHODS

75 patients with obesity were studied. At baseline 38 patients of them had circadian rhythm sleep-wake disorders (shift work disorder), which was established according to according to the criteria of International Classification of Sleep Disorders (ICSD-3,2) and DSM V (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) by next criteria: complaints of insomnia or severe sleepiness that occur in connection with working hours scheduled during the normal sleep period [16-18]. According to this, patients were divided into 2 groups: I (37 patients with obesity) and II (38 patients with obesity and shift work disorder).

In the 1st group, patients were given motivational counseling regarding the correction of their lifestyle according to the "5 A's" and "5R" system, where goals of weight loss of 5-10% in 6 months were set, the patient-oriented approach included recommendations regarding the regime and caloric content of food, physical activity (control with a pedometer), compliance with sleep hygiene, correction of psycho-emotional disorders. In the 2nd group, the same technique of motivational counseling was used, but with the use of armodafinil in a dose of 150 mg once a day, in the morning, according to the U.S. Food and Drug Administration (FDA) and AASM for shift work sleep disorder [19, 23]. To assess the effectiveness of the applied approach, patients were measured at the beginning of the study and after 1 month, 3 months and 6 months of BMI, waist circumference (WC) and hip circumference (HC) and anthropometric indicators were calculated - body surface area (BSA), Waist -to-Hip Ratio (WHR), Conicity Index (ConI) and A body shape index (ABSI), Abdominal Volume Index (AVI). Clinical and laboratory research included measurement of blood pressure, determination of blood levels of serotonin and leptin, indicators of lipid profile, glucose, insulin, HOMA index. Psychosocial status was assessed using the HADS Hospital Anxiety and Depression Scale, the Beck's Scale, the Hamilton Scale (HAM-A), the Dutch Eating Behavior Questionnaire (DEBQ), the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), quality of life - SF-36, International Physical Activity Questionnaire (IPAQ), diabetes risks were assessed using the FINDRISC questionnaire. Statistical analysis was performed using IBM SPSS Statistics, Statistica 12, Excel 2010.

RESULTS

At baseline the body weight of the patients of the 1st group was 94.44±2.33 kg and of the 2nd group was 97.76±2.16 kg, there was no significant difference between groups ($p>0.05$) (Table 1). Changes in BMI did not depend on gender in any of the groups. there were no significant differences in BMI between groups I and II. The waist circumference (WC) of the 1st group was 1.04±0.02 m, in the 2nd - 1.05±0.02 m, there were no differences between groups or by gender ($p>0.05$). A similar trend was observed with defined hip circumference (HC). The WHR, ConI, ABSI and AVI indices did not have a significant difference between the groups ($p>0.05$) (Table 1).

The patients of 1st group had 7.41±0.59 points on Epworth scale and 2nd group had an average of 9.55±0.66 points ($p<0.05$) (Table 2). A significant difference was found between levels of sleep quality in groups according to the PSQI Global score (I=7.54±0.46 points, II=9.32±0.49 points) and its component Habitual sleep efficiency (I=0.35± 0.08 points, II=0.63±0.10 points) ($p<0.05$), with no significant difference in other indicators ($p>0.05$) (Table 2).

Blood pressure levels in group were: BP_{sI}=135.54±2.36 mm.Hg, BP_{sII}=136.18±2.58 mm.Hg and BP_{dI}=86.76±1.78 mm.Hg, BP_{dII}=86.58±1.59 mm.Hg. Violations of carbohydrate and lipid metabolism, risk of developing diabetes did not have a significant difference between groups (Table 3).

Physical activity of patients (IPAQ) in 1st group was 21.08±1.76 points and in 2nd group - 16.08±1.42 points ($p<0.05$) (Table 4). The eating behavior of patients according to Dutch Eating Behavior Questionnaire (DEBQ) significantly exceeded the reference values of indicator and had no significant difference between groups ($p>0.05$) (Table 4). The anxiety according to scales in 1st group was $HADS_{anxiety}$=8.59±0.61 points, Hamilton's=9.70±0.53 points, in 2nd group –

Table 1. Dynamics of anthropometric indicators between groups for 6 months of observation

Indicator	Group	Baseline M±m	1 month M±m	3 month M±m	6 month M±m
Weight, kg	I(n=37)	94.44±2.33	92.75±2.27	91.61±2.26	89.13±2.08
	II(n=38)	97.76±2.16	97.27±2.72	87.47±2.36	81.67±2.17^{0}
% of body weight loss	I(n=37)	1.77±0.17$^{***###}$		2.99±0.19$^{***###}$	5.51±0.2$^{***###}$
	II(n=38)	0.81±0.98		10.65±0.96^{000}	16.52±0.98^{000}
BMI, kg/m^2	I(n=37)	33.47±0.50	32.88±0.49	32.47±0.48	31.62±0.46$^{##}$
	II(n=38)	33.85±0.54	33.69±0.78	30.31±0.67$^{**##0}$	28.30±0.62$^{***###000}$
WC, m	I(n=37)	1.04±0.02	1.01±0.02	1.01±0.02	0.99±0.02
	II(n=38)	1.05±0.02	1.05±0.02	0.95±0.02$^{*#}$	0.89±0.02$^{**###000}$
HC, m	I(n=37)	1.16±0.02	1.14±0.02	1.14±0.02	1.12±0.02
	II(n=38)	1.15±0.03	1.15±0.03	1.13±0.74	1.05±0.03$^{#0}$
BSA, м^2	I(n=37)	2.13±0.03	2.12±0.03	2.10±0.03	2.08±0.03
	II(n=38)	2.19±0.04	2.18±0.04	2.08±0.04$^{#}$	2.02±0.03$^{#}$
WHR	I(n=37)	0.90±0.01	0.89±0.01	0.89±0.01	0.88±0.01
	II(n=38)	0.92±0.01	0.92±0.01	0.85±0.01$^{***###0}$	0.86±0.01$^{##}$
ConI, m$^{3/2}$/kg$^{1/2}$	I(n=37)	1.27±0.02	1.25±0.02	1.25±0.02	1.25±0.02
	II(n=38)	1.27±0.02	1.27±0.02	1.22±0.02	1.18±0.02$^{#0}$
ABSI, m$^{5/3}$·kg$^{-2/3}$	I(n=37)	0.0770±0.0009	0.0763±0.0009	0.0765±0.0009	0.0765±0.0009
	II(n=38)	0.0770±0.0010	0.0773±0.0011	0.0755±0.0009	0.0740±0.0013
AVI	I(n=37)	21.89±0.82	21.02±0.81	20.78±0.79	20.03±0.75
	II(n=38)	22.40±0.87	22.35±0.89	18.76±0.83$^{**##}$	16.42±0.72$^{*###000}$

*p<0.05, **p<0.01, ***p<0.001 – in comparison with previous control point.
$^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.01 – in comparison with baseline.
^{0}p<0.05, ^{00}p<0.01, ^{000}p<0.01 - in comparison between groups.

Table 2. Comparative assessment of sleep indicators of both groups for 6 months

	Indicator	Group	Baseline M±m	1 month M±m	3 month M±m	6 month M±m
PSQI, points	Global score	I(n=37)	7.54±0.46	6.08±0.27$^{**##}$	4.76±0.24$^{***###}$	3.76±0.20$^{**###}$
		II(n=38)	9.32±0.49^{0}	6.84±0.28$^{***###}$	5.58±0.23$^{**##0}$	3.63±0.19$^{***###}$
	Sleep quality	I(n=37)	1.89±0.15	1.92±0.04	1.05±0.04	0.97±0.09
		II(n=38)	2.21±0.12	1.84±0.07$^{*#}$	1.18±0.07$^{***###}$	1.11±0.05$^{###}$
	Sleep latency	I(n=37)	1.54±0.14	1.16±0.11	1.05±0.09	0.70±0.10
		II(n=38)	1.92±0.14	1.50±0.12$^{*#0}$	1.11±0.08$^{**###}$	0.87±0.09$^{*###}$
	Sleep duration	I(n=37)	0.92±0.17	0.43±0.14	0.41±0.11	0.14±0.08
		II(n=38)	1.34±0.17	0.68±0.16$^{**##}$	0.66±0.11$^{##}$	0.29±0.11$^{*###}$
	Habitual sleep efficiency	I(n=37)	0.35±0.08	0.24±0.07	0.16±0.06	0.08±0.04
		II(n=38)	0.63±0.10^{0}	0.29±0.07$^{*#}$	0.34±0.08$^{#}$	0.03±0.03$^{***###}$
	Sleep disturbance	I(n=37)	1.49±0.08	1.24±0.07	1.16±0.06	1.05±0.04
		II(n=38)	1.71±0.09	1.37±0.09$^{*###}$	1.16±0.06$^{*###}$	1.05±0.04$^{###}$
	Use of sleeping medication	I(n=37)	0.03±0.03	0.03±0.03	0.03±0.03	0.03±0.03
		II(n=38)	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
	Daytime dysfunction	I(n=37)	1.32±0.10	1.05±0.08$^{*#}$	0.89±0.08$^{#}$	0.78±0.09$^{##}$
		II(n=38)	1.50±0.13	1.16±0.08$^{*#}$	1.13±0.08$^{#0}$	0.29±0.10$^{***###000}$
Drowsiness (ESS), points		I(n=37)	7.41±0.59	8.70±0.67	8.05±0.58	6.73±0.50
		II(n=38)	9.55±0.66^{0}	9.03±0.65	7.42±0.51$^{#}$	5.39±0.36$^{**###0}$

*p<0.05, **p<0.01, ***p<0.001 – in comparison with previous control point.
$^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.01 – in comparison with baseline.
^{0}p<0.05, ^{00}p<0.01, ^{000}p<0.01 – in comparison between groups.

Table 3. Carbohydrate, lipid metabolism and blood pressure level in the groups during the entire observation period

Indicator	Group	Baseline M±m	1 month M±m	3 month M±m	6 month M±m
BPs, mmHg	I(n=37)	135.54±2.36	133.65±1.81	130.00±1.44	$128.24±1.69^{\#\#}$
	II(n=38)	136.18±2.58	137.24±2.51	$127.63±1.37^{**\#\#}$	$123.55±0.89^{**\#\#\#0}$
BPd, mmHg	I(n=37)	86.76±1.78	84.46±0.99	$81.49±0.87^{*}$	$80.54±0.91^{\#\#}$
	II(n=38)	86.58±1.59	84.34±1.38	$79.21±0.93^{**\#\#\#}$	$79.08±0.80^{\#\#\#}$
Glucose, mmol/l	I(n=37)	6.29±0.16	6.58±0.15	6.31±0.15	6.08±0.15
	II(n=38)	6.34±0.16	6.33±0.16	6.02±0.15	$5.70±0.13^{\#}$
Insulin, μIU/ml	I(n=37)	17.02±0.75	15.82±0.92	15.13±0.84	$14.54±0.95^{\#}$
	II(n=38)	17.14±0.74	17.01±0.73	$15.11±0.68^{\#}$	$12.71±0.55^{**\#\#\#}$
HOMA index, μmol·μl·ml2	I(n=37)	4.87±0.29	4.78±0.34	4.37±0.31	4.06±0.33
	II(n=38)	4.94±0.29	4.90±0.28	$4.13±0.24^{*\#}$	$3.28±0.18^{**\#\#\#0}$
Total cholesterol, mmol/l	I(n=37)	5.64±0.16	5.46±0.19	5.37±0.21	5.42±0.24
	II(n=38)	5.25±0.16	5.20±0.16	5.11±0.20	5.09±0.18
HDL, mmol/l	I(n=37)	1.55±0.05	1.63±0.05	1.58±0.05	$1.69±0.04^{\#}$
	II(n=38)	1.57±0.04	1.66±0.05	$1.72±0.05^{\#0}$	$1.85±0.06^{\#\#\#0}$
LDL, mmol/l	I(n=37)	3.88±0.15	3.90±0.17	3.85±0.15	3.50±0.19
	II(n=38)	3.70±0.16	3.54±0.16	$3.36±0.15^{0}$	$3.08±0.14^{\#\#}$
VLDL, mmol/l	I(n=37)	0.82±0.05	0.73±0.05	0.81±0.04	$0.70±0.04^{*\#}$
	II(n=38)	0.80±0.04	0.76±0.04	0.70±0.04	$0.61±0.03^{*\#\#\#}$
Atherogenic index	I(n=37)	2.86±0.20	2.55±0.20	2.61±0.22	2.40±0.22
	II(n=38)	2.49±0.18	2.28±0.17	2.12±0.18	$1.90±0.17^{\#}$

$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ – in comparison with previous control point.
$^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.01$ – in comparison with baseline.
$^{0}p<0.05$, $^{00}p<0.01$, $^{000}p<0.01$ - in comparison between groups.

$HADS_{anxiety}$=12.13±0.74 points, Hamilton's=13.76±0.91 points, (p<0.01). Level of depression in 1st group was $HADS_{depression}$=10.19±0.75, Beck's scale=10.70±0.95, in 2nd group - $HADS_{depression}$=13.84±0.74, Beck's scale =15.47±1.15, p<0.001 (Table 4).

The quality of life at initial visit in both groups according to the SF-36 questionnaire for all components was at average and below average levels most of the components did not have a significant difference between themselves Bodily Pain - BP (I=64.97±4.58, II=62.24 ±3.67 points), Role-Physical Functioning - RP (I=50.68±6.08, II=45.39±4.89 points), General Health - GH (I=49.72±3.54, II=44.54±3.45 points), Social Functioning- SF (I=55.41±4.07, II=55.33±3.51 points), Vitality – VT (I=51.62±2.36, II=54.37±2.67 points), Mental Health – MH (I=51.78±4.14, II=52.95±4.37 points), Role Emotional – RE (I=45 ,93±6.78, II=49.10±5.99 points), exception is level of physical functioning (Physical Functioning – PF (I=69.32±2.57, II=62.89±1.80 points), whose average scores in II group were lower than in I group (p<0.05) (Table 5).

The levels of serotonin and leptin in the patients' blood at the first visit did not differ significantly (Table 5).

The first control point was carried out at 1 month after start of treatment of patients, as can be seen from Table 1. The anthropometric indices, blood pressure, ideces of carbohydrate and lipid metabolism in dynamics did not have reliable difference between groups p>0.05 (Table 1). The level of physical activity (IPAQ) increased in both groups, although not significantly: in 1st group it was 23.30±1.40 points, in 2nd group it was 19.55±1.40 points (p>0.05) (Table 4). The prediction of occurrence of diabetes in next 10 years (FINDRISC) in 2nd group (11.61±0.64 points) significantly decreased compared to 1st group (13.51±0.57 points), p<0.05 (Table 4).

A significant difference was observed in level of anxiety according to the $HADS_{anxiety}$ questionnaire, where in 1 month there was an increase in average score in 1st group to 10.49±0.47 points, and a decrease in 2nd group to 7.84±0.58 points (p<0.001), results of other anxiety and depression questionnaires did not differ significantly p>0.05 (Table 4).

The level of serotonin in blood of patients did not changed significantly but level of leptin decreased in both groups, mainly in the first (p>0.05) (Table 5).

Sleep disturbances improved according to the Epworth and PSQI scales but without significant difference, the exception was the PSQI Sleep latency component, which significantly decreased compared to baseline in 2nd group after a month of treatment (1.50±0.12 points, p<0.05) but remained higher than in 1st group (1.16±0.11 points, p<0.05) (Table 2).

Changes in eating behavior in patients (DEBQ) had significant difference, patients treated with armodafinil showed a better result after 1 month. According to the

Table 4. Assessment of the state of mental health, physical activity and the risk of developing diabetes when comparing groups in dynamics

Indicator		Group	Baseline M±m	1 month M±m	3 month M±m	6 month M±m
Hamilton anxiety scale, points		I(n=37)	9.70±0.53	9.41±0.54	8.35±0.38$^{\#}$	7.54±0.30$^{\#\#\#}$
		II(n=38)	13.76±0.91^{000}	10.79±0.71$^{*\#}$	8.82±0.48$^{*\#\#\#}$	6.29±0.36$^{***\#\#\#00}$
HADS, points	anxiety	I(n=37)	8.59±0.61	10.49±0.47$^{*\#}$	9.51±0.44	8.24±0.31*
		II(n=38)	12.13±0.74^{000}	7.84±0.58$^{***\#\#\#000}$	6.79±0.51$^{\#\#\#000}$	5.39±0.49$^{*\#\#\#000}$
	depression	I(n=37)	10.19±0.75	7.70±0.63$^{*\#}$	6.92±0.53$^{\#}$	5.30±0.46$^{*\#\#\#}$
		II(n=38)	13.84±0.74^{000}	8.16±0.58$^{***\#\#\#}$	6.66±0.54$^{\#\#\#}$	4.03±0.41$^{***\#\#\#0}$
Beck's (depression scale), points		I(n=37)	10.70±0.95	13.84±1.12$^{*\#}$	12.78±0.79	12.11±1.13
		II(n=38)	15.47±1.15^{00}	12.08±0.72$^{*\#}$	10.61±0.77$^{\#\#\#0}$	8.29±0.56$^{*\#\#\#00}$
DEBQ, балл	Emotional eating type	I(n=37)	2.82±0.16	2.91±0.14	2.64±0.12	2.08±0.12$^{**\#\#\#}$
		II(n=38)	3.02±0.14	2.48±0.10$^{**\#\#0}$	2.16±0.08$^{*\#\#\#00}$	1.70±0.05$^{***\#\#\#00}$
	Externality eating type	I(n=37)	3.38±0.15	2.76±0.16$^{**\#\#}$	2.56±0.16$^{\#\#\#}$	2.32±0.16$^{\#\#\#}$
		II(n=38)	3.66±0.14	2.39±0.08$^{***\#\#\#0}$	2.15±0.07$^{*\#\#\#0}$	1.90±0.08$^{*\#\#\#0}$
	Restrained eating type	I(n=37)	3.87±0.12	3.42±0.13$^{*\#}$	3.13±0.13$^{\#\#\#}$	2.75±0.14$^{*\#\#\#}$
		II(n=38)	3.79±0.13	3.39±0.07$^{**\#\#}$	2.95±0.09$^{***\#\#\#}$	2.35±0.14$^{***\#\#\#0}$
IPAQ, points		I(n=37)	21.08±1.76	23.30±1.40	26.08±1.53$^{\#}$	30.16±1.64$^{\#\#\#}$
		II(n=38)	16.08±1.42^{0}	19.55±1.40	23.24±1.40$^{\#\#\#}$	29.29±1.42$^{**\#\#\#}$
FINDRISC		I(n=37)	14.16±0.61	13.51±0.57	12.32±0.56$^{\#}$	11.14±0.55$^{\#\#\#}$
		II(n=38)	12.50±0.72	11.61±0.64^{0}	10.84±0.58	9.42±0.53$^{\#\#\#0}$

$^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ – in comparison with previous control point.
$^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.01$ – in comparison with baseline.
$^{0}p<0.05$, $^{00}p<0.01$, $^{000}p<0.01$ – in comparison between groups.

Emotional type scale, patients of 1st group had 2.91±0.14 points, 2nd group had 2.48±0.10 points, (p<0.05); according to External type scale, 1st group had 2.76±0.16 points, and 2nd group - 2.39±0.08 points, (p<0.05); according to the Restrained type scale: 1st group - 3.42±0.13 points, 2nd group - 3.39±0.07, p<0.05. The quality of life of patients after 1 month of treatment for all components of questionnaire (SF36) had moderate positive results in both groups in parallel, which did not show a significant difference between them (p>0.05) (Table 4).

After 3 months of therapy an increase in weight loss was observed in 1st group to 2.99±0.19% (p<0.001) and in 2nd group to 10.65±0.96% (p<0.0001), difference between groups was significant (p<0.0001) (Table 1). Anthropometric indicators with exception of BMI and WHR did not differ significantly, although they had positive trends (Table 1). Blood pressure, indicators of carbohydrate and lipid metabolism, as can be seen from Table 3, did not have a significant difference between groups (p>0.05), with exception of LDL and HDL (p<0.05) (Table 3). The 10-year prediction of development of diabetes (FINDRISC) in 1st group remained the same and had a decrease in 2nd group to 1/25 patients, without a significant difference between groups (Table 4). Physical activity in all patients significantly increased (I=26.08±1.53 points, II=23.24±1.40 points) also without significant difference between groups (p>0.05) (Table 4). Similar to previous data, anxiety and depression did not differ between groups, except for $HADS_{anxiety}$ questionnaire, according to which after 3 months of treatment in 2nd group (6.79±0.51 points) we see more pronounced positive dynamics than in 1st group (9,51±0.44 points), p<0.001 (Table 1). Eating behavior according to scales of Emotional (I=2.64±0.12, II=2.16±0.08 points) and External (I=2.56±0.16, II=2.15±0.07 points) types had significantly better dynamics in the 2nd group (p<0.05), and it did not differ reliably on the Restrained type scale (I=3.13±0.13, II=2.95±0.09 points) (Table 4). The number of points on sleep quality questionnaire for 3 months of treatment decreased in both groups, without a significant difference in all components (p>0.05) with exception of Daytime dysfunction, which remained at a higher level in 2nd group (p<0.05). The level of sleepiness (Epworth) during 3 months of observation did not differ between groups (I=8.05±0.58, II=7.42±0.51 points), p>0.05 (Table 2). Quality of life according to the SF-36 questionnaire, were significantly higher mostly in 2nd group for components PF, BP, MH, GH (p<0.05) (Table 5). The values of serotonin and leptin had more pronounced changes in 2nd group, however, without a significant difference (p>0.05) (Table 4).

The last point of control was the examination of patients after 6 months of treatment, when a decrease in percentage of body loss was observed in 2nd group to 16.52±0.98% and in 1st group to 5.51±0.2% (p<0.0001) (Table 1). BMI in 1st group was 31.62±0.46 kg/m^2 and in 2nd group 28.30±0.62 kg/m^2 (p<0.001). WC (I=0.99±0.02, II=0.89±0.02 m) and HC (I=1.12±0.02, II=1.05±0.03 m) in

Table 5. Comparison of quality of life, serotonin and leptin levels in experimental groups

Indicator		Group	Baseline M±m	1 month M±m	3 month M±m	6 month M±m
Serotonin, µg/l		I(n=37)	155.46±3.07	160.03±3.50	163.68±3.80	166.35±3.57$^{\#}$
		II(n=38)	154.37±3.89	156.97±3.99	171.53±4.18$^{*\#\#}$	212.87±5.95$^{***\#\#\#000}$
Leptin, ng/ml		I(n=37)	10.56±1.14	9.88±1.16	9.48±1.17	8.70±1.15
		II(n=38)	12.84±0.92	12.36±0.93	8.85±0.60$^{**\#\#\#}$	6.22±0.40$^{***\#\#\#0}$
SF-36, points	PF	I(n=37)	69.32±2.57	79.19±2.14$^{**\#\#}$	81.76±2.38$^{\#\#\#}$	88.11±2.08$^{\#\#\#}$
		II(n=38)	62.89±1.80^{0}	84.08±2.14$^{***\#\#\#}$	90.53±1.76$^{*\#\#\#0}$	97.89±0.79$^{**\#\#\#000}$
	RP	I(n=37)	50.68±6.08	56.76±5.54	57.43±4.95	65.54±4.81
		II(n=38)	45.39±4.89	57.24±4.61	68.42±3.73$^{\#\#\#}$	88.82±2.44$^{***\#\#\#000}$
	BP	I(n=37)	64.97±4.58	65.76±4.61	64.86±4.25	78.54±3.20$^{*\#}$
		II(n=38)	62.24±3.67	69.89±4.07	79.29±3.46$^{\#\#0}$	94.21±1.44$^{***\#\#\#000}$
	GH	I(n=37)	49.72±3.54	48.58±3.64	57.04±3.53	71.26±3.43$^{**\#\#\#}$
		II(n=38)	44.54±3.45	57.87±3.53$^{**\#\#}$	73.49±2.95$^{**\#\#\#000}$	83.97±1.89$^{**\#\#\#00}$
	VT	I(n=37)	51.62±2.36	59.46±2.75$^{*\#}$	63.24±2.92$^{\#\#}$	71.62±2.77$^{*\#\#\#}$
		II(n=38)	54.37±2.67	63.16±2.14$^{*\#}$	70.39±2.17$^{*\#\#\#}$	79.08±2.23$^{**\#\#\#0}$
	SF	I(n=37)	55.41±4.07	58.78±3.97	62.84±3.19	72.64±3.47$^{*\#\#}$
		II(n=38)	55.33±3.51	61.71±3.16	70.33±2.71$^{*\#\#}$	83.88±2.55$^{***\#\#\#0}$
	RE	I(n=37)	45.93±6.78	52.23±5.77	52.74±5.38	68.43±4.41$^{*\#\#}$
		II(n=38)	49.10±5.99	50.84±4.83	63.12±4.84	80.67±3.70$^{**\#\#\#0}$
	MH	I(n=37)	51.78±4.14	55.46±3.81	61.62±3.29	71.78±3.13$^{*\#\#\#}$
		II(n=38)	52.95±4.37	58.11±2.74	75.05±3.20$^{***\#\#\#0}$	82.95±2.82$^{\#\#\#0}$

*p<0.05, **p<0.01, ***p<0.001 – in comparison with previous control point.
$^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.01 – in comparison with baseline.
^{0}p<0.05, ^{00}p<0.01, ^{000}p<0.01 - in comparison between groups.

2nd group had more pronounced decrease than in 1st group (p<0.001; p<0.05). Indices of abdominal obesity ConI (I=1.25±0.02, II=1.18±0.02 $m^{3/2}/kg^{1/2}$), AVI (I=20.03±0.75, II=16.42±0.72) were lower in 2nd group (p<0.05); while ABSI (I=0.0765±0.0009, II=0.0740±0.0013 $m^{5/3}\cdot kg^{-2/3}$), BSA (I=2.08±0.03, II=2, 02±0.03m^2), WHR (I=0.88±0.01, II=0.86±0.01) did not differ between groups (p>0.05) (Table 1). Hemodynamic indicators differed by level of systolic pressure (Table 3, p<0.05). Indicators of physical activity (IPAQ) did not differ between experimental groups (I=30.16±1.64, II=29.29±1.42; p>0.05). The HOMA index in 2nd group (3.28±0.18 µmol·µU·ml) was lower compared to 1st group (4.06±0.33 µmol·µU·ml), p<0.05; glucose, insulin and lipidogram parameters showed no difference between groups (p>0.05) (Table 3). FINDRISC in 1st group was 11.14±0.55 points, in 2nd group 9.42±0.53 points (p<0.001) (Table 4.). Levels of serotonin in blood of patients of 1st group were 166.35±3.57 µg/l, 2nd - 212.87±5.95 µg/l. Leptin gradually decreased in both groups (I=8.70±1.15 ng/ml, II=6.22±0.40 ng/ml), however, according the results in 2nd group were significantly lower (p<0.05), the difference between women (I(f)=9.43±1.28 ng/ml, II(f)=6.23±0.36 ng/ml) and men (I(m)=7.84±0.94 ng/ml, II(m)=6.22±0.45 ng/ml) was not found (p>0.05). All scales for determining levels of anxiety and depression showed significantly lower scores (HADS, Beck's) in 2nd group (p<0.05) exception was Hamilton scale, where positive changes over 6 months of treatment did not differ between patients (p>0.05) (Table 4). Eating behavior and level of daytime sleepiness in 2nd group (Epworth=5.39±0.36 points) differed significantly from 1st group (Epworth=6.73±0.50 points) (Table 2, p<0.05). The Pittsburgh Sleep Quality Index did not have a significant difference between groups (p>0.05) although, within 6 months of treatment, the sleep quality indicator according to the Global score normalized (p<0.001). Only for Daytime dysfunction scores were lower in 2nd group (0.29±0.10) than scores in 1st group (0.78±0.09, p<0.05) (Table 2). The quality of life indicators for all components of SF-36 questionnaire in 2nd group significantly exceeded indicators of 1st group (p<0.05) at 6 months of treatment (Table 5).

DISCUSSION

At initial examination patients of both groups had obesity of I and II degrees according to BMI, without a significant difference, as well as anthropometric indicators indicating presence of abdominal obesity. The waist circumference in both 1st and 2nd groups exceeded the WHO recommended values for men (>94 cm) and women (>80 cm) in Europe, which indicates an increase in cardiovascular risks in patients [24, 25]. A similar trend was observed with defined hip circumference (HC). The WHR, ConI, ABSI and AVI indices confirmed the abdominal type of obesity in bouth groups. Blood pressure levels were normal high, carbohydrate

tolerance disorders aand insulin resistance were found, risk of diabetes was moderate and diabetes could occur in every 6th patient according to forecast for next 10 years, the lipid profile was characterized by exceeded levels of total cholesterol and LDL; levels of HDL, VLDL, and atherogenicity index were within acceptable limits with no significant difference between groups. Physical activity of the patients (IPAQ) at baseline was on the border of hypodynamia, which was more pronounced in 2nd group. The subclinically expressed anxiety and depression was determined in 1st group and clinically expressed anxiety and depression in 2nd group. The eating behavior of patients at baseline was disturbed, tendency to «eat emotionally», to overeat when food was available and habit of eating without restrictions was noted, which did not significantly differ between in groups. Patients of 1st group had moderate daytime sleepiness, and 2nd group had excessive daytime sleepiness caused by shift work disorder, that had significantly difference. The low quality of sleep was determined in both groups, however a significant difference between PSQI Global score and Habitual sleep efficiency was determined in 2nd group, which indicates poor sleep efficiency; other components of questionnaire did not differ significantly. The patients of 2nd group characterized their sleep, as a sleep of poor quality, they could not fall asleep within 30-60 minutes, the duration of their sleep did not exceed 6 hours per night, there were episodes of waking up at night, difficulty breathing, snoring, feeling pain, cold, heat, bad dreams 1-2 times a night and difficulty for patients 1-2 times a week to maintain a sufficient mood to be socially active and perform their tasks. Quality of life at baseline in both groups according to SF-36 questionnaire was at average and below average levels for all components without significant difference between groups (BP, GH, SF, VT, MH, RE) with exception of level of physical functioning (PF) that was lower in 2nd group than in 1st group ($p<0.05$), and indicates limitation of physical activity by patient's state of health. The patients' blood serotonin and leptin levels at baseline were not significantly different, and serotonin corresponded to low reference values and leptin exceeded normal values, that confirm its interrelation between hormonal, metablic, psychosocial, behavioral and sleep disorders in obesity.

Thus, the patients in both groups at baseline had a complex of psychosocial, behavioral and clinical-laboratory disorders. In 2nd group, the excessive daytime sleepiness, poorer sleep quality, more pronounced levels of anxiety and depression, hypodynamia phenomena and a low level of physical functioning were found, which distinguished from 1st group and needed an additional intervention. The shift work disorder was established according to the criteria of ICSD-3,2 and DSM V in patients of 2nd group and according to this the armodafinil was prescribed due to FDA and AASM in addition to comprehensive patient-oriented approach in motivational counseling regarding the correction of their lifestyle according to the "5 As" and "5R" [1-3, 6, 19, 23].

Taking into account all indications and contraindications, first control point of effectiveness of therapy was carried out after 1 month. Anthropometric indexes, blood pressure, indeces of carbohydrate and lipid metabolism in dynamics had no significant difference between groups, while psychosocial indicators had a positive trend relative to baseline. A significant difference was observed in level of anxiety according to HADS questionnaire, it decreased to a "subclinical" level in 2nd, while in the first group, a significant increase in values within the range of "clinically expressed" anxiety was noted. The prediction of occurrence of diabetes mellitus in next 10 years (FINDRISC) in 2nd group also significantly decreased compared to 1st group, however, it also corresponded to 1/6. The level of physical activity (IPAQ) increased in both groups, although not significantly, however, phenomena of hypodynamia was more persisted in 2nd group also. The level of serotonin and leptin in blood of patients did not significantly changed in both groups.

Patients who received armodafinil showed a better result of changes in eating behavior (DEBQ) after 1 month, they began better control their behavior during emotional experiences, while tendency to "eat emotions" increased in patients of 1st group, ($p<0.05$). According to scales of the External type, patients of 2nd group also showed a better control of behavior in presence of food $p<0.05$, however, tendency to overeat did not differ significantly between patients after first month of treatment, although it significantly decreased relative to initial level. Sleep disturbances on the Epworth and PSQI scales improved, however, their level also corresponded to poor sleep quality and excessive daytime sleepiness, there was no significant difference between groups. The quality of life of patients after 1 month of treatment was at an average level for all components of questionnaire (SF-36) in both groups. The obtained results indicate that 1 month of using armodafinil is not enough time to stabilize the pathogenetic mechanisms of the hypothalamic area, although it indicates a positive role in therapy.

After 3 months of determining effectiveness of proposed models, a rapid increase in weight loss was noted in armodafinil group, which made it possible to achieve desired result. The blood pressure indicators between groups did not have any significance and were at average normal values, although positive changes were quite pronounced in 2nd group, relative to previous two control points. Indicators of carbohydrate and lipid metabolism were at same level as after one month, which was equally manifested in both groups, with exception of LDL and HDL, which underwent positive changes, which were more pronounced in 2nd group, although LDL did not reach target values. The risk of developing diabetes in patients receiving armodafinil decreased, while it remained at same level in 1st group. Physical activity at this stage of study in all patients corresponded to normal values, with no significant difference between groups. The anxiety score on the $HADS_{anxiety}$ scale in 1st group corresponded to level of "subclinical depression", while the other scales showed absence of anxiety and depression in both groups with no difference between them. The dynamics of eating behavior

according to scales of External and Emotional types was significantly better in 2nd group ($p<0.05$). According to scale of the Restrained type, it did not differ significantly, which indicates that patients are able to control themselves when food is available, however, emotional component and possibility of sufficient restrictions on food consumption were not adjusted at this stage. The quality of sleep according to PSQI questionnaire improved in both groups after 3 months of treatment, the overall PSQI score showed a more pronounced positive trend in the 2nd group. But there was no significant difference in all components of questionnaire, with the exception of Daytime dysfunction, which was significantly higher in 2nd group points, which in turn indicates the insufficiency of patients' strength to be sufficiently socially active relative to first group. The level of sleepiness during 3-month follow-up did not differ between the groups, however, in 2nd group it corresponded to normal values. Scores for assessing quality of life of patients according to SF-36 questionnaire had positive changes in both groups significantly higher indicators were observed in 2nd group for components PF, BP, MH, GH, which corresponded to high and above average values. The positive dynamics in values of serotonin and leptin (especially in women of both groups and corresponding to reference values) was more pronounced in 2nd group, although, without a significant difference ($p>0.05$).

In both groups, after 6 months of treatment with a patient-centered approach, body weight loss goals of more than 5% according to Canadian obesity treatment guidelines and the DUODECIM guidelines were achieved [2, 3]. In course of the study, BMI decreased significantly in both groups, however, more significant changes were observed in 2nd group ($p<0.001$). WC and HC in the 2nd group also had more pronounced positive changes compared to the 1st group, the WC in men of the 2nd group reached the WHO recommended values. Calculated indicators of abdominal obesity ConI and AVI showed a significant decrease in 2nd group, while ABSI, BSA, WHR did not differ between groups. The WHR indicator in men of both groups after 6 months of treatment reached normal values, which may indicate a decrease in amount of visceral fat in these patients. Blood pressure levels corresponded to normal mean values in both groups.

A sufficient level of physical activity was achieved in both groups. The HOMA index in 2nd group had significantly better changes ($p<0.05$) compared to 1st group, however, it exceeded 3 μmol·μl·ml2 in all patients. The indicators of carbohydrate and lipid metabolism showed no difference, indicating violation of tolerance to carbohydrates in 1st group, insulin resistance and dyslipidemia in both groups. The prognosis of occurrence of diabetes in next 10 years was also better in 2nd group, although in both groups it corresponded to occurrence rate in 1 out of 25 patients. Levels of serotonin in blood of patients when comparing groups did not exceed reference values, but were significantly higher in 2nd group, which may indicate contribution of method using armodafinil to its concentration in blood. At last control point, concentration of leptin in blood gradually decreased, there was no difference between women and men of different groups, however according to total average values of indicator results were significantly lower in the 2nd group.

The evaluation of level of anxiety and depression showed their absence in 2nd group and "subclinical anxiety" in 1st group according to HADS scale. A similar situation was observed when determining compulsive behavior and level of daytime sleepiness according to the Epworth scale, where normalization of indicators in 2nd group differed from 1st ($p<0.05$), the patients were able to control consumption of food in emotional situations, availability of food and if necessary, limit its use. The sleep quality questionnaire did not show a reliable difference between the groups in most of the questionnaire components, which may be related to better quality of sleep at the initial level in the 1st group, and does not fully reflect positive dynamics of the 2nd group. However, according to Daytime dysfunction, it is clear that patients had able to function better socially in relation to 1st group and previous control points. During 6 months of treatment, patients normalized their sleep quality and eliminated excessive daytime sleepiness with help of the proposed therapy. The quality of life indicators were significantly better in both groups and achieved high and above average values, patients using armodafinil demonstrated better positive dynamics in all components in relation to patients using only motivational counseling.

The addition of armodafinil in patients with shift work disorder helhed to affect dynamics of geometric indicators somewhat differently depending on gender. Combined therapy in women significantly reduced WC after 3 months. when the use of motivational counseling alone did not lead to significant changes in body geometry in either women or men. In men, on the contrary, combined therapy led to a significant decrease in HC after 6 months and WC decreased faster and with greater reliability. In psychosocial indicators gender differences were not observed in both groups of examined patients. Anxiety and depression showed better values at the end of the study in group with combined therapy.

While the level of sleepiness according to Epworth scale eliably reduced on combined therapy already after 3 months and continued to reliably decrease until end of study. We mentioned the improvement of sleep quality, which was normalized at the end point of control.

Combined therapy with armodafinil in 2nd group in contrast to the 1st group leaded to significant decrease in blood pressure, total cholesterol, VLDL, atherogenicity index HOMA index and glycemia for 6 months. Armodafinil also affected level of serotonin and leptin after 3 months, concentration of serotonin increased reliably all time and leptin decreased reliably.

Thus, our results confirmed the hypothesis of a placebo controlled, double-blind, randomized study (Julia L Chapman at all., 2018), that armadafinil in complex therapy can influence on BMI and has additional metabolic positive effect in patients [26].

Thus, results of conducted study allow us to state that use of motivational counseling is advisable to combine with armodafinil therapy in patients with shift work and excessive daytime sleepiness.

CONCLUSIONS

The patient-oriented approach in motivational counseling for lifestyle correction in patients of working age with obesity can be used effectively with 5,51% reduction in body weight for 6 months period and lead to positive trends in the dynamics of such indicators as blood pressure, eating behavior, level of anxiety and depression, level of quality of life, quality of sleep, leptin level. In patients with concomitant shift work sleep disorder additional armodafinil therapy allows to achieve the reduction in body weight in more than 15% (16.52±0.98%) for six months and initiate more significant improvement in sleepiness, sleep quality, quality of life, eating behavior, anxiety and depression levels, physical activity, metabolic disturbance, diabetes risk, serotonin and leptin levels. The use of armodafinil was not accompanied by side effects. Armodafinil can be considered in the complex treatment of obesity, especially with accompanying shift work sleep disorder.

REFERENCES

1. Wharton S, Lau DCW, Vallis M, et al. Obesity in adults: a clinical practice guideline. CMAJ 2020;192(31):875-891. doi:10.1503/cmaj.191707.
2. Nastanova 00500. Obesity treatment guideline DUODECIM MedicalPublications, Ltd. 2017 [cited 2023 May 10]. https://guidelines.moz.gov.ua/documents/3336
3. Obesity Canada published First Update to 2020 Adult Clinical Practice Guidelines: press release. 2022 Oct 21 [cited 2023 May 10]. https://obesitycanada.ca/
4. North American Association for the Study of Obesity National Heart Lung and Blood Institute National Institutes of Health (U.S.) NHLBI Obesity Education Initiative. The Practical Guide: Identification Evaluation and Treatment of Overweight and Obesity in Adults. Bethesda Md: National Institutes of Health National Heart Lung and Blood Institute NHLBI Obesity Education Initiative North American Association for the Study of Obesity [serial online]. 2000 Oct [cited 2023 May 10]. https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf
5. Yumuk V, Tsigos C, Fried M, et al. European Guidelines for Obesity Management in Adults. Obes Facts 2016; 9(1):642015. doi:10.1159/000442721.
6. Mayer SB, Graybill S, Raffa SD, et al. Synopsis of the 2020 U.S. VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity. Mil Med 2021;186(9-10):884-896. doi: 10.1093/milmed/usab114.
7. Obesity: identification, assessment and management Clinical guideline [CG189]. Published: 27 November 2014. [serial online] 2022 September 08 [cited 2023 May 10]. https://www.nice.org.uk/guidance/cg189/chapter/Recommendations#pharmacological-interventions
8. Call for authors - Special issue: Interventions for the treatment of persons with obesity Deadline of submission. [serial online] 17 June 2022 [cited 2023 May 10]. https://www.who.int/news-room/articles-detail/call-for-authors-special-issue-interventions-for-the-treatment-of-persons-with-obesity
9. Weight Loss Agents. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases [serial online] 2020 June [cited 2023 May 10]. https://pubmed.ncbi.nlm.nih.gov/31644235/
10. Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int. J. Obes. 2011;36(6):843-854. doi: 10.1038/ijo.2011.158.
11. Raatz, Sarah, and Amy C Gross. "Clinical Assessment and Treatment of Early-Onset Severe Obesity." Current obesity reports. 2021;10(1):31-38. doi:10.1007/s13679-020-00418-6.
12. National clinical evidence based guideline «Obesity in adults» [serial online] 2023 March [cited 2023 May 10]. https://www.dec.gov.ua/mtd/ozhyrinnya-u-doroslyh/
13. Pedersen SD, Manjoo P, Wharton S. Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy for Obesity Management. Adult Obesity Clinical Practice Guidelines are a living document, with only the latest chapters posted at obesitycanada.ca/guidelines. Update History Version 2, [serial online] 2022 October 21 [cited 2023 May 10]. https://obesitycanada.ca/guidelines/pharmacotherapy
14. Bray GA, Frühbeck G, Ryan DH, et al. Management of obesity. Lancet. 2016 May 7; 387(10031):1947-56. doi: 10.1016/S0140-6736(16)00271-3.
15. Gadde KM, Martin CK, Berthoud HR, et al. Obesity: Pathophysiology and Management. J Am Coll Cardiol. 2018 Jan 2; 71(1):69-84. doi: 10.1016/j.jacc.2017.11.011.
16. American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine. 2014:215-220.
17. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013, p. 391. doi: 10.1176/appi.books.9780890425787.
18. Thorpy MJ. Classification of sleep disorders. Neurotherapeutics. 2012;9(4):687-701. doi: 10.1007/s13311-012-0145-6.
19. Food and Drug Administration. FDA-approved Labeling Text for NDA 21-875/NUVIGIL™ (armodafinil) Tablets; 2007 June 15. http://www.accessdata.fda.gov
20. Ferraro L, Fuxe K, Tanganelli S, Tomasini MC, Rambert FA, Antonelli T. Differential enhancement of dialysate serotonin levels in distinct brain regions of the rat by modafinil: possible relevance for wakefulness and depression. J Neurosci Res. 2002;68(1):107-112.
21. Mitchell HA, Bogenpohl JW, Liles LC, et al. Behavioral responses of dopamine beta-hydroxylase knockout mice to modafinil suggest a dual noradrenergic – dopaminergic mechanism of action. Pharmacol Biochem Behav. 2008;91(2):217-222.
22. Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y. Dopaminergic D 1 and D2 receptors are essential for the arousal effect of modafinil. J Neurosci. 2008;28(34):8462-8469.
23. Maski, Kiran et al. "Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline." Journal of clinical sleep medicine: JCSM : official publication of the American Academy of Sleep Medicine. 2021;17(9):1881-1893. doi:10.5664/jcsm.9328
24. Waist Circumference and Waist-Hip Ratio Report of a WHO Expert Consultation. 2008 Dec 8-11; GENEVA; 2008. p.14. [cited 2023 May 10]. http://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf?sequence=1

25. Order of the Ministry of Health of Ukraine №564 dated 13.06.2016. Unified clinical protocol of primary, secondary (specialized) and tertiary (highly specialized) medical care for the prevention of cardiovascular diseases. Kyiv. 2016. 18 p.
26. Chapman JL, Cayanan EA, Hoyos CM, Serinel Y, Comas M, Yee BJ, Wong KKH, Grunstein RR, Marshall NS. Does Armodafinil Improve Driving Task Performance and Weight Loss in Sleep Apnea? A Randomized Trial. Am J Respir Crit Care Med. 2018 Oct 1;198(7):941-950. doi: 10.1164/rccm.201712-2439OC.

ORCID AND CONTRIBUTIONSHIP
Victoria I. Tkachenko: 0000-0002-0789-5340[A,C,E,F]
Taisiia O. Bagro: 0000-0001-6881-8229[A,B,C,D]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 04.06.2023
ACCEPTED: 05.09.2023

ADDRESS FOR CORRESPONDENCE
Victoria I. Tkachenko
Family Medicine Department,
Shupyk National Healthcare University of Ukraine
Dorogozhytska 9, 04112, Kyiv, Ukraine
e-mail: witk@ukr.net

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 558-562

ORIGINAL ARTICLE

DOI: 10.36740/Merkur202305116

USING THE SENSORY INTEGRATION TECHNIQUE FOR PEOPLE WITH AUTISM SPECTRUM DISORDERS DURING TRAINING AT THE CLIMBING SECTION

Tereza M. Klymus[1], Tetyana V. Ravchyna[2], Olha Herus[1] , Marta Ya. Kozak[1], Tamara G. Tiurina[1], Mariana V. Shkoliar[1], Gianpaolo Marcucci[3]

[1]LVIV POLITECHNIK NATIONAL UNIVERSITY, LVIV, UKRAINE
[2]SEPARATE STRUCTURAL UNIT "TECHNICAL VOCATIONAL COLLEGE OF LVIV POLYTECHNIC NATIONAL UNIVERSITY", LVIV, UKRAINE
[3]HUMAN ADVISOR PROJECT, SCIENTIFIC COMMITTEE, ROME, ITALY

ABSTRACT

Aim: To analyze the practical application of the sensory integration technique for individuals with autism spectrum disorder at a climbing section, and to investigate the impact of physical activity on improving their proprioceptive and vestibular systems.

Materials and Methods: The method of included participant observation at the climbing classes with constant recording the behavior (desirable and undesirable) was used. The sensory screening (developed by J. Ayres) was applied for recording and determining the sensory systems of the people with ASD before the start of training and again after a month. The scale of Sensory Integration and Praxis Tests (SIPT) was used for assessing certain aspects of participants' sensory processing or perception according to the goals set during the climbing classes.

Results: The results of the research showed that the application of the sensory integration technique for individuals with ACD at a climbing section promoted the dynamics of changes in their sensory system during training considering the characteristics of their sensory system. The positive changes were observed in the way the people with ACD felt about their own bodies and their involvement in sports activities that in its turn made it possible to be active and develop their sensory system. It has been identified that while planning training for the people with ASD it is necessary to take into account sensory modulation (reading sensory signals) and apply exercises for stimulating sensory sensations that will improve the motor activity of persons with ASD, their social interaction, and safety, as well.

Conclusions: During training at the climbing section sensory information processing of the individuals with ASD have the impact on their body control, hand-eye coordination, and hand sensitivity during training. The improvement of sensory information processing in its turn enables people with ASD to master climbing.

KEY WORDS: autism spectrum disorder, sensory system, climbing classes, sensory integration technique, sensory information processing, screening, Sensory Integration and Praxis Tests

INTRODUCTION

Autism spectrum disorders (ASD) are a spectrum of complex disorders resulting in the impaired brain development and characterized by a pronounced and comprehensive deficit in social and emotional interaction and communication, as well as limited interests and repetitive actions. These disorders are not connected with general development delay. They are associated with the sensory dysfunction that is the functioning of one or more sensory channels (transmitters of information from the senses) is disturbed. The persons with autism spectrum disorders (ASD) have the disrupted editor that interprets the information about senses, so there is the distortion or disconnection of perceiving any type of feelings. Physical therapy is an effective method of rehabilitation for ASD. Systematic physical therapy classes promote the child's physical development, and help improve his or her academic achievements. Mental development is closely related to the physical one, so the use of physical therapy in rehabilitating the individuals with ASD is very important and essentially effective. Such persons are not only interested in new movement skills but also adapt faster to the team. Physical therapy has not only physical aspects, but also social ones.

An excellent substitute for physical therapy is adaptive climbing - paraclimbing. Paraclimbing classes for the people with ASD have a positive impact on their intellectual development, and motor skills. By performing various combinations and elements of movements on the climbing wall, persons with ASD learn to think differently, find their own ways of passing the track, and keep their balance.

The effects of adaptive climbing for the people with ASD are as follows:

1. Physical effects:
   a. active classes contribute to positive changes in behavior;
   b. vigorous exercises to reduce non-adapted behavior are defined as the aerobic activity in which oxygen is used as the main source of energy;
   c. as a result of physical exercises, two types of nerve cells develop in the body: those that make a person more alert, and those that help control the level of arousal and concentration;
   d. physical exercises promote the formation of new neural connections in the human brain.
2. Psychological effects:
   a. the reduction of anxiety, and depression;
   b. the increase of self-esteem;
   c. the increase of the ability to self-regulate;
   d. the improvement of the attention concentration [1].

AIM

The purpose of the study is to analyze the practical application of the sensory integration technique for individuals with autism spectrum disorder at a climbing section, and to investigate the impact of physical activity on improving their proprioceptive and vestibular systems. We have hypothesized that the use of sensory integration technique for people with ASD during climbing would contribute to their better physical development and social interaction with others.

MATERIALS AND METHODS

The study involved five young people aged 15-17 years who were diagnosed with ASD. The participants demonstrated stereotypical behavior, impaired coordination of movements, and aggression. The classes took place at the climbing wall in Lviv. All participants had the individual classes that made it possible to observe everyone.

The study was conducted by the method of included participant observation at the climbing classes with constant recording the behavior (desirable and undesirable). The researcher (instructor) determined the capabilities of the participants and the corresponding available tasks. While observing, the sensory systems were recorded to determine hypo/hypersensitivity and enter data into the sensory screening.

Research stages:

1. Preparatory stage. Developing the sociological research program.
2. Field stage. Gathering the empirical material, accumulating the necessary information.
3. Analytical stage. Analyzing the research results and developing the recommendations.

Research period: August-September 2021.

We analyzed the sensory screening developed by J. Ayres, which we applied observing the people with ASD before the start of training and again after a month [2].

It is important to note that the sensory screening is not a complete set of diagnostic criteria for defining a diagnosis of "sensory signal processing disorders, sensory disintegration". It is rather a tool for those who communicate directly with a person in order to take into consideration certain peculiarities while planning classes. Specialists who are authorized to diagnose this disorder use other diagnostic tools to test a person for this disorder.

RESULTS

It should be noted that the screening at the first stage was carried out during the first 3 days of the first week, as the Applied Behavioral Analysis (ABA) technique indicates that only three to four days of observation is sufficient to determine the function of sensory system impairment of individuals with ASD [3]. Thus, based on the screening, the following signs of sensory system disorders of the participants were identified: vestibular hypofunction, proprioceptive hyperfunction, and tactile hyperfunction. The data are presented in Table 1.

There were also signs of sensory overload. Suddenly there were:

- screaming;
- aggression;
- autoaggression;
- attempts to run away or hide;
- refusal to perform tasks.

At the first stage of our research, we also identified stereotypic movements, sensory self-stimulation (rocking, knocking on objects), fear of entering an unfamiliar room, which manifested itself through shouting and refusal. Three out of five had the manifestations of aggression (beating others and strangers, hitting objects with hands and feet). All the five examined participants had manifestations of autoaggression (hitting themselves on the head, legs, arms, biting their hands) [5]. Three of them showed awkward movements of large muscle groups, a predisposition to stoop, and unnecessary movements while performing their tasks.

Table 1. Manifestations of sensory system disorders [2, 4]

Sensory system	Type of dysfunction	Manifestations
Vestibular	Hypofunction	Chaotic motor activity during classes: climbing on different surfaces, on any high surfaces, running around the hall, not sitting still for a minute
Proprioceptive Tactile	Hyperfunction	Unsystematic movement of hands while walking, increased muscle tone, motor stereotypies
Tactile	Hyperfunction	Selective about touching different textures of materials when changing clothes and climbing.

Table 2. A set of special games and exercises on sensory integration

A set of special games and exercises	The target of influence
Rotation in a circle; swinging in a hammock; rolling from the back to the stomach on a large ball; the need to get out of a confined space; balancing on a board; crawling and walking on an uneven, sloping, unstable surface	Vestibular and proprioceptive systems
Playing with brushes, feathers, fur balls, thorns, spikes of different shapes and degrees of hardness; using natural materials (cones, chestnuts, sea stones, wooden blocks); dipping hands in rice, peas, flour and small stones; playing with glass balls and small figures immersed in water; walking barefoot on large stones, pebbles, wooden logs, hard prickly rugs.	Tactile system

During the classes, we used the set of special games and exercises on sensory integration aimed at stimulating the work of analyzers in the conditions of the coordination of different senses, as shown in Table 2.

The purpose of these exercises was to improve the sensory systems, as the climbing:

involves hands, feet, which grasp various surfaces of different smoothness, and develops the precision of movements;

activates proprioceptive muscles - a sense of security, and own body, the coordination of movements;

promotes the balancing of the body at a height [6].

There are two types of movement planning disorders in the theory of sensory integration: bilateral integration and sequencing (BIS), and somatodyspraxia (SD). In terms of progressive deficit, the following indicators are important: tone of the extensor muscles, maintenance of balance, stability of the proximal parts of limbs, ability to bend the neck against gravity. Praxis (Greek: pragma - action) is a complex set of analytical and synthetic processes aimed at organizing a complete motor act, that is, the automated implementation of learned movements. Performing such movements "in one breath" requires sufficient visual and spatial orientation, and a constant flow of information about the progress of the performed actions [7-9].

According to our observation, individuals with ASD who attended the classes did not show fear of moving at heights but on the contrary, all of them sought to climb high enough, showing the so-called gravitational confidence disproportionate to their motor disorders [10]. It was the desire to climb as high as possible that influenced the implementation of the trainer's instructions. At the beginning, all the participants protested the exercises before climbing up, while three months later they clearly followed the trainer's instructions in the warm-up at the beginning of the class that lasted 5 minutes [11].

As a result, Table 3 shows the data before the start of training for climbing classes and three months later. It should be noted that each young person had the individual classes. Assessments of the changes were recorded before the start of the classes, when all participants were tested, and three months later. Points were assigned from – 0 to 3, where 0 is non-fulfillment, 3 is 100% fulfillment, and 0 is the median.

DISCUSSION

The trainer monitored the participants every three months in accordance with the goals set during the climbing classes. The data were analyzed using the SIPT scale (Sensory Integration and Praxis Tests). Sensory Integration and Praxis Tests (SIPT)

Table 3. Assessments of the changes before the start of the classes and three months later

	July, 1								September, 30							
Eye control																
Smooth follow up of movement	0	-1	-2	-2	-1	-1	-1	0	2	1	1	2	2	1	1	1
Separate movement eye/head	1	2	2	1	1	1	0	2	2	3	3	3	2	2	1	1
Fast localization	-3	-3	-3	-2	-2	-3	-2	-2	1	1	1	1	1	0	1	1
Adaptive responses																
Reaction to passive stimuli	-3	-3	-3	-3	-3	-3	-3	-3	-2	-1	-2	0	-2	-1	-1	-1
Strong grip in a stationary position	1	0	0	1	1	1	1	1	2	2	1	2	2	3	3	1
Pushing, moving, rolling out (swinging out)	2	2	2	3	2	2	2	2	3	3	3	3	3	3	3	3
Impaired modulation of sensory perceptions																
Vestibular	0	1	0	0	1	0	1	1	1	2	1	1	2	2	2	2
Tactile	-2	-2	-1	-1	-2	-2	-1	-1	0	0	1	1	1	0	0	1
Proprioceptive	1	0	0	1	1	1	1	1	1	2	1	1	2	2	2	2

help us understand why some individuals have difficulty learning or behaving in the way we expect them to. The SIPT does not measure intelligence in the usual sense of the word, but it does assess some of the important abilities needed to live in the world. It does not measure language development, academic achievement, or social behavior, but it does assess certain aspects of sensory processing or perception that are related to these functions [12].

In the course of the assessment, the participants completed four types of overlapping subtests: (1) non-motor visual perception, (2) somatosensitivity, (3) praxis, (4) sensorimotority [1,6].

NON-MOTOR VISUAL PERCEPTION

This test assesses the ability to visually perceive and distinguish between shape and space without the need for coordination. Space visualization is a puzzle-like test where a person indicates which of the two shapes is a right choice. The examiner monitors whether the persons used their right or left hand while picking up the cubes, and in doing so whether they crossed the midline of the body or tended to use each hand on their side of the body. The test measures how well an image is visually perceived against a confusing background [13-15].

SOMATOSENSITIVITY

This test assesses tactile, muscle and joint perception ("Soma" means "body"). During somatosensory testing it is recommended to "feel" rather than "see". A large piece of cardboard held over the area where the hands and arms are working helps to focus on what the person being tested is feeling. Touching where a person cannot see the touch often causes discomfort, even if none of the tactile stimuli causes harm. If the negative reaction to testing is strong, the response is called the "tactile defense."

On the manual perception of a form a person recognizes with the help of tactile and kinesthetic senses unusual shapes that are held in the hand. In kinesthesia the conscious feeling of joint position and movement is assessed by trying to put the finger in the same place where the trainer previously put it. Three tests measure the tactile perception: a) finger identification, during which the person points to the finger that the trainer touched; b) grapheme, in which the individual draws with the finger the same simple pattern that the trainer drew on the back of the palm; c) localization of the tactile stimuli, in which the person points to the place where the trainer lightly touched the person's hand.

PRAXIS

Praxis is assessed in five different ways:

1. Verbal command assesses the ability to interpret verbally given instructions to take up certain positions and then assume them. A typical test task might be "Put your hands on your head".
2. Design Copying assesses the ability to copy simple designs.
3. Constructional Praxis assesses an individual's ability to build with bricks using the structures built by the trainer as models. Both design copying and constructional praxis require the visual form and spatial perception in addition to practical ability.
4. Postural practice requires a person to imitate unusual body postures adopted by the trainer.
5. Sequencing Praxis asks the individual to imitate a series of simple arm and hand positions [16].

SENSORIMOTORITY

Four sensorimotor tests are included in the SIPT because their tasks require sensory integration. Bilateral motor coordination assesses the ability to coordinate two sides of the body in a series of hand movements. Standing and walking balance assesses the degree of sensory integration of proprioceptive (muscle and joint) and vestibular (gravity and head movement) senses. In terms of movement accuracy, hand-eye coordination is measured by how well a person draws a line on top of a printed line. Completing the task requires the control of eye muscles, practical skills, visual perception, and coordination of movements. Finally, postrotational nystagmus measures the duration of reflexive eye movements back and forth after body rotation (10 times in 20 seconds). This observation is one way of saying how well the nervous system integrates senses from the vestibular system [15,17-20].

The summarized results presented in Table 3 for each training participant according to SIPT showed the dynamics of changes in the sensory system of young people with ASD during training, taking into account the characteristics of their sensory system. We also observe positive changes in the way people feel about their own bodies and their involvement in sports activities, which in turn makes it possible to be active and develop their sensory system.

Therefore, we conclude that when planning training for people with ASD, it is necessary to take into account sensory modulation (reading sensory signals) and plan exercises to stimulate sensory sensations that will improve the motor activity of persons with ASD, their social interaction, safety and leisure.

CONCLUSIONS

The research methods presented above make it possible to identify and determine the impact of sensory information processing of the individuals with ASD on their body control, hand-eye coordination, and hand sensitivity during training. We also conclude that the outcome of forming the climbing skills of individuals with ASD is closely connected with the impairment and development of their sensory system. The analysis of scientific sources shows that the ergotherapist is the specialist who is aware of sensory integration, and directly identifies the system of disorders, draws up the training plan, taking into account the impact of the training class on the development of the sensory system. We have analyzed SIPT diagnostics as a tool for determining disorders and a point of reference (support) for organizing sports training. The research results show the positive dynamics in the improvement of sensory information processing, which in its turn enables people with ASD to master climbing.

REFERENCES

1. Rincover A. How to use Sensory Extinction. Part of the series Teaching the Autistic. Pro-Ed, 1981.
2. Ayres AJ, Tickle LS. Hyper-responsibility to touch and vestibular stimuli as a predictor of positive response to sensory integration procedures by autistic children. The American Journal of Occupational Therapy. 1980;34:375-381.
3. Fedorenko MV. Tekhnolohiyi rehulyatsiyi povedinky u ditey z rozladamy autystychnoho spektru. Psykholohichnyy chasopys: zbirnyk naukovykh prats' Kyyiv. Instytut psykholohiyi imeni H. S. Kostyuka Natsional'noyi akademiyi pedahohichnykh nauk Ukrayiny. 2017;1(5):53-65.
4. Skrypnyk TV. Fenomenolohiya autyzmu: monohrafiya. Kyiv: Feniks. 2010
5. Watling RL, Deitz J, Kanny EM, McLaughlin JF. Current practice of occupational therapy for children with autism. American Journal of Occupational Therapy. 1999;53:489-505
6. Horak FB, Macpherson JM. Postural orientation and equilibrium. In: Rowell LB, Shepard JT, eds. Handbook of Physiology: Section 12, Exercise Regulation and Integration of Multiple Systems. New York: Oxford University Press. 1996;255-92.
7. Ayres J. Sensory Integration and the Child. Los Angeles: Western Psychological Services, 1979:1-269.
8. Teasdale N, Simoneau M. Attentional demands for postural control: the effects of ageing and sensory reintegration. Gait Posture. 2001;14:203-10. doi: 10.1016/s0966-6362(01)00134-5.
9. American Occupational Therapy Association. Occupational therapy practice framework: Domain and process (2nd ed). American Journal of Occupational Therapy. 2008;62:625-683.
10. Bundy A. Consultation and sensory integration theory. In A.G. Fisher, E.A. Murray, A.C. Bundy (Eds.), Sensory integration: Theory and practice. Philadelphia: F.A. Davis. 1991:318-332.
11. Jim Hinojosa, Paula Kramer, Charlotte Brasic Royeen. Perspectives on Human Occupations: Theories Underlying Practice. F.A. Davis.2017:378 p.
12. Shmonin AA. Ergoterapiya v reabilitatsyi nevrologicheskikh patsientov [Ergotherapy in the rehabilitation of neurological patients]. Consilium Medicum. 2016;2:59-60. (Russian)
13. Lovaas O.I. Behavioral treatment and normal intellectual and educational functioning in autistic children. Journal of Consulting and Clinical Psychology. 1987;55:3-9.
14. Baranek G. Efficacy of sensory and motor interventions for children with autism. J Autism Dev Disord. 2002;32(5): 397-422. doi: 10.1023/a:1020541906063.
15. Case-Smith J, Nastro MA. The effect of occupational therapy intervention on mothers of children with cerebral palsy. American Journal of Occupational Therapy. 1993;47:811-817.
16. Camicioli R, Howieson D, Lehman S. Talking while walking: the effect of a dual task in ageing and Alzheimer's disease. Neurol. 1997;48:955-8.
17. Sinha Y, Silove N, Wheeler D, Williams K. Auditory integration training and other sound therapies for autism spectrum disorders: a systematic review. Arch Dis Child. 2006;91(12):1018-1022. doi: 10.1136/adc.2006.094649.
18. Johnson-Ecker C, Parham LD. The evaluation of sensory processing: a validity study using contrasting groups. American Journal of Occupational Therapy. 2000;54:494-503.
19. Case-Smith J, Bryan T. The effects of occupational therapy with sensory integration emphasis on preschool-age children with autism. Am J Occup Ther. 1999;53(5):489-97. doi: 10.5014/ajot.53.5.489.
20. Tarbox J, Wallace MD. Functional analysis and treatment of low-rate problem in individuals with developmental disabilities. Behav Interv. 2004;19:73-90. doi: 10.1002/bin.156.

ORCID AND CONTRIBUTIONSHIP

Tereza M. Klymus: 0000-0003-0954-7275[A-F]
Tetyana V. Ravchyna: 0000-0002-0361-1347[A,D,E]
Olha Herus 0000-0003-1780-3793[B,C]
Tamara G. Tiurina: 0000-0001-9421-9350[B,E]
Marta Ya. Kozak: 0000-0002-8204-11OX[B,C,E]
Mariana V. Shkoliar 0000-0003-1890-2363[F]
Gianpaolo Marcucci: 0000-0003-4653-0851[E,F]

ADDRESS FOR CORRESPONDENCE

Marta Ya. Kozak
Lviv Polytechnic National University
12 Bandera St., 79013 Lviv, Ukraine
e-mail: m_fedyk@yahoo.com

CONFLICT OF INTEREST

The Authors declare no conflict of interest

RECEIVED: 22.04.2023
ACCEPTED: 09.09.2023

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 563-568

REVIEW ARTICLE

DOI: 10.36740/Merkur202305117

PSYCHIATRIC DISORDERS IN AUTOIMMUNE ENCEPHALITIS – LITERATURE REVIEW

Sandra Wcisło[1], Katarzyna Bojkowska-Otrębska[2], Beata Łabuz-Roszak[3,4]

[1]STUDENT SCIENTIFIC ASSOCIATION AT THE DEPARTMENT OF NEUROLOGY, INSTITUTE OF MEDICAL SCIENCES, UNIVERSITY OF OPOLE, OPOLE, POLAND
[2]CLINICAL DEPARTMENT OF GERIATRICS, INSTITUTE OF MEDICAL SCIENCES, UNIVERSITY OF OPOLE, OPOLE, POLAND
[3]DEPARTMENT OF NEUROLOGY, INSTITUTE OF MEDICAL SCIENCES, UNIVERSITY OF OPOLE, OPOLE, POLAND
[4]DEPARTMENT OF NEUROLOGY, ST. JADWIGA REGIONAL SPECIALIZED HOSPITAL, OPOLE, POLAND

ABSTRACT

Autoimmune encephalitis (AE) is a non-infectious inflammatory disease caused by the presence of autoantibodies directed against neuronal surface or intracellular antigens. Its incidence in Western countries is about 0.8 per 100,000 people. AE requires differentiation primarily with psychiatric diseases, but it also requires oncological vigilance. On the other hand, in the case of an acute episode of psychosis, differentiation with AE should always be pursued. This paper discusses the most common psychiatric disorders that occur in autoimmune encephalitis.

KEY WORDS: autoimmune encephalitis, onconeuronal antibodies, psychosis

INTRODUCTION

Autoimmune encephalitis (AE) is a non-infectious inflammatory disease caused by the presence of antineuronal antibodies (autoantibodies directed to neuronal surface antigens or intracellular antigens). The incidence of AE in Western countries is about 0.8 per 100,000 inhabitants [1]. The disease is more common in women (the female-to-male ratio is about 8:2), and about 37% of patients are younger than 18 years at the time of onset [2].

Onconeuronal (intracellular) antibodies are believed to be a biological indicator of concurrent cancer, but are not a pathogenic mediator of the disease. Under physiological conditions, these antibodies cannot bind to the antigen, since exposure of the antigen would require cell damage. In contrast, antibodies to neuronal surface antigens are pathogenic, that is responsible for the development of the disease.

AE is characterized by a wide spectrum of clinical manifestations, ranging from typical limbic system inflammation to a complex neuropsychiatric manifestation with memory disorders, psychosis, epileptic seizures and movement disorders, and even coma [3].

The aim of the paper was to review the current literature in the field of autoimmune encephalitis, with particular emphasis on psychiatric disorders.

REVIEW AND DISCUSSION

ANTINEURONAL ANTIBODIES AND NEOPLASMS

If AE is suspected, testing for antineuronal antibodies is recommended. A specific type of antibody is most often associated with a specific type of cancer and/or clinical manifestation.

Antibodies directed against intracellular antigens (so-called onconeuronal) are directed against the following antigens, among others: Hu, Yo, Ri, Ma2, CV2/CRMP5, amphiphysin and glutamic acid decarboxylase. These antibodies are associated with cancer and can cause specific neurological syndromes. For clinical presentation to occur, nerve cell damage must be present.

The presence of anti-Hu antibodies (ANNA-1) is mainly associated with encephalomyelitis, limbic encephalitis, brainstem inflammation, cerebellar syndrome, myelitis, autonomic system disorders. These autoantibodies are associated with small-cell lung cancer (SCLC). Anti-Yo antibodies (PCA-1) coexist with cancers of the reproductive system in women and breast cancer. They can give symptoms of cerebellar syndrome. Anti-Ri onconeuronal antibodies (ANNA-2) most often cause opsoclonus-myoclonus syndrome. Anti-Tr antibodies (DNER), on the other hand, are associated with Hodgkin's lymphoma and can cause clinical symptoms in the form of cerebellar syndrome. An association of SCLC and/or thymoma with the presence of anti-CV2/CRMP5 antibodies has been noted, which most often manifests itself in the form of encephalomyelitis, cerebellar syndrome, chorea and/or peripheral polyneuropathy. The presence of onconeuronal antibodies to the Ma2 protein can be associated with testicular germ cell tumor and lung cancer. Encephalitis caused by the presence of these antibodies will produce symptoms of limbic encephalitis and damage to the hypothalamus. The association of breast and lung cancer with amphiphysin antibodies has been noted, which can present clinical manifestations in the form of stiff-person syndrome and encephalomyelitis [3].

Antibodies directed against neuronal surface antigens, such as glutamate receptor selectively stimulated by N-methyl-D-aspartate (NMDAR), glycine receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolopropionate (AMPAR)-stimulated receptor, gangliosides GQ1b, DPPX, CASPR2 and LGI1 are pathogenic antibodies, i.e. responsible for the development of the disease. The essence of autoimmune encephalitis is the presence of autoantibodies in serum and cerebrospinal fluid (CSF), mainly of the IgG class, which attach to the extracellular domain of the surface protein (antigen) [4]. Unlike onconeuronal antibodies, autoantibodies to surface antigens can attach to the antigen without damaging the cell, thus leading to the development of various clinical manifestations. In 63% of cases, autoimmune encephalitis caused by autoantibodies directed against surface antigens coexists with cancer, most often of the lung, breast, thymus or ovary [3].

Antibodies directed against the NMDA receptor are by far the most frequently detected in young women (four times more often than in men), and are mainly associated with ovarian teratoma. The presence of antibodies directed against LGI1 is associated with thymoma, thyroid, lung or kidney cancer. Antibodies to CASPR2, AMPA, against the GABA-A, GABA-B receptor often co-occur with thymoma, as well as small cell lung cancer. The average age of patients is 60 years. A correlation of mGluR5 antibodies with the co-occurrence of malignant granuloma was noted. Other autoantibodies directed against the α1 glycine receptor, DPPX, are marginally associated with the presence of cancer (in <10% of patients). In the case of DR2 antibodies, no association with cancer coexistence was detected [3].

CLINICAL CHARACTERISTICS OF AUTOIMMUNE ENCEPHALITIS

Autoimmune encephalitis is a severe inflammatory disease of the brain, clinically manifested by a rapidly progressive encephalopathy of acute or subacute onset (usually developing in no more than six weeks) [5]. Specific clinical syndromes include anti-NMDAR encephalitis, limbic system encephalitis and Bickerstaff brainstem encephalitis [6].

Anti-NMDAR antibodies are the most commonly identified cause of autoimmune encephalitis. The relative incidence of different forms of antibody-induced encephalitis is difficult to assess. According to 2011 data, anti-NMDAR antibodies are responsible for 50% of autoimmune encephalitis, 30% of anti-LGI1 antibodies, 3% of CASPR2 antibodies, 5% of AMPA antibodies, and GABAB receptor antibodies and 1% of anti-glycine antibodies, respectively [3].

Autoimmune encephalitis caused by anti-NMDAR antibodies is characterized by a distinctive clinical picture. 80% of patients are female, with an average age of 21 years [4]. In 70% of patients, there is a prodromal phase that begins the disease with: headache, fever, vomiting, diarrhea and/or features of upper respiratory tract infection, preceding the onset of encephalitis symptoms by about 1-2 weeks. Prodromal symptoms are less common in older patients [7].

This is followed by a sudden change in personality and the appearance of other mental disorders. Anxiety, insomnia, delusions, hallucinations, manic behavior and/or hypersexuality are very common [3]. Anti-NMDAR antibodies of the IgG class found in CSF are directed against the GluN1 subunit of the receptor. Tumors coexist with encephalitis with anti-NMDAR antibodies in about 58% of women >18 years of age (ovarian teratoma is the most common). Adolescents and adults usually show behavioral disturbances (psychosis, delusions, hallucinations, agitation, aggression or catatonia) with irritability and insomnia, followed by speech disorders, dyskinesias, memory deficits, autonomic instability and decreased level of consciousness. Cohort studies show that children have a markedly higher incidence of movement disorders and epileptic seizures in the course of this disease compared to adult patients [6]. Movement disorders also occur in the later phase of the disease. They can be diverse in nature: choreiform movements, stereotypy, ataxia, dyskinesias, rigidity and/or postural disturbances [3].

Epileptic seizures can occur early or later in the course of the disease, and can be focal or generalized. They appear earlier in men and require antiepileptic treatment, sometimes with multiple drugs [6, 7]. The frequency and intensity of epileptic seizures decrease as the disease progresses.

An observational cohort study conducted between 2007 and 2012 involving 577 patients with autoimmune encephalitis associated with NMDA receptor antibodies found that by the end of the first month of illness, 87% of patients had four or more of the following symptoms:

- behavioral disorders;
- memory disorders;
- speech disorders;
- disorders of other cognitive functions;
- epileptic seizures;
- dyskinesias of the limbs, trunk and/or orofacial;
- loss of consciousness;
- autonomic disorders;
- central hypoventilation;
- focal symptoms.

In <5% of patients, the disease manifestation was monosymptomatic [6]. It is likely that about 1% of patients will have a purely monosymptomatic disease manifestation, such as isolated psychosis, after a few months [1].

Criteria for the diagnosis of autoimmune encephalitis include:

- occurrence of ≥4 symptoms listed above <3 months with the exception of memory impairment and hemiparesis/cerebellar ataxia;
- abnormal electroencephalographic (EEG) findings (focal or diffuse slowing or basal abnormalities, epileptiform activity, strongly expressed delta waves) and/or pleocytosis and/or oligoclonal striations on CSF examination;
- exclusion of other causes of the disease.

Memory disorders were excluded because of the difficulty of evaluation in young children and patients with psychosis and/or agitation. Symptoms of hemiparesis and/or ataxia are less common and mainly affect children in combination with other symptoms [6].

A diagnosis of certainty can also be made if the patient presents with only one of the above symptoms and anti-NMDAR antibodies have been detected in its CSF or serum. With respect to the clinical picture, antibodies in the CSF are decisive (in 14% of patients antibodies are not present in serum).

The following tests can help in making the correct diagnosis: general CSF examination, EEG, magnetic resonance imaging (MRI) of the head, positron emission tomography (PET) with fluorodeoxyglucose, and determination of relevant antibodies in serum and CSF. Patients with cognitive impairment often have hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIDAH). Occasionally, patients may have paroxysmal arrhythmias, including mild changes in the electrocardiogram (ECG) up to complete heart block [1].

Autoimmune encephalitis caused by anti-NMDAR antibodies needs to be differentiated primarily from herpes encephalitis. Herpes simplex virus infection takes many clinical forms, ranging from asymptomatic, mucocutaneous infections and keratitis to the most severe, highly fatal central nervous system inflammation. Post-herpetic encephalitis is an autoimmune disease that mimics encephalitis with anti-NMDAR antibodies. The disease occurs in about 20% of patients after herpes encephalitis, so performing an anti-NMDAR antibody assay is mandatory if symptoms recur after previously diagnosed herpes encephalitis. In children, the disease usually manifests as choreoathetosis, while in adults it manifests as psychiatric disorders developing weeks or months after infection [6]. Despite tremendous advances in research on Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) infections, they remain an important clinical problem, dependent on the biological properties of the virus, such as neuroinvasiveness, neurotoxicity and latency, and because of the virus' widespread prevalence in the population [8, 9].

Inflammation of the limbic system can have a paraneoplastic or infectious background. The main areas of the limbic system are the hippocampus and the amygdala, which are the structures responsible for, among other things, memory, learning and emotions, including aggression. The disease is characterized by typical clinical symptoms in the form of subacute, less often acute onset of cognitive impairment, focal seizures with disturbances of consciousness or awareness, as well as epileptic seizures and psychiatric disorders (behavioral, affective disorders, especially disinhibition and emotional lability, as well as anxiety, psychosis) [10]. A characteristic symptom of limbic system inflammation is a particular form of epileptic seizures - facial-arm dystonic seizures, usually preceding the onset of memory disorders. These seizures show a strong association with anti-LGI-1 antibodies (against voltage-dependent potassium channels) [4]. They consist of very short, sudden, shock-like movements of one or more limbs, neck and facial muscles. They can occur dozens or even hundreds of times per day. Consciousness during a seizure is usually preserved. Characteristically, their frequency increases rapidly within a few days of onset. Seizures tend to be highly responsive to steroids and less responsive to antiepileptic drugs [1]. Limbic encephalitis is characterized by characteristic RM imaging in the form of a pathological increase in signal intensity of the medial part of the temporal lobe unilaterally or bilaterally, in T2-weighted images and in FLAIR sequences. Infective limbic encephalitis is usually caused by herpes simplex virus (HSV), including human herpes virus type 6 [10].

Bickerstaff brainstem inflammation is usually preceded by infection and is characterized by a subacute onset (less than 4 weeks), progressive impairment of consciousness along with ataxia and bilateral, mostly symmetrical ophthalmoparesis. Patients often have pupillary abnormalities, bilateral facial muscle paralysis, positive Babinski sign and palsy. There may be muscle weakness in the limbs, which overlap with features of Guillain-Barré syndrome. CS fluid pleocytosis is observed in almost half of the patients. IgG anti-GQ1b antibodies are highly specific for Bickerstaff inflammation [6].

PSYCHIATRIC DISORDERS

At the onset of symptoms, it is difficult to distinguish the disease from a primary psychiatric disorder. Other than clinical assessment, there are no specific predictive biomarkers. A study of nearly 600 cases has shown that, although rare, some patients may exhibit only psychiatric symptoms without neurological symptoms during a first episode or relapse [11].

Usually within 2 weeks of the onset of the disease, clear psychiatric symptoms and personality changes appear. Typical symptoms include anxiety, insomnia, hallucinations, delusions, agitation, and manic behavior. Social withdrawal and stereotypical behavior may also develop. Consequently, most patients in this phase see a psychiatrist. Cognitive changes, particularly attentional impairment, short-term memory loss and confusion are always present and increase with the duration of the disease. Speech problems, ranging from deterioration of verbal fluency to mutism, are commonly observed. Many patients often experience mental state fluctuations resembling delirium [5, 12].

In the later stages of the disease, the patient's state changes rapidly, and alternating agitation along with catatonia and an inability to follow verbal commands occur. The patient may present with a range of abnormal movements: various types of dyskinesias, choreoathetosis of the limbs and trunk, complex movements of the arms and legs, rigidity and opisthotonic postures [5].

Autonomic dysregulation, including thermodysregulation, cardiac arrhythmias, blood pressure instability and excessive drooling are late and severe manifestations of the disease and require treatment in an intensive care setting. Ultimately, coma, hypoventilation, and even death of the patient can occur [12].

The overlap in the clinical course of epidemiological and genetic associations raises the idea that autoimmune mechanisms may underlie some psychoses. Researchers are increasingly interested in the immunological basis of psychiatric disorders. In patients in acute psychosis, an increase in CD19+ lymphocytes and a decrease in CD3+ lymphocytes have been observed, along with an

altered CD4:CD8 ratio. In contrast, postmortem studies of patients have shown infiltration of CD3+ and CD20+ lymphocytes in areas of the brain that are functionally relevant to psychosis [13].

There is a report suggesting that passive antibody transmission in humans can potentially transmit severe neuropsychiatric disease. In one case, a 7-year-old boy developed autoimmune encephalitis after a bone marrow transplant with prominent behavioral features and measurable antibodies to VGKC, LGI1 and thyroglobulin [14].

A study was conducted in which serum was collected from 459 patients with schizophrenia, major depression or borderline personality disorder. Only two patients with classic encephalitis with anti-NMDAR antibodies (who had previously been misdiagnosed) were found to have GluN1 IgG antibodies. It was observed at the time that about 10% of patients with schizophrenia had IgA and/or IgM subtype antibodies. However, a year later, work by the same authors, again examining the sera of a control group, showed that the frequency of IgA and IgM antibodies in patients with schizophrenia was actually similar to that of patients in the control group. These studies underscore the fact that, unlike IgG anti-GluN1 antibodies, which are highly specific for encephalitis with anti-NMDAR antibodies, serum IgA and IgM antibodies to NMDAR subunits are similarly elevated in healthy controls and many of the disease groups studied, and the clinical significance of IgA and IgM antibodies is uncertain [11, 15, 16]. Anti-NMDAR antibody titers have also been shown to be higher at relapse compared to the first episode [11].

Psychosis also shares environmental risk factors with other autoimmune disorders, such as the influence of time of birth and latitude, which are hypothesized to be related to vitamin D status in newborns [17].

We retrospectively reviewed the medical records of children with a certain diagnosis of autoimmune encephalitis with anti-NMDAR antibodies from 2009 to 2019. One boy and nine girls, whose median age of onset was 3.6 years, were included in the study. The most common initial manifestation was verbal reduction and psychiatric symptoms immediately after flu-like prodromal symptoms. Almost all patients then developed reduced level of consciousness, mutism, seizures and oral-facial-tongue dyskinesias. Autonomic instability occurred in five patients, particularly in pre-pubertal children. Only one adolescent patient had ovarian teratoma. All patients survived immunotherapy and were followed up for several years after discharge from the hospital. Four developed epilepsy within 2 years after encephalitis, four had cognitive decline, one had mild psychiatric symptoms in the form of hallucinations, and none of the patients had involuntary movements. In addition, two pre-adolescent children developed central precocious puberty approximately three years after autoimmune encephalitis. Central precocious puberty may be a consequence of encephalitis with anti-NMDAR antibodies in children before puberty [18].

According to a 2008-2015 study in New Zealand, Maori and Pacific Islander children have a higher prevalence of encephalitis with anti-NMDA receptor antibodies and a more severe course. These data suggest a genetic predisposition to this type of autoimmune encephalitis in certain populations [19].

AUTOIMMUNE PSYCHOSIS

Many cases of isolated psychosis have been described in patients with antibodies to neuronal surface antigens, mainly anti-NMDAR, showing a favorable response to immunomodulatory treatment. So far, atypical or mild forms of autoimmune encephalitis have been diagnosed in these cases. Anti-NMDAR antibodies in the IgG class are detected in the blood in 0-12% of patients with a first episode of psychosis [20]. Only by detecting the presence of antibodies can a confident diagnosis of autoimmune psychosis be made. In patients with an acute episode of psychosis, an autoimmune background should be thought of if:

- symptoms of infection were present before the illness;
- the patient developed a severe headache with a new onset;
- mental disorders are progressing rapidly;
- there is hypersensitivity or unresponsiveness to antipsychotic medications/ malignant neuroleptic syndrome has occurred;
- the patient presents with movement disorders (e.g., catatonia or dyskinesias) and/or signs of focal CNS damage;
- patient has impaired consciousness, autonomic dysfunction, aphasia, mutism and/or dysarthria, epileptic seizures, paresthesias;
- current or recent diagnosis of malignancy;
- the patient has hyponatremia unexplained by an adverse drug reaction (e.g., selective serotonin reuptake inhibitors, carbamazepine);
- The patient has other coexisting autoimmune diseases (e.g. thyroid) [7].

SLEEP DISORDERS

Little attention has been paid to sleep disorders in patients with autoimmune encephalitis, probably due to the presence of other neurological and psychiatric symptoms in this group of conditions. However, sleep disorders are common, severe and usually persist beyond the acute stage of the disease, hindering recovery and worsening patients' quality of life. Autoimmune encephalitis can affect any of the brain networks involved in sleep initiation and regulation, and all types of sleep disorders with different and distinct associations, frequency and intensity can occur. Encephalitis directed by antibodies to the IgLON5 receptor and NMDA receptor is an example of two diseases in which sleep disorders predominate. In anti-IgLON5 disease, sleep disturbances were the main symptoms that led to the description of the disease, while in encephalitis with anti-NMDA receptor antibodies, sleep disturbances vary depending on the stage of the disease [21]. In autoimmune encephalitis with antibodies to the IgLON5 receptor, there are four main disease symptoms:

- sleep disorders (parasomnias during REM and NREM sleep, sleep apnea);
- Worster-Drought syndrome;
- syndrome resembling progressive supranuclear palsy;
- cognitive decline and/or chorea.

The disease, caused by anti-IgLON5 antibodies, presents with multiple sleep disorders and symptoms resembling progressive supranuclear palsy with spinal muscle stiffness and episodes of stasis. It mainly affects the elderly [22]. Antibodies to the cell adhesion protein IGLON5 can cause obstructive sleep apnea, inspiratory stridor, disorganized sleep with non-rapid eye movements, and excessive movements and parasomnias that cause fragmented sleep with non-rapid and rapid eye movements. The symptoms of Worster-Drought present themselves mainly in the form of dysphagia and dysarthria. Patients typically show a strong association with HLA-DRB 10:01 and HLA-DQB1 05:01 haplotypes [23].

NMDAR encephalitis is often accompanied by insomnia, followed by hypersomnia and sleep-related central hypoventilation. Profound insomnia and behavioral disturbances during the REM sleep phase are observed in patients with antibodies to the voltage-gated potassium channel complex [24].

An observational study was conducted in Beijing between 2014 and 2021 to investigate the prevalence of sleep disorders and risk factors for these disorders in patients with autoimmune encephalitis. 121 patients were recruited, of whom 52.9% had sleep disorders. They found that smoking, hyperhomocysteinemia, higher levels of neurospecific enolase and Hamilton depression index increased the risk of sleep disorders in patients with autoimmune encephalitis. It has also been shown that the higher the MoCA (Montreal Cognitive Assessment scale) score, the lower the risk of sleep disorders [25].

A study was also conducted to assess fatigue after autoimmune encephalitis, as it is not fully explained by depression and poor sleep quality. In the first cohort, 220 of 338 participants (65%) reported fatigue, 175 of 307 (57%) reported depressive symptoms, and 211 of 285 (74%) reported poor sleep quality. In the second cohort, 42 of 69 participants (61%) reported fatigue, while 23 of 68 (34%) reported depressive symptoms and 44 of 66 (67%) reported poor sleep quality. Those with inflammation with anti- NMDAR antibodies had worse scores on fatigue rating scales than those with other types of autoimmune encephalitis [26].

TREATMENT AND COMPLICATIONS

The treatment of choice is corticosteroid therapy - methylprednisolone administered intravenously at a dose of 1 g/day for 5-7 days. If there is no improvement, intravenous immunoglobulins in a total dose of 2 g/kg body weight (0.4 g/kg body weight/day for 5 days) and/or plasmapheresis are used. Second-line drugs are rituximab and cyclophosphamide. An extensive panel of diagnostic tests for cancer should be performed in each patient. If diagnosed, appropriate treatment should be implemented.

Symptomatic treatment of autoimmune encephalitis is clinically beneficial and should include: therapy of sleep disorders, normalization of the sleep-wake cycle, and control of agitation, psychiatric disorders and epileptic seizures.

Recovery is a multi-step process that often follows the opposite sequence of disease symptom presentation. Many patients require hospitalization for an extended period of time, followed by months of physical and behavioral rehabilitation. Recovery is a gradual and slow process, taking up to 18 months [8].

In a cohort of 360 patients, 75% experienced complete or near-complete recovery (mRS score of 1-2). The remaining survivors had sequelae that severely affected their quality of life (mRS > 2 points). Among those who made a full or near-full recovery, 85% still had significant neuropsychiatric symptoms at the time of discharge, and in some cases these deficits were permanent (memory deficits and impaired executive function). [27] The most common symptoms that persist after treatment include deficits in memory, impairment of executive function, behavioral and language impairment, and social skills disorders [5]. Approximately 10-15% of patients had a recurrence of symptoms within 2 years [8].

CONCLUSIONS

Autoimmune encephalitis is an increasingly recognized severe neurological condition that significantly affects patients' quality of life. It requires differentiation primarily with psychiatric diseases, as well as requires oncological vigilance. On the other hand, in the case of an acute episode of psychosis, differentiation with autoimmune encephalitis should always be pursued.

REFERENCES

1. Goodfellow JA, Mackay GA. Autoimmune encephalitis. J R Coll Physicians Edinb. 2019;49(4):287-294.
2. Dalmau J, Armangué T, Planagumà J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol. 2019;18(11):1045-1057.
3. Żur-Wyrozumska K. Autoimmunologiczne zapalenie mózgu związane z przeciwciałami przeciwko neuronalnym antygenom powierzchniowym – ścieżka diagnostyczno-terapeutyczna dla lekarza praktyka. Med Prakt. Neurologia. 2021;1:27-31. (Polish)
4. Nosadini M, Mohammad SS, Ramanathan S, Brilot F, Dale RC. Immune therapy in autoimmune encephalitis: a systematic review. Expert Rev Neurother 2015; 15(12): 1391-419.
5. Newman MP, Blum S, Wong RC, et al. Autoimmune encephalitis. Intern Med J. 2019;46(2):148-157.
6. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391-404.

7. Pollak TA, Lennox BR, Müller S, et al. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. Lancet Psychiatry. 2020;7(1):93-108.
8. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol. 2013;12:157-165.
9. Zajkowska J, Ustymowicz A, Kondrusik M. Opryszczkowe zapalenie mózgu – trudności diagnostyczne. Neurol Dypl. 2013;8(2):24-36. (Polish)
10. Gołąb-Janowska M, Nowacki P. Limbiczne zapalenie mózgu – przegląd piśmiennictwa. Annales Academiae Medicae Stetinensis 2011;57(3):5-11. (Polish)
11. Kayser MS, Titulaer MJ, Gresa-Arribas N, Dalmau J. Frequency and characteristics of isolated psychiatric episodes in anti–N-methyl-d-aspartate receptor encephalitis. JAMA Neurol. 2013;70:1133-1139.
12. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti--NMDAR encephalitis. Lancet Neurol. 2011;10:63-74.
13. Al-Diwani AAJ, Pollak TA, Irani SR, Lennox BR. Psychosis: an autoimmune disease? Immunology. 2017;152(3):388-401.
14. Rathore GS, Leung KS, Muscal E. Autoimmune encephalitis following bone marrow transplantation. Pediatr Neurol. 2015;53:253-256.
15. Kayser MS, Dalmau J. Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. Schizophr Res. 2016;176(1):36-40.
16. Steiner J, Walter M, Glanz W, et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. JAMA Psychiatry. 2013;70:271-278.
17. Chiang M, Natarajan R, Fan X. Vitamin D in schizophrenia: a clinical review. Evid Based Ment Health. 2016;19:6-9.
18. Wu PM, Teng CK, Chou YY, Tu YF. Precocious puberty as a consequence of anti-NMDA receptor encephalitis in children. Pediatr Neonatol. 2021;62(4):361-368.
19. Jones HF, Mohammad SS, Reed PW, et al. Anti-N-methyl-d-aspartate receptor encephalitis in Māori and Pacific Island children in New Zealand. Dev Med Child Neurol. 2017;59(7):719-724.
20. Pollak TA, McCormack R, Peakman M, Nicholson TR, David AS. Prevalence of anti-N-methyl-D-aspartate (NMDA) receptor [corrected] antibodies in patients with schizophrenia and related psychoses: a systematic review and meta-analysis. Psychol Med. 2014;44(12):2475-2487.
21. Muñoz-Lopetegi A, Graus F, Dalmau J, Santamaria J. Sleep disorders in autoimmune encephalitis. Lancet Neurol. 2020;19(12):1010-1022.
22. Uy CE, Binks S, Irani SR. Autoimmune encephalitis: clinical spectrum and management. Pract Neurol. 2021;21(5):412-423.
23. Chung HY, Wickel J, Voss A, et al. Autoimmune encephalitis with anti-IgLON5 and anti-GABAB-receptor antibodies: A case report. Medicine (Baltimore). 2021;98(20):e15706.
24. Ralls F, Cutchen L, Grigg-Damberger MM. Recognizing new-onset sleep disorders in autoimmune encephalitis often prompt earlier diagnosis. J Clin Neurophysiol. 2022;39(5):363-371.
25. Liu X, Yu T, Zhao X, et al. Risk factors and brain metabolic mechanism of sleep disorders in autoimmune encephalitis. Front Immunol. 2021;12:738097.
26. Diaz-Arias LA, Yeshokumar AK, Glassberg B, et al. Fatigue in survivors of autoimmune encephalitis. Neurol Neuroimmunol Neuroinflamm. 2021;8:e1064.
27. Kayser MS, Kohler CG, Dalmau J. Psychiatric manifestations of paraneoplastic disorders. Am J Psychiatry. 2010;167:1039-1050.

ORCID AND CONTRIBUTIONSHIP
Sandra Wcisło: 0009-0004-4732-7534[B,D,F]
Katarzyna Bojkowska-Otrębska: 0009-0003-1498-2113[B,D,F]
Beata Łabuz-Roszak: 0000-0001-9835-8240[A,E,F]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 05.05.2023
ACCEPTED: 10.09.2023

ADDRESS FOR CORRESPONDENCE
Beata Łabuz-Roszak
Department of Neurology, Institute of Medical Sciences, University of Opole, Opole, Poland
e-mail: beatamaria.pl@hoga.pl

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 569-574

REVIEW ARTICLE

DOI: 10.36740/Merkur202305118

ASSESSMENT OF LABORATORY ANIMAL FUNCTIONAL STATUS: MODERN METHODOLOGICAL APPROACHES FOR CONDUCTING BIOMEDICAL RESEARCH

Larysa Ya. Fedoniuk[1], Yulia V. Lomakina[2], Yaroslav O. Bilyk[1]

[1]I. HORBACHEVSKY TERNOPIL NATIONAL MEDICAL UNIVERSITY, TERNOPIL, UKRAINE

[2]BUKOVINIAN STATE MEDICAL UNIVERSITY, CHERNIVTSI, UKRAINE

ABSTRACT

Aim: to outline modern scientific approaches for evaluating the functional condition of small laboratory animals in experimental research.

Materials and Methods: Scientific publications on the rules of using laboratory animals in scientific experiments, testing, educational process have been studied. The bioethical norms and principles of animal care and use of material for medical, veterinary and biological profiles were also studied, for example modern methodological approaches for conducting biomedical research, since it is the responsibility of the scientist to achieve reproducible research results using the minimum number of laboratory animals.

Conclusions: The main conditions for their implementation and effectiveness include: adherence to the "Ethical Code" published by the International Council for Medical Scientific Organizations in the early 1980s, the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 18 March 1986), and Directive 2010/63/EU adopted on 22 September 2010; the use of advanced and modern diagnostic equipment that enables low-invasive yet highly informative research on small laboratory animals; conducting comprehensive, multi-level studies on an optimal number of animals in laboratories that meet international standards.

KEY WORDS: laboratory animals, rats, mice, experiment, research, functional condition

INTRODUCTION

In the context of modern trends in medicine and biology, knowledge of theoretical principles for conducting biomedical research and proficiency in practical skills related to working with laboratory animals are essential for every researcher.

With the continuous advancement and increasing complexity of methodologies in medical and biological experiments, which require the development of pathology models that closely resemble human conditions, there arises a critical need for the utilization of contemporary animal strains and improve the diagnostic equipment used in scientific laboratories [1]. The American Association for Laboratory Animal Science (AALAS) regards the minimization of invasiveness, the absence of pain-inducing interventions, and the preservation of animal life as pivotal factors ensuring the ethical and effective conduct of research [2]. Following these requirements allows for precise modeling of physiological and pathological processes, decreases experimental variability, and reduces the risk of misinterpreting obtained data [3].

These underlying principles should serve as the foundation for the establishment of experimental laboratories in the educational centers of medical universities. Moreover, these laboratories should be supplied with new, standardized, and high-tech equipment developed by leading global manufacturers. Based on extensive research and experience gained from working with various physiological parameter recording systems in small laboratory animals, the optimal solution lies in the implementation of software-hardware complexes that align with modern methodologies in biological and medical research.

1. Non-invasive electrocardiogram registration system, ecgTUNNEL (emka TECHNOLOGIES, France).
2. Non-invasive blood pressure measurement system, Blood Pressure Analisis SystemsTM BP-2000Series II (Visitech Systems, USA) c with automatic temperature control in immobilized tunnel.
3. Body composition analyzer for laboratory animals – bioimpedance system VET BIS1 (ImpediMed Limited, Australia).
4. Radial maze with 8 arms, AgnTho's LE760 (PanLab Harvard Apparatus, Spain) with video fixation Video Tracking System (SONY, Japan).
5. Treadmill for small rodents, Tredmill Control LE8710 (PanLab Harvard Apparatus, Spain) with electric shocker.
6. High-end cardiovascular research instrument, Vivid E9 XD Clear Console 4D Expert 100 (General Electric, USA), equipped with a high-frequency matrix linear probe ML6-15-D capable of scanning at a maximum frequency of 15 MHz.

Such software-hardware complexes enable automated monitoring of the investigated parameters with minimal invasiveness during the registration process. They facilitate conducting experiments on non-anesthetized animals, thus creating conditions that closely resemble physiological states. Additionally, these complexes allow for efficient processing of large volumes of electronic experimental data and enable computer-based analysis of physiological parameters in animals [4, 5, 6].

AIM

The aim of this study is to outline modern scientific approaches for evaluating the functional condition of small laboratory animals in experimental research.

MATERIALS AND METHODS

Scientific publications on the rules of using laboratory animals in scientific experiments, testing, educational process have been studied. The bioethical norms and principles of animal care and use of material for medical, veterinary and biological profiles were also studied, for example modern methodological approaches for conducting biomedical research, since it is the responsibility of the scientist to achieve reproducible research results using the minimum number of laboratory animals.

REVIEW AND DISCUSSION

British zoologist William Russell (1925-2006), also known as Bill Russell, together with Rex Leonard Burch (1926-1996), introduced the concept of humane animal usage in research, education, and testing, which they published in their book "The Principles of Humane Experimental Technique" (Russell & Burch, 1959; Balls, 2014). This concept became known as the "3R" concept, representing Replacement, Reduction, and Refinement. The main principle of the concept is promoting alternative research methods to animal testing, improving the handling of experimental animals, or reducing the number of animals used when it is unavoidable, while simultaneously enhancing the quality of scientific and applied medical research [7, 8, 9].

Replacement – in the context of animal experimentation – refers to substituting animal models with methods that achieve the research goals without conducting experiments on animals [10]. This concept includes the replacement of animal models with cellular, mathematical, and computer models. Partial replacement involves using animal species that, according to current scientific understanding, are incapable of experiencing suffering. This category includes invertebrate animals such as fruit flies, nematodes, and amoebas.

Reduction, within the realm of animal experimentation, refers to using the minimum number of animals necessary for a study, utilizing methods that employing techniques that extract data from fewer animals or obtain more information from the same number of animals [11].

Refinement – signifies the use of methods that minimize or eliminate pain, suffering, and distress in animals, as well as improve the overall quality of life for the animals involved [12].

Currently, the concept of the "3R" (Replacement, Reduction, Refinement) is included in legislative acts and standards that regulate the use of animals worldwide. The "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" (Strasbourg, 18.03.1986) was developed as a result. According to the European Union Directive on the protection of animals used for scientific purposes (Directive 2010/63/EU), procedures that assess the pain and suffering of animals and eight procedures accompanied by severe and long-lasting pain or suffering that cannot be alleviated are prohibited. In 1978, the Federation of European Laboratory Animal Science Associations (FELASA) was established by European countries. FELASA has developed a specialized training system for obtaining permission to work with experimental animals. Certificates issued by FELASA are recognized worldwide and serve as evidence of a researcher's qualification to work with animal subjects [7, 13].

Rats are curious, intelligent, and social animals. In laboratory practice, the most used species are the brown rats (Latin name: Rattus norvegicus, also known as the Norway rat; the name was given by the English naturalist John Berkenhout in 1769). The outbreded laboratory strains include the Wistar rats, which were developed in 1906 at the Wistar Institute in the USA, and the Sprague-Dawley rats, which are an albino strain of Rattus norvegicus developed in 1925 at the University of Wisconsin-Madison, USA [14, 15, 16].

Mice are territorial animals characterized by aggression when defending their territory. One of the most common species of laboratory animals is the house mouse, Mus musculus L. Initially, white mice, traditionally referred to as albinos or, according to modern terminology, outbred animals, were used in research [17, 18, 19]. The first inbred mice were developed through breeding by a group of American oncologists in 1909. Subsequently, through inbreeding and selection of offspring based on survival and the presence of mammary gland tumors, the first mouse strain known as DBA has been established since 1950. Currently, the main mouse strains used in laboratory practice are C57BL/6 (accounting for up to 43.25% of studies conducted using this strain) and BALB/c (accounting for up to 19.93% of studies conducted using this strain).

Achieving the modern level of biomedical research is possible through strict standardization of all factors that impact laboratory animal organisms, including both their living conditions and the animals themselves. The introduction of Good Laboratory Practice (GLP) standards for conducting preclinical drug trials has imposed even more rigorous requirements on the standardization of animals and the monitoring of their health [20].

In accordance with international experience, the standardization of laboratory animals is ensured through modern breeding and housing technologies within barrier systems, along with unified criteria for evaluating their health condition.

The basis of these criteria is the principle of non-carriage of several pathogenic and opportunistic agents of infectious and invasive nature, such as viruses, bacteria, and parasites.

In other words, animal standardization is based on the prevention of infectious and invasive pathology [11, 21].

For the safety of the researcher and the welfare of the animal, it is important to use recommended methods for handling and restraining laboratory animals. By employing confident and practiced movements, along with specific techniques, animals can be securely held without causing pain. When working with mice, it is worth noting that regular interaction between the animal and the researcher leads to habituation and calming of the animals in the presence of the researcher. Rats tend to be more obedient than mice, and with regular and gentle interaction, through repeated careful handling, ats will remain calm when being held [6, 20, 22].

Animal models occupy a central position in research, and there is a wealth of data demonstrating the advantages of animal experimental models in elucidating the mechanisms of human diseases [2, 23, 24].

Electrocardiography (ECG) in rats is a widely used experimental method for studying the cardiovascular system. ECG recording reflects the electrical activity of the heart and can provide valuable information about the functional and structural characteristics of the myocardium. The technique of ECG recording in laboratory animals is relatively simple, but the interpretation of electrocardiographic parameters is a complex task. This is because, unlike humans, there are no established criteria for ECG reference values in rats: there are significant differences in ECG parameters between studies involving these animals. According to the most scientists, this is due to various experimental setups, such as the type of anesthesia, the strain of rats used, gender, age of the animals, and heart rate (HR) [4, 25].

Recording ECG in rats using the ecgTUNNEL system helps eliminate most of the mentioned issues as the animals are not subjected to anesthesia but are immobilized within the tunnel. Important conditions for effective ECG recording include a preliminary 2–3-day period of animal preparation for adaptation and stress reduction, as well as creating maximum noise isolation within the temperature range of 24-26 °C. High heart rates pose a significant challenge during ECG recording in rats, exceeding 500 beats per minute and reaching 700-800 beats in certain experimental models. To solve this problem, the ecgTUNNEL system is equipped with standard filters that reduce interference and electrical artifacts, as well as programmable high-pass and low-pass frequency filters. This allows for the identification of specific patterns of cardiac electrical activity. During ECG recording, simultaneous registration is performed in six leads: standard leads (I, II, III) and augmented leads (aVR, aVL, aVF). This enables the assessment of not only standard parameters such as the duration and configuration of PQRST intervals and waves but also the software-based determination of average ST segment displacement, S wave area, peak amplitude, calculation of efficiency indices (% ratio of registered impulses to the total number of signals in one session), and average number of registered impulses within a session.

Currently, three main methods are widely used for recording arterial blood pressure in small rodents: non-invasive measurement using a tail cuff on the tail artery, invasive or direct measurement using an intra-arterial catheter, and radiotelemetry method. Each method has its own advantages and disadvantages. The main advantage of the first method is the absence of surgical procedures and anesthesia, allowing for multiple measurements on the same animal at different time points. For a long time in our country, outdated equipment with limited capabilities was used for measuring blood pressure in rats (only systolic pressure was measured), with high error rates and inability to automatically record and save the acquired data. The use of the computerized VR-2000 system for non-invasive blood pressure measurement in rats has eliminated the limitations. Moreover, in the 1990s, J.H. Krege et al. conducted comparative studies on mice with different models of arterial hypertension using this blood pressure recording system, comparing it to the direct invasive intra-arterial method. They concluded that the VR2000 system provides reproducible results and would be useful for research where a non-invasive approach is desirable, especially in long-term experiments [26].

To measure blood pressure, rats are placed in special fixtures equipped with a thermostatic platform, which maintains a constant temperature of 37-39 °C. The animal fixtures are light-tight to rapidly reduce their stress levels. The average recording time for blood pressure is 3-7 minutes, during which 3-5 preliminary and 3-5 control measurements are taken, calculating the average values of heart rate, systolic and diastolic pressure. The system is equipped with software for maintaining a database, allowing for the storage of digital and graphical data, generating reports, and preserving the results of all experiments. The particulars of body composition assessment using the bioimpedance technique in small laboratory animals are as follows. Bioelectrical impedance analysis of body composition is widely used in sports and clinical medicine. This method is based on the ability of biological tissues to conduct electrical current. The resistance of tissues to electrical current depends on their fluid content. Highly hydrated tissues, such as muscle, act as conductors of electrical current, while poorly hydrated adipose tissue acts as an insulator. Thus, impedance is inversely proportional to the fluid content in the body tissues.

Bioelectrical impedance analysis of body composition allows for monitoring the status of lipid, protein, and water metabolism in the body, assessing the risk of developing metabolic syndrome, and determining tissue hydration levels. In patients with cardiovascular diseases, this method is used to evaluate disturbances in fluid balance, fluid redistribution in the body, and the selection of pharmaceutical agents. Over the past three decades, bioelectrical impedance analysis of hydration and body composition in laboratory animals has made significant progress. With the development of bioimpedance spectroscopy, it has become possible to calculate extracellular and intracellular fluid volumes, fat mass, and fat-free mass without removing the animal from the experiment [27]. Assessing fluid distribution in the body is essential for analyzing nutritional status, the direction of

metabolic processes, kidney function, and cardiovascular function. Current researchers consider bioimpedance spectroscopy to be a universal non-invasive method for assessing not only body fluid balance but also the porosity of the cell membrane [28].

Before conducting the study on rats, it is necessary to weigh and measure the length from the nose tip to the base of the tail. These parameters are directly entered into the analysis system. The animals are anesthetized (ketamine, 50 mg/kg body weight) and subcutaneously implanted with electrodes according to the scheme. Three to five measurements are taken, and the average value is calculated. The assessment of the speed of formation of the search reflex, spatial and non-spatial memory in laboratory animals is widely used in the field of neuroscience and preclinical trials. These assessments provide reliable data in the field of fundamental and clinical psychopharmacology, including the determination of phenotypic characteristics (differences between animal strains, effects of genetic modifications) and the study of behavioral effects of pharmacological substances.

The use of video recording allows for the recording and analysis of activity, trajectory, and movement speed, as well as social interaction events. A specialized video recording system for animals not only enables the identification of the rat in the maze but also determines the position of specific body parts (head, center and/or base of the tail) in object recognition tests, social interaction studies, and the registration of behavioral patterns (rearing on hind limbs, turns). This technology helps eliminate the need for marking animals and allows for a more precise assessment of specific behavioral elements such as exploratory activity, location preference, turns, and the investigation of cyclic behavior patterns in animals.

For studying motor function, conducting exercise tests, and assessing fatigue and endurance levels in laboratory animals, LE8700 series treadmills are used. The speed of the treadmill can be set within a range of 5 to 150 cm/s. The system is equipped with two treadmills, each having its independent grid under voltage. The incline of the treadmill can be adjusted within a range of -25 to +25 degrees with 5-degree increments.

During the course of the study, the following parameters are displayed on the device's screen or entered into the computer analysis system: the distance covered by the animal, the cumulative time during which the animal received electrical stimulation, the number of stimulations received, the current speed of the treadmill, and the duration of the experiment.

The rapid development of ultrasound technology in recent years has made it possible to non-invasively assess the structural and functional status of the heart (echocardiography) in small laboratory animals, including rodents. The main technical limitations for conducting research on experimental mice and rats traditionally include the small size of the heart and the high heart rate. The emergence of ultrasound probes with high scanning frequency, as well as specialized software packages, has overcome these challenges.

Prior to conducting echocardiographic research, the animal's chest is shaved. The most used anesthetic drugs for this procedure are ketamine (50-100 mg/kg body weight) in combination with xylazine (5-6 mg/kg) or phenobarbital (30-40 mg/kg), which are administered intraperitoneally. The dosage range significantly affects heart rate, cardiodynamic parameters, and the duration of anesthesia, which should be considered when planning the experiment [29, 30]. The animal is positioned on its back with its limbs fixed during the examination. Ultrasound gel is applied to the chest to create an acoustic window, and it is important to avoid exerting pressure from the transducer on the animal's body. Echocardiography in rodents is performed using ultrasound scanners equipped with a high-frequency linear probe (at least 10 MHz) or a phased array sector probe that also supports high frequencies (at least 8 MHz) [31].

Measurement of myocardial wall thickness and calculation of myocardial mass are essential measurements in experimental models of arterial hypertension [32, 33].

Accurate positioning of the ultrasound beam perpendicular to the assessed structures is achieved using the "anatomical" M-mode. In this same position, tissue Doppler mapping can be activated, which allows for the assessment of myocardial motion amplitude during systole and diastole, indirectly evaluating the structural condition of the studied cardiac regions. From the apical position, the transmitral flow is assessed using pulsed-wave Doppler, providing information about the diastolic function.

CONCLUSIONS

The past decade has brought a shift in scientific thinking in Ukraine, opening new possibilities and perspectives for planned experimental research by implementing modern approaches and new methodological opportunities in biomedical studies. The main conditions for their implementation and effectiveness include: adherence to the "Ethical Code" published by the International Council for Medical Scientific Organizations in the early 1980s, the principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 18 March 1986), and Directive 2010/63/EU adopted on 22 September 2010; the use of advanced and modern diagnostic equipment that enables low-invasive yet highly informative research on small laboratory animals; conducting comprehensive, multi-level studies on an optimal number of animals in laboratories that meet international standards.

REFERENCES

1. Zutphen van LFM. Principles of Laboratory Animal Science. In: LFM. van Zutphen, Vera Baumans, Anton C. Beynen. Principles of Laboratory Animal Science: A Contribution to the Humane Use and Care of Animals and to the Quality of Experimental Results. Amsterdam; New York: Elsevier; 2015, 416p.
2. The 2014 Lush Prize: A Global View of Animal Experiments 2014, 42p. https://www.lushprize.org/wp-content/uploads/Global_View_of Animal_Experiments_2014.pdf
3. Turner PV, Brabb T, Pekow C, et al. Administration of substances to laboratory animals: routes of administration and factors to consider. J Am Assoc Lab Anim Sci. 2011;50(5):600-613. PMCID: PMC3189662.
4. Konopelski P, Ufnal M. Electrocardiography in rats: a comparison to human. Physiol Res. 2016;65(5):717-725. doi:10.33549/physiolres.933270.
5. Code of practice for the housing and care of laboratory mice, rats, guinea pigs and rabbits / Victorian Government department of primary industries. Australia. https://agriculture.vic.gov.au/livestock-and-animals/animal-welfare-victoria/pocta-act-1986/victorian-codes-of-practice-for-animal-welfare/code-of-practice-for-the-housing-and-care-of-laboratory-mice-rats-guinea-pigs-and-rabbits
6. Kaliste E. The welfare of laboratory rats. In: Kaliste, E. (eds) The Welfare of Laboratory Animals. Animal Welfare, vol 2. Springer, Dordrecht. 2007, 258p. doi: 10.1007/978-1-4020-2271-5_8/.
7. European convention for the protection if vertebrate animals used for experimental and other scientific purposes. Appendix A. Strasbourg, 2006. https://awionline.org/lab-animal-search/council-europe-2006-appendix-european-convention-protection-vertebrate-animals
8. Olfert E. Guide for the Care and Use of Laboratory Animals In: Olfert E., Cross B. McWilliam A. National Research Council. Guide to the Care and Use of Experimental Animals, Volume 1, 2nd Edition. 2020, 209p. https://ccac.ca/Documents/Standards/Guidelines/Experimental_Animals_Vol1.pdf
9. National Research Council. Guide for the Care and Use of Laboratory Animals: Eighth Edition. Washington, DC: The National Academies Press. 2011, 246p. doi: 10.17226/12910.
10. Convenor M, Berard M, et al. FELASA recommendations for the health monitoring of mouse, rat, hamster, guinea pig and rabbit colonies in breeding and experimental units: Lab Anim. 2014;48(3):178-192. doi:10.1177/0023677213516312.
11. Ritskes-Hoitinga, J. Nutrient Requirements, experimental design and feeding schedules in animal experimentation. In: Ritskes-Hoitinga J., Chwalibog A., Hau J. et al. Boca Raton: CRC Press, 2003:281-310.
12. Russell WMS. The Principles of Humane Experimental Technique. In: WMS. Russell RL. Burch. London: Methuen & Co. Limited, 1959, 252p.
13. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. Text with EEA relevance, https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF
14. DeSesso JM, Jacobson CF. Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. Food Chem Toxicol. 2001;39(3):209-228. doi: 10.1016/s0278-6915(00)00136-8.
15. Wang-Fischer Y. Manual of stroke models in rats. In: Y. Wang-Fischer. Manual of stroke models in rats. Taylor & Francis Group, 2008, 352 p.
16. Perret-Gentil MI. Rat biomethodology. The University of Texas at San Antonio: Animal User Training Program, 2015. https://research.utsa.edu/fund-dev/
17. Burkholder T, Foltz C, Karlsson E, et al. Health Evaluation of Experimental Laboratory Mice: Curr Protoc Mouse Biol. 2012;2:145-165. doi: 10.1002/9780470942390.mo110217.
18. Ullman-Culleré M, Foltz C. Body condition scoring: a rapid and accurate method for assessing health status in mice. Lab Anim Sci. 1999;49(3):319-323. PMID: 10403450.
19. Van Loo P, Mol J, Koolhaas J et al. Modulation of aggression in male mice: influence of group size and cage size: Physiol Behav. 2001;72(5):675-683. doi:10.1016/s0031-9384(01)00425-5.
20. Parvova I, Danchev N, Hristov E Animal models of human diseases and their significance for clinical studies of new drugs: J. Clin. Med. 2011; 4(1):19-29.
21. Ritskes-Hoitinga M, Strubbe J Nutrition and animal welfare. In: Kaliste, E. Eds. The Welfare of Laboratory Animals. Animal Welfare. Springer, Dordrecht. 2007;2:51-80. doi: 10.1007/978-1-4020-2271-5_5.
22. Barclay R. The disturbance index: a behavioral method of assessing the severity of common laboratory procedures on rodents. In: Barclay R, Herbert W, Poole T, eds. UK: Universities Federation for Animal Welfare, Potters Bar. 1988, 35 p.
23. Danneman P. The Laboratory Mouse. In: Danneman P, Suckow M, Brayton C, eds. Boca Raton: CRC Press. 2001, 184 p.
24. Balls M. Humane Scientist and Gentle Man. In: Balls M, Burch R eds. Alternatives to laboratory animals: ATLA. 2014;42:57-59.
25. Dragoi G, Ciobanu A, Rimbas R et al. New Echocardiographic Protocol for the Assessment of Experimental Myocardial Infarction in Rats: Maedica (Bucur). 2015;10(2):85-90. PMCID: PMC5327796.
26. Krege J, Hodgin J, Hagaman J et al. A noninvasive computerized tail-cuff system for measuring blood pressure in mice: Hypertension. 1995. 25(5):1111-1115. doi: 10.1161/01.hyp.25.5.1111.
27. Smith D Jr, Johnson M, Nagy T. Precision and accuracy of bioimpedance spectroscopy for determination of in vivo body composition in rats. Int J Body Compos Res. 2009;7(1):21-26. PMCID: PMC2722071.
28. Yokoi K, Lukaski H, Uthus E et al. Use of bioimpedance spectroscopy to estimate body water distribution in rats fed high dietary sulfur amino acids. J Nutr. 2001;131(4):1302-1308. doi: 10.1093/jn/131.4.1302.
29. Kawahara Y, Tanonaka K, Daicho T, et al. Preferable anesthetic conditions for echocardiographic determination of murine cardiac function. J Pharmacol Sci. 2005;99(1):95-104. doi: 10.1254/jphs.fp0050343.
30. Xu Q, Ming Z, Dart A et al. Optimizing dosage of ketamine and xylazine in murine echocardiography: Clin Exp Pharmacol Physiol. 2007;34(5-6):499-507. doi: 10.1111/j.1440-1681.2007.04601.x.
31. Gao S, Ho D, Vatner D t al. Echocardiography in Mice. Curr Protoc Mouse Biol. 2011;1:71-83. doi: 10.1002/9780470942390.mo100130.
32. Darbandi Azar A, Tavakoli F, Moladoust H, e A. Echocardiographic evaluation of cardiac function in ischemic rats: value of m-mode echocardiography. Res Cardiovasc Med. 2014;3(4):e22941. doi: 10.5812/cardiovascmed.22941.
33. Watson L, Jewell C, Song J, et al. Dostal DE. Echocardiographic effects of eplerenone and aldosterone in hypertensive rats. Front Biosci (Elite Ed). 2013;5(3):922-927. doi: 10.2741/e671.

The work is carried out within the framework of the initiative research work of the I. Horbachevsky Ternopil National Medical University (Ternopil, Ukraine) „Systemic and organ disorders due to the action of extraordinary factors on the body, the mechanisms of their development and pathogenetic correction" (0116 U003390).

ORCID AND CONTRIBUTIONSHIP
Larysa Ya. Fedoniuk: 0000-0003-4910-6888 [A, B, D, E, F]
Yulia V. Lomakina: 0000-0002-8020-5254 [B, C, D]
Yaroslav O. Bilyk: 0000-0001-8971-1420 [B, C]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 02.04.2023
ACCEPTED: 07.09.2023

ADDRESS FOR CORRESPONDENCE
Larysa Ya. Fedoniuk
Medical Biology Department
I. Horbachevsky Ternopil National Medical University
Valova Street, 9, Ternopil, 46000, Ukraine
e-mail: Fedonyuk22Larisa@gmail.com

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.

Pol Merkur Lek, 2023; LI, 5: 575-580

CASE STUDY

DOI: 10.36740/Merkur202305119

SHARK FIN ECG PATTERN IN A PATIENT WITH TAKOTSUBO SYNDROME – CASE STUDY AND LITERATURE REVIEW

Waldemar Elikowski[1], Patryk Szczęśniewski[2], Natalia Fertała[1], Magdalena Zawodna-Marszałek[1], Joanna Albrecht[2], Marcin Żytkiewicz[1]

[1]DEPARTMENT OF INTERNAL MEDICINE, JÓZEF STRUŚ HOSPITAL, POZNAŃ, POLAND
[2]INTENSIVE CARE UNIT, JÓZEF STRUŚ HOSPITAL, POZNAŃ, POLAND

ABSTRACT

Shark fin or triangular QRS-ST-T waveform ECG pattern, also known as lambda-wave ST elevation or giant R wave syndrome, is a particular ECG presentation where QRS complex, ST-segment and T-wave are fused in a unique complex. Originally described in some patients with ST-segment elevation myocardial infarction (STEMI) during the acute phase, it has been found to be associated with a high risk of ventricular fibrillation and cardiogenic shock as well as with a high in-hospital mortality. However, shark fin ECG pattern has also been reported in patients with non-acute coronary syndrome related ST-elevation (NASTEP), including stress-induced takotsubo syndrome (TTS). Fourteen such cases (all females) have been reported so far. The authors present a case of a 56-year-old male with shark fin ECG pattern associated with TTS triggered by burn injuries of head, back, upper, lower limbs and the respiratory tract. Due to respiratory insufficiency and heart failure with hemodynamic compromise, he required mechanical ventilation and catecholamines use. Echocardiography showed apical and midventricular akinesia with left ventricular ejection fraction and global longitudinal strain reduced to 30% and -6.8%, respectively and a high segmental post-systolic index. Shark fin pattern maintained within 2 days, then ST-T evolution was observed. Echocardiographic improvement followed by almost normalization were seen after 6 and 9 days, respectively. No cardiac arrhythmias were recorded as in most of the described cases with shark fin ECG and TTS.

KEY WORDS: shark fin ECG, triangular QRS-ST-T waveform pattern, lambda-wave ST-elevation, giant R-wave syndrome, takotsubo syndrome, longitudinal strain, post-systolic shortening

INTRODUCTION

Shark fin or triangular QRS-ST-T waveform (TW) ECG pattern [1-3], also known as lambda-wave ST-segment elevation (lambda-wave STE) [4, 5] or giant R wave syndrome (GRWS) [6] is a particular ECG presentation where QRS complex, ST-segment and T-wave are fused in a unique complex [5]. Originally described in 1.9-3.0% of patients with ST-segment elevation myocardial infarction (STEMI) during the acute phase, it has been found to be associated with a high risk of ventricular fibrillation and cardiogenic shock as well as with a high in-hospital mortality [3-5]. However, shark fin ECG pattern has also been reported in patients with non-acute coronary syndrome related ST-elevation (NASTEP), including stress-induced takotsubo syndrome (TTS) [7]. Fourteen such cases (all females) have been described so far [8-17]. In the first of those reports describing 5 female subjects, which constituted 3.2% of the studied TTS group, poor outcome of patients with this ECG marker was suggested [8].

AIM

The purpose of this paper is to describe first male case of concomitant shark fin ECG pattern and TTS as well as to analyze clinical data of all similar published cases.

CASE REPORT

A 56-year-old male with burn injuries of head, back, upper, lower limbs and respiratory tract was admitted to Intensive Care Unit (ICU) due to severe shortness of breath, respiratory insufficiency and heart failure with hemodynamic compromise. He required mechanical ventilation and catecholamines use. Troponin I was elevated to 1060 µg/L (normal range up to 26 µg/L). ECG showed shark fin pattern in precordial leads (Fig. 1) which maintained within 2 days, then ST-T evolution as well as transient attenuation of QRS complexes amplitude were observed (Fig. 2). Echocardiography revealed apical and midventricular akinesia with left ventricular (LV) ejection fraction (EF) and global longitudinal strain (GLS) reduced to 30% and to -6.8 %, respectively and a high segmental post-systolic shortening expressed by post-systolic index (PSI) (Fig. 3). Echocardiographic improvement followed by almost normalization were observed after 6 and 9 days, respectively. No cardiac arrhythmias were reported. After the patient's stabilization, he was transferred to Burn Unit. Control cardiological examination after 4-months follow-up showed only flattened T waves in ECG and normal echocardiographic LV function.

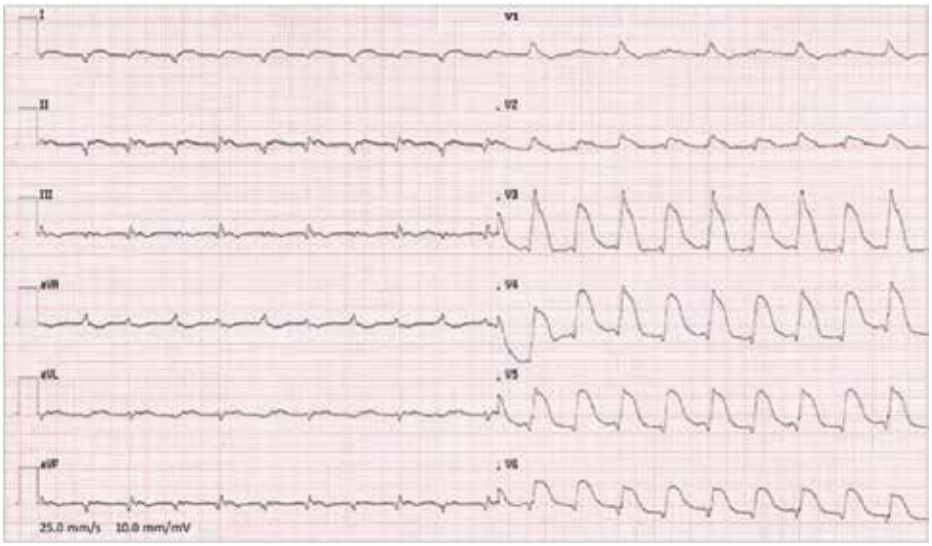


Fig. 1. Initial ECG with shark fin pattern in precordial leads. See QRS-ST-T alternation (shark fin/lambda pattern) especially in V3

Fig. 2. ECG: precordial leads from TTS onset (with shark fin pattern lasting two days) to trace normalization. See transient attenuation of QRS complexes amplitude

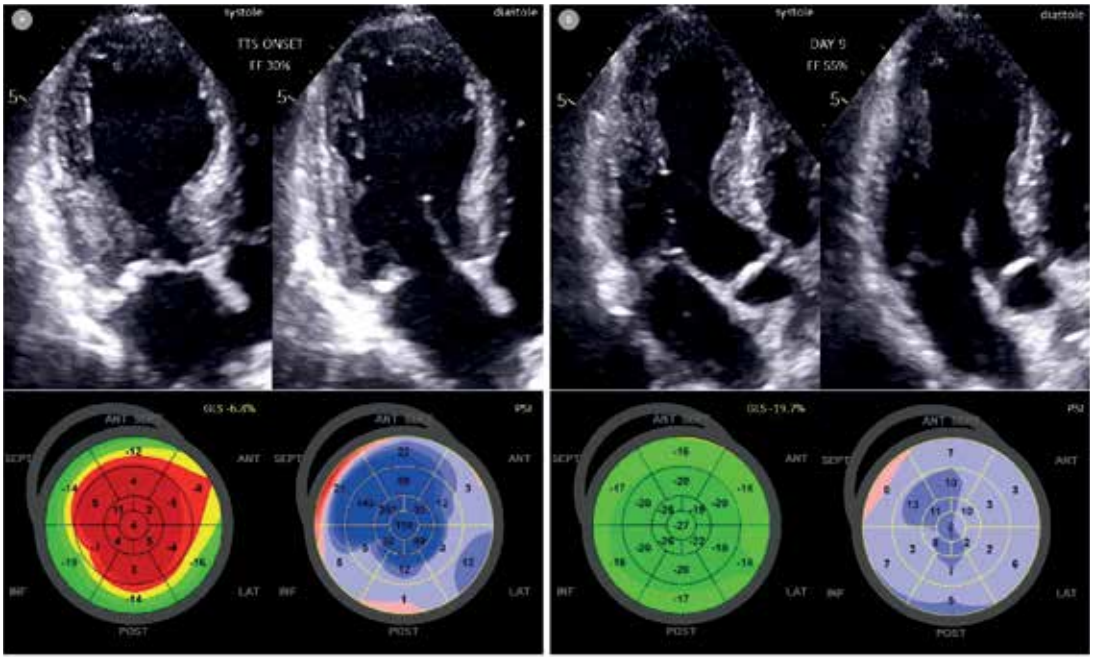


Fig. 3. Echocardiography at TTS onset and 9 days after: left ventricle in systole and diastole in apical long axis view; global and segmental longitudinal strain (red/yellow/green bull's eye map), segmental post-systolic index (blue/red bull's eye map)

Table 1. Clinical data of cases with shark fin (triangular) ECG pattern and TTS

Case number. Author publication date	Age/gender/ triggering factor	Clinical presentation	ECG leads involved (description of ECG pattern)	TTS type/ LV EF	Life- -threatening arrhythmia	Therapy/ Outcome
1-5. Tarantino (2018) [8]	mean age 81 (73-86) /all F/ high prevalence of physical stressor: pneumonia and fever (2), subocclusive fecaloma (1), femoral fracture (1), clostridium difficile (1)	chest discomfort (2), dyspnea (2), fatigue (1) cardiogenic shock (4)	precordial leads, mostly V2-V4 (lambda-wave STE)	all apical, mean EF 32%	1 episode of self-limiting TdP in 1 patient	dopamine (2), dopamine + noradrenaline (2), noninvasive ventilation (3)/ 2 died during hospitalization
6. Kashiura (2018) [9]	70/F/ alcoholism, hypokalemic periodic paralysis	chest tightness	I, II, V2-6 (tombstone STE)* on day 2 of hospitalization	apical	not mentioned	bisoprolol/ LV function improvement after 4 days
7. Wang (2019) [10]	71/F/ not described	chest pain on admission	precordial leads (GRWS)* on day 3 of hospitalization	apical mid segments, EF 42%	not mentioned	levosimendan, furosemide/ LV function improvement before discharge, 1-year follow up
8. Joki (2020) [11]	67/F/ emotional stress during the funeral of a close relative	chest pain 4 days after the funeral, shortness of breath, cardiogenic shock	anterolateral and inferior (TW)	apical, EF 20%	repeated episodes of nsVT	levosimendan, amiodarone, lidocaine, non-invasive ventilatory support (ICU)/ normal LV function after 1 month, asymptomatic in 2-year follow up
9. Celli (2021) [12]	32/F/ Covid-19, extubation, cardiopulmonary resuscitation, hypokalemia, hypernatremia	pulseless electrical activity after extubation/ cardiogenic shock	I, avL V6 (TW) On day 6 of hospitalization	midventricular/ EF 40-45%	pulseless electrical activity after extubation	vasopressors, mechanical ventilation (ICU)/ LV function normalization after 4 days/ pulmonary embolism, RV dysfunction, clinical deterioration, palliative care
10. Verdoia (2021) [13]	51/F/ epileptic attacks, pyometra, surgery, sepsis	septic/ cardiogenic shock	I, II, aVL and precordial leads (shark fin) on day 6 of hospitalization	apical, EF 30%	1 episode of sustained VT	vasopressors, antibiotics, mechanical ventilation (ICU)/ progressive LV function recovery with complete normalization at discharge (after 25 days)

11. Prakash (2021) [14]	57/F/ severe COVID-19 pneumonia, neoplastic disease after radiotherapy, 1 months after laparotomy for intestinal obstruction, abdominal infection	hypotension/ cardiogenic shock	mostly precordial leads - V4-6 (lambda-wave STE)	apical	not observed	inotropic support, invasive ventilation
12. Zhang (2022) [15]	54/F/ septic shock, intraabdominal infection	septic/ cardiogenic shock	II, avF, V3-V6 (shark fin)	apical, EF 38%	not mentioned	vasopressors, levosimendan, antibiotics, mechanical ventilation (ICU)/ normal LV function 5 weeks after discharge
13. Arroyo--Rodríguez (2022) [16]	74/F/ COVID-19, mechanical ventilation	ARDS, cardiogenic shock	I, avL, V4-V6** (shark fin) on day 15 of hospitalization	apical, EF 38%, LVOT obstruction	not mentioned	multiorgan failure, mechanical ventilation (ICU)/ died after 4 days
14. Almutairi (2023) [17]	57/F/ bowel perforation, history of colorectal carcinoma	chest pain day latter, cardiogenic shock	anterolateral leads (shark fin)	apical/EF 25%	not mentioned	bowel resection, vasopressors, antibiotics (ICU)/ LV normalization after several days, 15 years follow-up
15. Elikowski (2023) present case	56/M/ burn injury	dyspnea, respiratory insufficiency, heart failure, cardiogenic shock	anterolateral leads (shark fin) lasts 2 days	apical/EF 30%	not observed	vasopressors, antibiotics, mechanical ventilation (ICU)/ LV function normalization after 9 days, 4 months follow-up

**met criteria of shark fin/TW pattern, **one of four patients with TTS and COVID-19; F – female; M - male; TTS – takotsubo cardiomyopathy; LV EF – left ventricular ejection fraction; STE – ST-segment elevation; GRWS – giant R wave syndrome; TW – triangular QRS-ST-T waveform; ICU – intensive care unit, RV – right ventricle; TdP – torsade de pointes; nsVT – non-sustained ventricular tachycardia, ARDS - acute respiratory distress syndrome; LVOT – left ventricular outflow tract*

Clinical data of our case and of similar patients previously reported by other authors are collected in table1. Seven patients were described as shark fin/TW ECG pattern, six as lambda-wave STE; one defined as GRWS and another one as tombstone pattern met the criteria for shark fin pattern. There were 14 females and only 1 male (our case), 8 of them were over 70-years-old; 6 patients were under 60-years-old. Typically, patients presented with chest pain and shortness of breath; cardiogenic shock developed in 12 cases. Apical ballooning was dominant TTS type seen in 14 persons, only in one female the midventricular form was reported. In 11 patients no serious ventricular arrhythmia was recorded. One female had a single episode of self-limiting torsade de pointes, one repeated episodes of non-sustained ventricular tachycardia, one a single incident of sustained ventricular tachycardia and in one case, pulseless electrical activity event occurred immediately after extubation. During the acute phase of TTS, most patients were hospitalized in ICU. Three patients died during hospitalization.

DISCUSSION

Different terms for ECG presentation where QRS complex, ST-segment and T-wave are fused in a unique complex exist. Shark fin ECG pattern, TW pattern, lambda-wave STE and GRWS are usually used alternatively [18, 19]. However, detailed differences between the definition of shark fin/ TW and other patterns may be indicated [5]. Shark fin pattern and TW mean exactly the same: R wave amplitude ≥1 mV followed by steep down-sloping ST-segment which conceals T-wave. Lambda wave pattern includes: R wave amplitude ≥1 mV, J-wave amplitude ≥1/4 R and ≤ R, steep down-sloping ST-segment and merge of QRS and inverted T-wave. So, shark fin/TW pattern appears to be an extreme form of lambda wave pattern [5]. These patterns not rarely coexist in corresponding ECG leads [12, 13] or alternately even in the same lead (like in our case). While analyzing consecutive tracings, certain pattern may precede [11] or follow another pattern [14]. GRWS may include tombstone pattern where peak of convex ST-segment is higher than

R-wave [5]. In presented review, all cases met criteria of shark fin/TW pattern even if ECG was originally described differently.

The prevalence of shark fin pattern in patients with TTS is similar to that observed in STEMI; in Tarantino group there were 5 such cases (3.2%) out of 158 consecutive TTS patients [8]. However, correlations with gender are quite different; in STEMI 80% of patients were males; in TTS, only 1 male case out of total 15 patients was reported. Association of shark fin ECG in MI and life-threatening arrhythmias raise no doubts [3-5]; although, even left main coronary artery occlusion might not forejudge poor outcome [20]. This association in TTS patients is less clear. Shark fin pattern reflects rather initially significant LV dysfunction [8,11], yet the marker is doubtful for impact LV abnormalities duration. On the other hand, there is a question if shark fin pattern duration may be related to TTS severity.

The mechanism of discussed ECG changes is still not clearly known, some theories are being considered, including catecholamine-induced increase of metabolic demand and local intermittent microvascular constriction [10]. Experimental studies showed that transmural systolic wall tension could influence action potentials through mechano-electric feedback [21]. Madias underlies the importance of mechanically induced STE in TTS [22]. It appears obvious that apical ballooning - TTS type producing most pronounced LV abnormalities, is distinctly dominating TTS type, which can trigger shark fin patter. Echocardiographic evaluation of our case with GLS and PSI (defined as myocardial shortening that occurs after aortic valve closure) indicated extensive decrease of LV deformation and increase in segmental contractile dysfunction and its dispersion.

One should remember that apart from myocardial infarction and TTS, shark fin pattern has also been seldom observed in other clinical situations such as multivessel coronary vasospasm [23], vasospasm of dominant left anterior descending coronary artery [24], myopericarditis [25, 26], thiamine deficiency [27], electrolyte abnormalities [28] and propofol action [29]. In some patients with vasospasm-related transient LV dysfunction, differential diagnosis with TTS may be a challenge, then cardiac magnetic resonance can allow the proper diagnosis [24]. Probably, new echocardiographic techniques could be also useful. It should be interesting to evaluate these techniques in patients with shark fine pattern and preserved systolic LV function [25-29].

CONCLUSIONS

Shark fin ECG pattern can be rarely observed in patients with TTS, usually in cases with severe initial LV dysfunction. However, contrary to STEMI, such pattern is not necessarily associated with life-threatening ventricular arrhythmias. Proper treatment of TTS acute phase, optimally in ICU, favors patient's survival. In some patients, poor prognosis may be determined by an underlying disease being the triggering factor.

REFERENCES

1. Jaiswal AK, Shah S. Shark Fin Electrocardiogram: A Deadly Electrocardiogram Pattern in ST-Elevation Myocardial Infarction (STEMI). Cureus. 2021;13:e15989.
2. Clark KAA, Rosenfeld LE. Shark Sighting in an Electrocardiogram. JAMA Intern Med. 2023;183:154-155.
3. Schreiber A, Inciong K, Ji W, et al. A single-center retrospective study on the incidence and clinical significance of the electrocardiographic "Triangular QRS-ST-T Waveform" pattern. Heart Lung. 2022;56:86-90.
4. Kukla P, Jastrzebski M, Sacha J, et al. Lambda-like ST segment elevation in acute myocardial infarction – a new risk marker for ventricular fibrillation? Three case reports. Kardiol Pol. 2008;66:873-877.
5. Cipriani A, D'Amico G, Brunetti G, et al. Electrocardiographic Predictors of Primary Ventricular Fibrillation and 30-Day Mortality in Patients Presenting with ST-Segment Elevation Myocardial Infarction. J Clin Med. 2021;10:5933.
6. Madias JE, Krikelis EN. Transient giant R waves in the early phase of acute myocardial infarction: association with ventricular fibrillation. Clin Cardiol. 1981;4:339-349.
7. Tarantino N, Santoro F, Brunetti ND. Triangular "shark fin-like" ST modification in takotsubo syndrome: Challenging the concept of ST-elevation patterns without coronary occlusion? J Electrocardiol. 2018;51:1157-1158.
8. Tarantino N, Santoro F, Guastafierro F, et al. "Lambda-wave" ST-elevation is associated with severe prognosis in stress (takotsubo) cardiomyopathy. Ann Noninvasive Electrocardiol. 2018;23:e12581.
9. Kashiura M, Amagasa S, Tamura H, et al. Tombstone ST elevation in Takotsubo cardiomyopathy. Acute Med Surg. 2018;6:87-88.
10. Wang Y, Guo W, Ma J. Takotsubo cardiomyopathy and giant R wave syndrome mimicking acute myocardial infarction: A case report. Medicine (Baltimore). 2019;98(9):e14677.
11. .Joki T, Nikus K, Laukkanen J. The electrocardiographic 'triangular QRS-ST-T waveform' pattern: a marker of severe haemodynamic compromise in Takotsubo syndrome-a case report. Eur Heart J Case Rep. 2020;4:1-6.
12. Celli D, Byer M, Sancassani R, et al. Triangular ECG Pattern in a Young Female with COVID-19. Am J Med. 2021;134:751-753.
13. Verdoia M, Viola O, Marrara F, et al. A 'shark'-masked electrocardiogram: case report of a Tako-Tsubo syndrome. Eur Heart J Case Rep. 2021;5:ytab132.
14. Prakash SD, Kapil A, Deepti S. ST-segment elevation in a critically ill patient: Greek letters, war helmets, and broken hearts. J Arrhythm. 2021;37:1588-1590.
15. Zhang B, Yin ZW, Chen W. Shark Fin Electrocardiogram in the Intensive Care Unit. Circulation. 2022;146:1099-1102.
16. Arroyo-Rodríguez C, Victoria-Nandayapa JR, López-Aceves M, et al. Takotsubo syndrome in COVID-19: a case series study. Echocardiography. 2022;39:920-934.
17. Almutairi AM, Alotaibi WS, Almuhana AH, et al. Shark Fin Electrocardiogram: A Deadly Electrocardiogram Pattern in Takotsubo Cardiomyopathy During 15 Years of Follow-Up. Cureus. 2023;15:e36509.
18. Madias JE. Other correlates of "lambda wave" in patients with takotsubo syndrome? Ann Noninvasive Electrocardiol. 2018 Nov;23:e12596.

19. Tarantino N, Santoro F, Di Biase M, et al. The non-acute coronary syndrome related ST-elevation patterns (NASTEP) conundrum: War helmets, Greek letters, and "shark fins". Ann Noninvasive Electrocardiol. 2018;23:e12605.
20. Miranda JM, de Oliveira WS, de Sá VP, et al. Transient triangular QRS-ST-T waveform with good outcome in a patient with left main coronary artery stenosis: A case report. J Electrocardiol. 2019;54:87-89.
21. Shimada M, Nakamura Y, Asakura K, et al. Induction of ST-segment elevation by regional myocardial stretch in normal canine hearts in vivo. Jpn Circ J. 1997;61:921-926.
22. Madias JE. Two possible mechanisms for the electrocardiogram diffuse ST-segment elevation in Takotsubo syndrome. J Electrocardiol. 2013;46:346-347.
23. Janaki Rami Reddy M, Garg J. Shark fin sign. J Arrhythm. 2021;37:1362-1363.
24. Landi A, Pavon AG, Valgimigli M. Sailing in the complexity of the "shark-fin" sign. Heart 2023;109:25,78.
25. Bulut M, Ekici F, Ülgen Tekerek N. "Triangular QRS-ST-T waveform ECG pattern" during SARS-CoV-2 infection in a paediatric case with multiple comorbidities. Cardiol Young. 2023;33:328-330.
26. Hasibuan FS, Intan RE, Wilujeng HRT, et al. Triangular QRS-ST-T Waveform Electrocardiographic Pattern in Acute Myopericarditis: A Case Report from a Limited-Resources Hospital. Am J Case Rep. 2020 Oct 26;21:e926360.
27. Martins Carvalho M, Proença T, Alves Pinto R, et al. Wernicke encephalopathy and beriberi disease presenting as STEMI-equivalent. Monaldi Arch Chest Dis. 2023 Feb 16. doi: 10.4081/monaldi.2023.2513. Epub ahead of print.
28. Chow HB, Lim CT, Ho YH, et al. Pseudo-infarction electrocardiographic changes in delayed onset hypoparathyroidism: A case report. Clin Case Rep. 2023;11:e7580.
29. Huang HT, Chen WJ, Li CH, et al. Early Recognition of Electrocardiographic Lambda-Wave ST Elevation during Propofol Infusion Prevents Ventricular Tachyarrhythmia and Cardiac Arrest. Acta Cardiol Sin. 2020; 36:517-519.

ORCID AND CONTRIBUTIONSHIP
Waldemar Elikowski: 0000-0003-4825-087X[A,B,D-F]
Patryk Szczęśniewski: 0009-0008-81344687[A,B,D]
Natalia Fertała: 0000-0001-9976-1667[A,B,D]
Magdalena Zawodna-Marszałek: 0000-0002-6878-3860[A,B,D]
Joanna Albrecht: 0009-0001-4455-8431[A,B,D]
Marcin Żytkiewicz: 0000-0002-0229-7093[E]

CONFLICT OF INTEREST
The Authors declare no conflict of interest

RECEIVED: 20.04.2023
ACCEPTED: 28.08.2023

ADDRESS FOR CORRESPONDENCE
Waldemar Elikowski
Department of Internal Medicine, Józef Struś Hospital
3 Szwajcarska St., 61-285 Poznań, Poland
e-mail: welikowski@wp.pl

* Contribution: A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval.