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# THE DIETARY HABITS AND NUTRITION BELIEFS OF PATIENTS WITH AORTIC STENOSIS

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## ABSTRACT

**Aim:** The analysis of dietary knowledge and habits of patients with aortic stenosis, both prior to and post valve implantation.

**Materials and methods:** Patient with diagnosed moderate or severe aortic stenosis were included into the study. Telephonic dietary interview was performed. It was based on the standard KOMPAN questionnaire developed and validated by the Behavioural Nutrition Team, Committee of Human Nutrition of Polish Academy of Sciences.

**Results:** The analysis was conducted in 94 consecutive patients. The pro-health diet index was 4.87 points (3.7; 5.96), while the optimal level was defined as 20 points. The 12.8% of the respondents had low knowledge about nutrition, 79.8% - moderate and 7.4% - good. From 94 patients, 37 had the patient-prosthesis mismatch and overweight. The 35.1% of patients with the patient-prosthesis mismatch and overweight considered their nutritional habits as bad, 62.2% as moderate and 2.7% as good. In a group of patients without the patient-prosthesis mismatch the self-opinion about diet was bad in 20.8%, moderate in 72.9% and good in 6.3%.

**Conclusions:** Dietary habits and nutritional knowledge in patients with aortic stenosis are inadequate. However, awareness of bad dietary habits in patients who are overweight and have patient-prosthesis mismatch is better compared to the remaining group of patients. The proper dietary education is needed in all patients with aortic stenosis.

**KEY WORDS:** aortic stenosis, patient-prosthesis mismatch, aortic valve, nutrition

## INTRODUCTION

Aortic valve stenosis (AS) is the most common acquired valvular heart disease. As a result of valve degeneration, the aortic valve opening area is reduced, causing increased left ventricle afterload. The treatment of severe AS is surgical aortic valve replacement with a prosthesis (SAVR) or minimally invasive, transcatheter aortic valve implantation (TAVI). Obesity, causing increased flow demand can be a reason of functional stenosis of both the native stenotic valve and of the valvular prosthesis, adversely influencing the prognosis. The diameter of the valve prosthesis is limited by the native annulus size. Disproportion between the diameter of a prosthesis and the body size is called the patient - prosthesis mismatch (PPM). It is a severe problem causing persistent left ventricle overload despite the valve replacement. PPM is defined as the valve opening area indexed to the body surface (iEOA) less than or equal to 0.85 cm<sup>2</sup>/m<sup>2</sup> [1, 2]. Both the small diameter of the valve prosthesis and the patient's body size play an important role in the pathomechanism of PPM. Obesity may significantly increase the risk of PPM, particularly in patients in whom, for anatomical reasons, a relatively small valve prosthesis have to be implanted. Excessive left ventricular afterload is of particular importance during exercise, which in obese patients is associated with a high metabolic demand. As-

sociated hypertension, common in obese patients, may be an additional factor increasing cardiac afterload. It has been shown that PPM is associated with a higher risk of postoperative cardiac events and a worse long - term prognosis [3]. Not only post surgery, but also prior to the procedure, obesity is an important factor increasing the left ventricular overload and the risk of procedural complications [4]. Moreover, atherosclerosis can independently affect the prognosis causing not only coronary disease but also accelerating the process of aortic valve degeneration [5]. Thus, patients with AS should pay every effort to avoid obesity and reduce the risk of atherosclerosis, both prior and post valve surgery.

## AIM

Little is known about the dietary knowledge and awareness in patients with native valve stenosis or after aortic valve prosthesis implantation. The aim of this study was the analysis of dietary knowledge and habits of patients with AS and post valve implantation in patients of Cracow registry of patients with aortic stenosis (KRAK-AS).

## MATERIALS AND METHODS

The KRAK-AS registry was carried out between July and October 2016 in the echocardiography laboratories in Cracow. The study was performed after obtaining a

positive opinion from the Bioethics Committee of the Jagiellonian University Collegium Medicum in Cracow (the ethic statement number: 122.6120.66.2015 from 30<sup>th</sup> April 2015). The study has been conducted in accordance with the principles set forth in the Helsinki Declaration. All consecutive patients undergoing echocardiographic study with diagnosed moderate or severe AS who gave informed consent were included in the study. Telephonic dietary interview after 3 years follow-up was performed in patients who gave additional informed consent. A standard KomPAN questionnaire, developed and validated by the Behavioural Nutrition Team, Committee of Human Nutrition of Polish Academy of Sciences was used [6]. On the basis of the data distribution, the mean or median values and quartiles were calculated.

According to the standard questionnaire used [6], each of the respondents specified the frequency of consumption of 10 groups of products constituting components of a healthy diet, which included: whole meal bread, whole grain cereals and pasta, milk, fermented milk drinks, cottage cheese, white meat, fish, fruits and vegetables. Depending on the frequency of consumption of a given product, each of them was assigned an appropriate point unit, which was then summed up for all 10 products, determining the pro-health diet index (pHDI-10) defining the level of intensity of normal eating habits.

The frequency of eating mentioned 10 groups of products were standardized to daily frequency (for example when a patient ate fish 1-3 times a month it was calculated as 2 (mean from 1-3 times) divided into 30 days (1 month) which gives point unit 0.06, etc) (Table 1).

Point units of all 10 products were summed up to give pHDI-10 index. The pro-health diet index (pHDI-10) was defined on a 20-point scale as: low (0-6.66); moderate (6.67-13.33) or high (13.34-20).

The respondents also answered 25 statements describing their knowledge about food and nutrition. Their task was to verify whether the given statement is true, false or whether it is difficult for them to answer the question. Each correct answer was assigned 1 point, while in

**Table 1.** Indicators of the frequency of food consumption in the KomPAN questionnaire\*.

The frequency of consumption	Daily frequency (times/day)
Never	0
1-3 times a month	0.06
Once a week	0.14
A few times a week	0.5
Once a day	1
A few times a day	2

\*Each of the respondents specified the frequency of consumption of 10 groups of products constituting components of a healthy diet. Depending on the frequency of consumption of a given product, each of them was assigned an appropriate point unit.

the case of a wrong answer or "don't know" answer, 0 points were given. Knowledge was defined as: low (0-8 points); moderate (9-16 points) or high (17-25 points).

## RESULTS

The analysis of dietary knowledge and habits was conducted in 94 patients who agreed to participate in the interview study. All respondents answered all questions. They were predominantly men (57%) with a median age of 69 years. The median body mass index (BMI) was 28.3 kg/m<sup>2</sup> (25.3; 31.2), while the median body surface area (BSA) was 1.89 m<sup>2</sup> (1.74; 2.04). Among all patients, 33 patients (35.1%) were obese (BMI ≥ 30 kg/m<sup>2</sup>), 38 patients (40.1%) were overweight (BMI between 25 and 29.99 kg/m<sup>2</sup>) and only 23 patients (24.5%) had a normal body weight (BMI between 18.5 and 24.99 kg/m<sup>2</sup>). The largest percentage of patients were retired or on disability benefits (68 patients, 72.3%), 24 respondents had permanent or temporary work (25.6%), while 2 patients were unemployed (2.1%). Most of the respondents (61%) had secondary or vocational education.

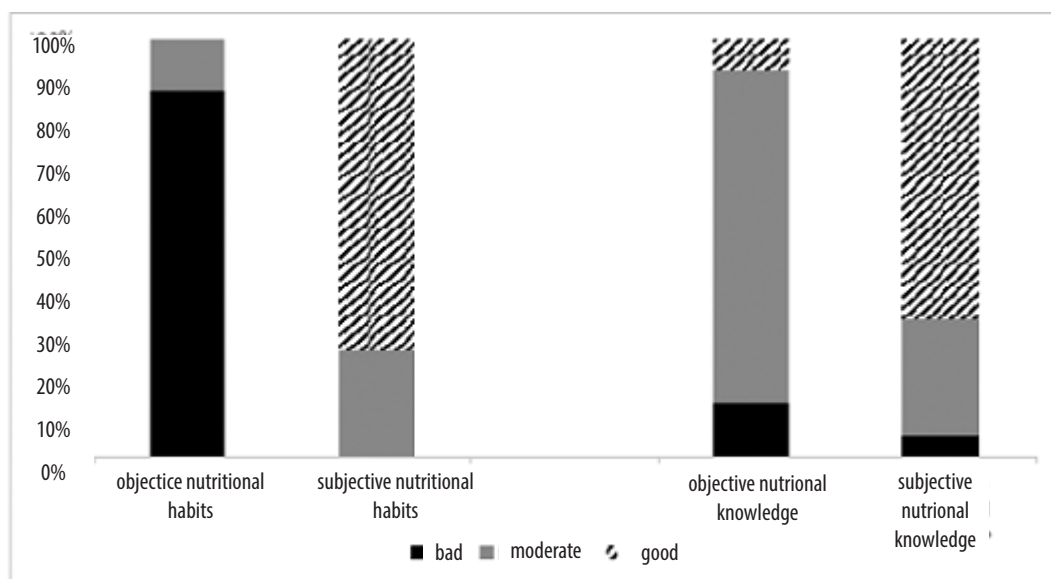
It has been shown that the median pHDI-10 index in the whole population of respondents was 4.87 points (3.7; 5.96), which showed that the intensity of normal eating habits in most patients was low. Among all respondents, 87.2% of them had a low level of normal dietary habits adoption, in 12.8% it was moderate, while no one showed a high level of dietary habits.

Dietary knowledge was assessed by interpretation of 25 statements about food and nutrition. In the entire group of respondents, the median of correct answers was 12 points on a 25-point scale. Based on the data analysis, it was shown that in 12.8% of the respondents the knowledge about nutrition turned out to be low, in 79.8% - moderate, and only in 7.4% - good.

The results concerning dietary habits assessed by the pHDI-10 index and the objective results of the assessment of patients' knowledge about nutrition were compared with their subjective assessment. Most of the patients concluded that their diet, as well as knowledge about food and nutrition were good (74.5% and 67% of the respondents, respectively), while the objective analysis showed that most patients showed a low level of pro-health nutritional features, and the knowledge of the majority people was only moderate (Fig. 1).

Surprisingly, more than half of the participants were unaware of the severity of their heart disease, despite being diagnosed with significant AS. Only 30.8% of the respondents considered their health worse, compared to other people of similar age; 44.8% assessed their condition as similar, and 24.4% as better compared to their peers.

PPM was diagnosed in 46 patients (48.9%). Out of the entire population of 94 patients 37 patients had PPM and a BMI over 25 kg/m<sup>2</sup>, while 47 patients did not meet the PPM criteria. In both subgroups a low level of good dietary habits and a moderate level of nutritional knowledge were observed (Table 2).



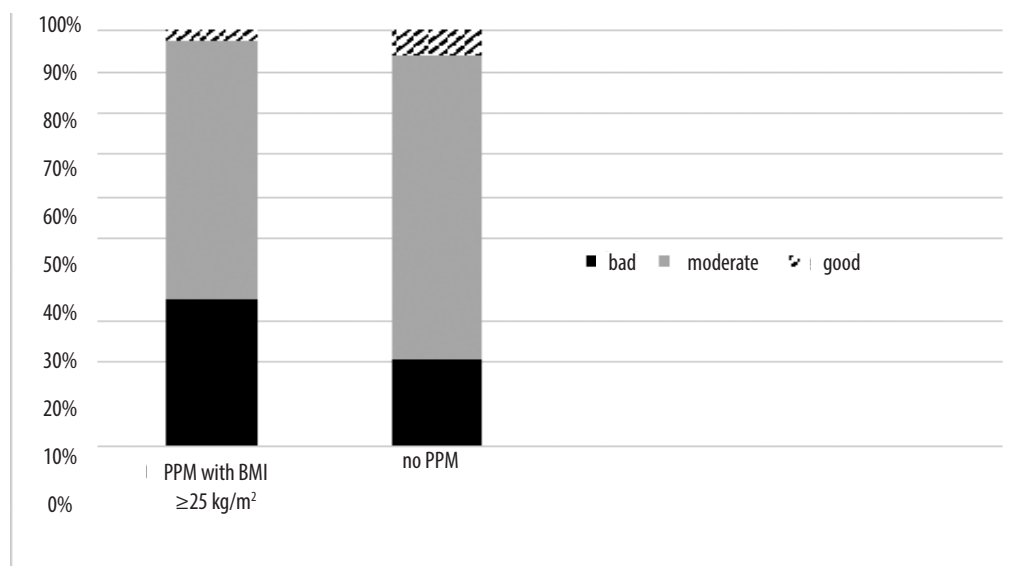
**Fig. 1.** A comparison of the subjective opinion of respondents about their dietary habits and nutritional knowledge with the objective results of the survey.

**Table 2.** Nutritional knowledge and the objective and subjective assessment of dietary habits in the subgroup of people with PPM and overweight and in the subgroup of people without PPM\*.

Value	Nutritional knowledge (points)	pHDI-10 (points)	Opinion about nutritional habits		
			bad	moderate	good
PPM with BMI $\geq 25$ kg/m <sup>2</sup>	12 (11;14)	4.92 (3.62;6.2)	35.1%	62.2%	2.7%
No PPM	12 (9.5;14)	4.9 (3.61;6.06)	20.8%	72.9%	6.3%

\*Respondents specified the frequency of eating of 10 groups of products which are components of a healthy diet. Depending on the frequency of eating of a given product, each of them was assigned an appropriate point unit, which was then summed up for all 10 products, determining the pro-health diet index (pHDI-10) defining the level of intensity of normal eating habits.

BMI - body mass index;  
 pHDI-10 - the pro-health diet index;  
 PPM - patient-prosthesis mismatch.



**Fig. 2.** The patients' opinion on their dietary habits in the subgroup of patients with PPM and BMI  $\geq 25$  kg/m<sup>2</sup> compared to the subgroup of patients without PPM.

BMI - body mass index;  
 PPM - patient prosthesis mismatch.

There were no significant differences between the subgroups. Importantly, a higher proportion of patients aware of poor nutrition was observed in the subgroup of patients with PPM and with overweight (Fig. 2) The 3-year observation of the respondents showed that in 28.4% of patients there was an increase in BMI by at least 0.5 kg/m<sup>2</sup>, while in 35.8% no significant change in BMI was observed (of which more than half of patients [54%] were overweight or obese), while 35.8% experienced a BMI reduction of at least 0.5 kg/m<sup>2</sup>.

## DISCUSSION

As many as 87.2% of the surveyed patients showed a low level of normal nutritional facts awareness, and only 7.4% of the patients had good nutritional knowledge. An incorrectly balanced diet causes not only excessive weight gain, but also increases the risk of many chronic comorbidities, accompanying and complicating severe heart valve disease [7, 8]. The key to increasing awareness and improving pro-health behaviour is patient education at the earliest possible stage, not only in hospital but also outpatient settings. Good nutritional habits in hospitalised patients should be implemented from the first day of hospitalisation proposing properly balanced diet accompanied with appropriate education [9].

When discussing diet in AS patients, it is important to consider if the progression of AS depends on dietary habits. S. Larsson et al. conducted a large prospective cohort study in which two models of nutrition were assessed among the Swedish community without concomitant cardiovascular disease: a diet to reduce hypertension and a modified Mediterranean diet. After 15 years of observation, no evidence was found that these models played a role in the development of AS [10]. On the other hand, the same researchers conducted a 15-year observation, assessing the impact of obesity on the risk of AS. They showed that both general and abdominal obesity, measured as a BMI and waist circumference, respectively, were significantly associated with the occurrence of AS [11]. Thus, an important factor influencing this type of valvular defect is primarily excess body weight, while the type of products consumed seems to be of less clinical significance.

According to our study, PPM patients are more aware of having incorrect eating habits, but their knowledge about proper diet is still at a low level. On one hand, the reason may be due to insufficient education of patients, on the other hand, patients' motivation to take radical dietary measures may turn out to be insufficient.

Not only excessive caloric intake, but also malnutrition can have negative effects. E. Wernio and colleagues assessed the effect of nutritional status on the incidence of postoperative complications and mortality in elderly patients with severe AS undergoing SAVR in a one-year follow-up [12]. The authors showed that unintentional weight loss > 2.8% in the six months preceding cardiac surgery turned out to be significant risk factor of mortality in the first year after SAVR surgery. On the other hand,

Fukui et al. pointed out that the problem of malnutrition in elderly people with AS is not a rare phenomenon [13]. The identified risk factors associated with malnutrition are female gender, poor left ventricular ejection fraction (LVEF), high New York Heart Association (NYHA) class, as well as a low Instrumental Activities of Daily Living Scale (IADL scale); the assessment of the degree of independence in performing complex everyday activities. Thus, not only excessive, but also insufficient energy supply has its adverse clinical consequences. Therefore, not only a restrictive, but also a properly balanced diet is important and this makes dietary education even more demanding.

The complexity of the problem is emphasized by another research group, which, analysing the nutritional status of patients undergoing SAVR, showed that despite the high prevalence of obesity in the study group, clinical symptoms of malnutrition were demonstrated in a significant proportion of patients [14]. Complications after surgery were found in 37.4% of patients. Importantly, patients who experienced complications were older and had a worse nutritional status assessed by the 7-point Subjective Global Assessment Score (SGA).

Our study shows that the awareness of the above problems is insufficient in AS patients. The 87.2% of all from examined patients had a low level of dietary habits, in 12.8% cases it was on moderate level and nobody presented a high level of dietary habits. Moreover, only 7.4% of patients showed good level of nutrition knowledge.

The question remains, what educational efforts and motivating factors could cause clinically important improvement.

## STUDY LIMITATIONS

Because the study was conducted with a questionnaire, the replies may have been subjective. However, the questionnaire was conducted by a physician, which probably increased the methodological accuracy. One third of the patients participating in the KRAK-AS registry did not consent to participate in the questionnaire. Approximately two thirds of patients from this subgroup were overweight or obese, and perhaps this was the reason of unwillingness to cooperate. Their answers could have added interesting information to the material presented here, but most probably this would even increase the proportion of AS patients presenting insufficient dietary knowledge and habits.

## CONCLUSIONS

Dietary habits and nutritional knowledge in patients with aortic AS are inadequate, despite patients' belief that they have good dietary habits and an understanding of good nutrition. Patients who are overweight and have a PPM are characterised by a greater awareness of bad dietary habits compared to the group of patients who do not have a PPM. Importantly, both the quality of diet and the level of knowledge of nutrition remain low in all patients. The proper dietary education is needed not only in the PPM patients but also in all patients with AS.

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## CONFLICT OF INTEREST

The Authors declare no conflict of interest.

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# TISSUE EXPRESSION OF NEURONAL PROTEINS DURING SCIATIC NERVE REGENERATION AND INFLUENCE OF DIFFERENT SPECTRUM LASER RADIATION

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## ABSTRACT

**Aim:** To determine the effect of laser irradiation of different spectrum on the expression of neuronal proteins (GFAP, S100, NSE and NF-L) in the sciatic nerve during its regeneration after crossing and surgical suturing.

**Materials and methods:** The experiment was performed on 60 laboratory rats of the Wistar line (200-250 g) with crossing of the left sciatic nerve and suturing with an epineural suture end to end 30 minutes after neurotomy. 90 days later, an immunohistochemical study was performed using specific antibodies (Thermo Fisher Scientific; USA).

**Results:** A study of the marker of non-myelin Schwann GFAP cells showed their pronounced activation with germination in nerve thickness and the formation of weaves of processes around regenerated nerve fibers. The number of S-100-positive myelin Schwann cells decreased, the heterogeneity of their color and the loss of processes were determined. It showed a general decrease in the intensity of NSE- and NF-L-positive staining of nerve fibers regenerated after neurotomy, which was less pronounced when irradiated with a laser with a wavelength of 450-480 nm and 520 nm.

**Conclusions:** In general, the use of laser radiation had a positive effect on the repair of nerve fibers after neurotomy. According to the immunohistochemical study of neuromarkers, the effect of laser irradiation of the blue spectrum was the most effective.

**KEY WORDS:** nerve regeneration, laser irradiation, GFAP, S100, NSE, NF-L

## INTRODUCTION

The most common variants of damage to the integrity of the peripheral nerve are its crushing or interruption of integrity [1]. As a result, nerve fibers remaining further from the site of injury degenerate during the first days due to activation of endogenous proteolysis with destruction of the axonal cytoskeleton and subsequent phagocytosis (so-called "Waller's" degeneration) [2, 3]. An active role in this process is played by non-myelin Schwann cells, which in the peripheral nervous system have the ability to germinate collaterally when damaged, which is not typical for myelin Schwann cells [4]. Glial fibrillar acidic protein (GFAP) is known to be a marker of the former, while astrologic calcium-binding protein S100 is a marker of the latter [5].

Schwann cells elongate along the basal plate of denervated endoneural tubes to guide, support, and myelinate the regenerating axon. Exercise and electrical stimulation of peripheral nerves promotes their regeneration by increasing the expression of neurotrophic factors in Schwann cells [6].

Markers of nerve fiber regeneration can be considered proteins expressed by them, such as glycolytic neu-

ronal enzyme neuron-specific enolase (NSE) and neurofilament proteins. It is shown that the content of NSE in neurons serves as a molecular marker of axon damage, regeneration and reinnervation of the target [7].

Neurofilaments (NF) form the framework of the myelin fiber and contain three main fractions that differ in molecular weight - heavy (NF-H), medium (NF-M) and light (NF-L). The latter are the main structural element of NF [8]. The content of NF-L increases significantly in the cerebrospinal fluid and serum in many neurological conditions, which allows the use of this indicator as a biomarker of nerve regeneration [9].

For the analysis of cellular and molecular processes of peripheral nerve regeneration, rat damage models are most often used, which allowed to establish the positive effect of neurotrophic and hormonal factors, the use of autografts, physical factors, including electrical stimulation [10].

Irradiation with a monochromatic low-frequency LED laser for 10 days in the sciatic nerve regeneration zone after neurotomy and surgical suturing, as we previously found, significantly reduced the recovery time, structure and function of the nerve [11].

**AIM**

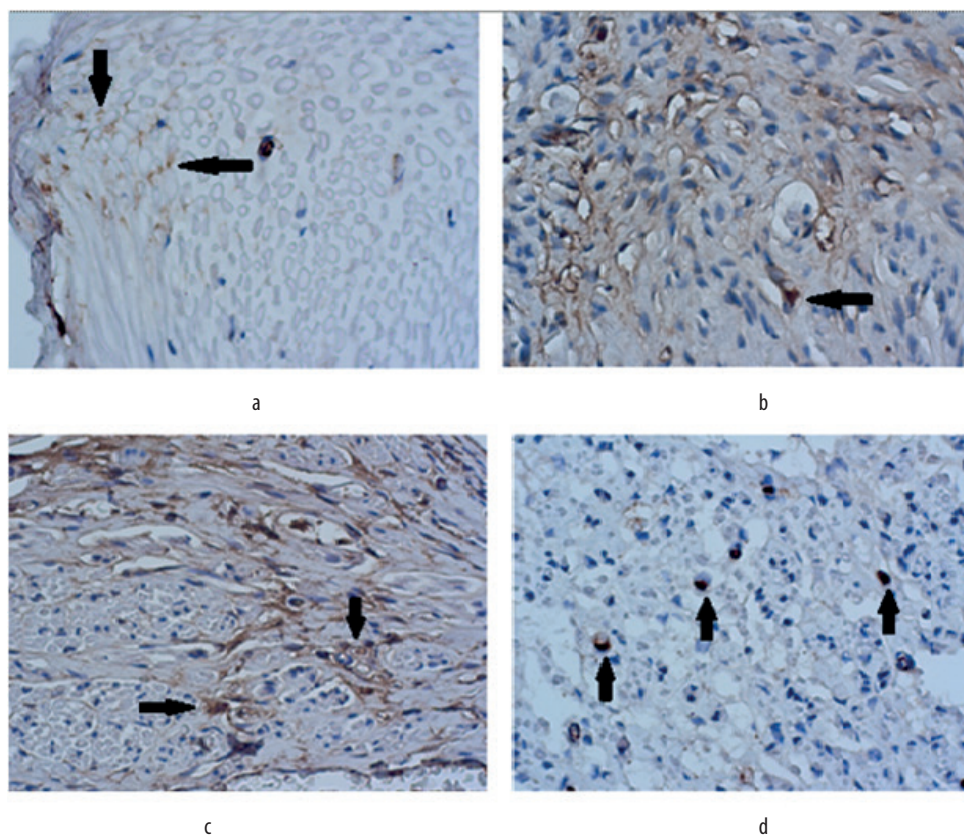
The aim of this study was to determine the effect of laser irradiation of different spectrum on the expression of neuronal proteins (GFAP, S100, NSE and NF-L) in the sciatic nerve during its regeneration after crossing and surgical suturing.

**MATERIALS AND METHODS**

The experiment was performed on 60 Wistar laboratory rats (200-250 g), which under thiopental anesthesia under asepsis and antiseptics underwent intersection of the left sciatic nerve with suturing epineural suture end to end 10, 20, 30 and 45 minutes after neurotomy. Animals were divided into 4 groups - 1<sup>st</sup> (control, before neurotomy, 5 animals), 2<sup>nd</sup> - the use of blue spectrum laser with a wavelength of 480-450 nm (20 animals), 3<sup>rd</sup> - the use of green spectrum laser with a wavelength of 520 nm (20 animals) and 4 - the use of a green spectrum laser with a wavelength of 560 nm (15 animals). In the experimental groups, 5 animals were taken for each suturing period. From the next day after the operation, the surgical intervention area, for 10 days, was irradiated with a laser of the appropriate spectrum using a low-frequency LED laser "Spectrum-LC", exposure 5 minutes. The experiment lasted 90 days. Studies of the restoration

of somato-visceral sensitivity were recorded on the response of animals to pain and temperature stimuli, and motor function with the help of a moving tape.

In pathomorphological examination, the obtained nerve fragments (distal part) were fixed in 10% solution of neutral buffered formalin (pH 7.4) for at least 24-36 hours, the material was performed according to standard methods and poured into paraffin. Serial histological sections 2-3  $\mu$ m thick were made from paraffin blocks on a rotating microtome NM 325 (Thermo Shandon; England). Sections were stained with hematoxylin and eosin for examination microscopy. In all cases, immunohistochemical study was performed to determine the morpho-functional state of nerve cells, features of regenerative abilities [12]. To do this, the sections were placed on adhesive glass Super Frost Plus (Menzel; Germany). Citrate buffer with pH 6 and EDTA buffer pH 8, Vitro Master Polymer Plus Detection System (Peroxidase), chromogen DAB Quanto (Master Diagnostica; Spain) were used for high-temperature treatment of antigen epitopes. Mouse polyclonal antibodies to GFAP and NSE (Thermo Fisher Scientific; USA) and monoclonal antibodies to NEFL (clone 2F11, Thermo Fisher Scientific (USA) and S100 roll (clone 4Cu9, Master Diagnostica, USA) were used.



**Fig. 1.** The sciatic nerve of the rat before (a) and 90 days (b, c, d) after intersection with suturing 30 minutes after neurotomy; representative results of immunohistochemical study of GFAP; additional staining with hematoxylin;  $\times$  400.

*a* - positively stained glial cells are concentrated mainly in the perineurium (arrows); *b* - the use of blue spectrum laser (450-480 nm); in the area of nerve regeneration clusters of positively stained Schwann cells (arrow); *c* - application of a green spectrum laser (520 nm); positive stained Schwann cells and their processes (arrows) between regenerating nerve fibers; *d* - application of green spectrum laser (560 nm); bodies of single large cells (arrows) diffusely located among regenerating nerve fibers

Evaluation of expression was performed according to the recommendations of D.J. Dabbs (2014) on the basis of visual-analog scale: 0 points - no color; 1 point (+) - low color intensity; 2 points (++) - average color intensity; 3 points (+++) - expressed color intensity [13].

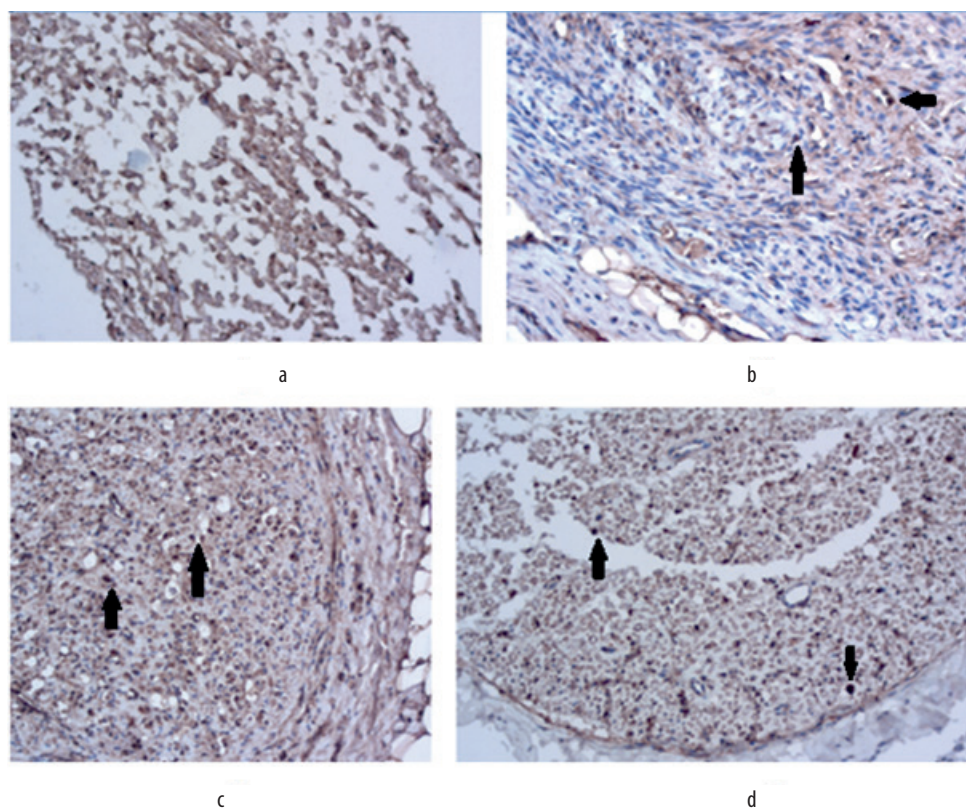
## RESULTS

Our previous studies have shown that after crossing the sciatic nerve with its suturing there are pronounced degenerative-dystrophic changes in nerve fibers, which were manifested by a decrease in the number of nerve fibers and their demyelination, spasm of perineural blood vessels, fibrosis and swelling of myelin [11]. There is no reaction to pain and temperature stimuli, the animal spared the paw on the conveyor belt without stepping on it. From the 15<sup>th</sup> day regenerative-reparative processes began with the gradual restoration of nerve blood supply, remyelination of nerve fibers.

On the 30<sup>th</sup> day, the animals began to respond to temperature and pain stimuli and step on the operated paw on the conveyor belt. From the 60<sup>th</sup> day there was a restoration of blood supply to the nerve, return of myelin nerve fibers, somato-visceral and motor sensitivity.

The time of nerve suturing after its crossing and application of laser radiation was critical. Under the conditions of the latter, satisfactory recovery of the nerve occurred when it was sutured up to 30 minutes after crossing. Increasing the duration of surgical restoration of nerve integrity to 45 minutes led to a delay in the recovery period to 75-90 days.

Based on these results, a comparison of the effects of radiation of different spectrum was performed by suturing the nerve 30 minutes after the intersection, and the results of recovery were compared after 90 days by immunohistochemistry. In fig. 2a tissue expression in the GFAP peripheral nerve in control is shown. This marker is expressed by non-myelin Schwann cells [5]. The perineural location of immunopositive glial cells with low color intensity (up to 1 point) was determined. In the thickness of the nerve fiber Schwann cells had no immunospecific color. When using blue spectrum laser irradiation (450-480 nm), a fairly large number of GFAP-positive Schwann cells with a color intensity of up to 2 points and interweaving of their processes with low color intensity were determined in the nerve fiber thickness (Fig. 2b). In the thickness of the regenerating nerve, a large number of



**Fig. 2.** Rat sciatic nerve before (a) and 90 days (b, c, d) after intersection with suturing 30 minutes after neurotomy; representative results of immunohistochemical study S100; to staining with hematoxylin;  $\times 200$ .

*a - a large number of Schwann cells and their processes in the thickness of the nerve; b - the use of blue spectrum laser (450-480 nm); the number of positively stained Schwann cells is reduced compared to the control; single immunopositive large regrown Schwann cells (arrows); c - application of a green spectrum laser (520 nm); numerous immunopositive Schwann cells of different sizes and color intensities (arrows); d - application of green spectrum laser (560 nm); the number of immunopositive Schwann cells is reduced compared to other groups; cells have a rounded shape, different sizes and intensity of color*



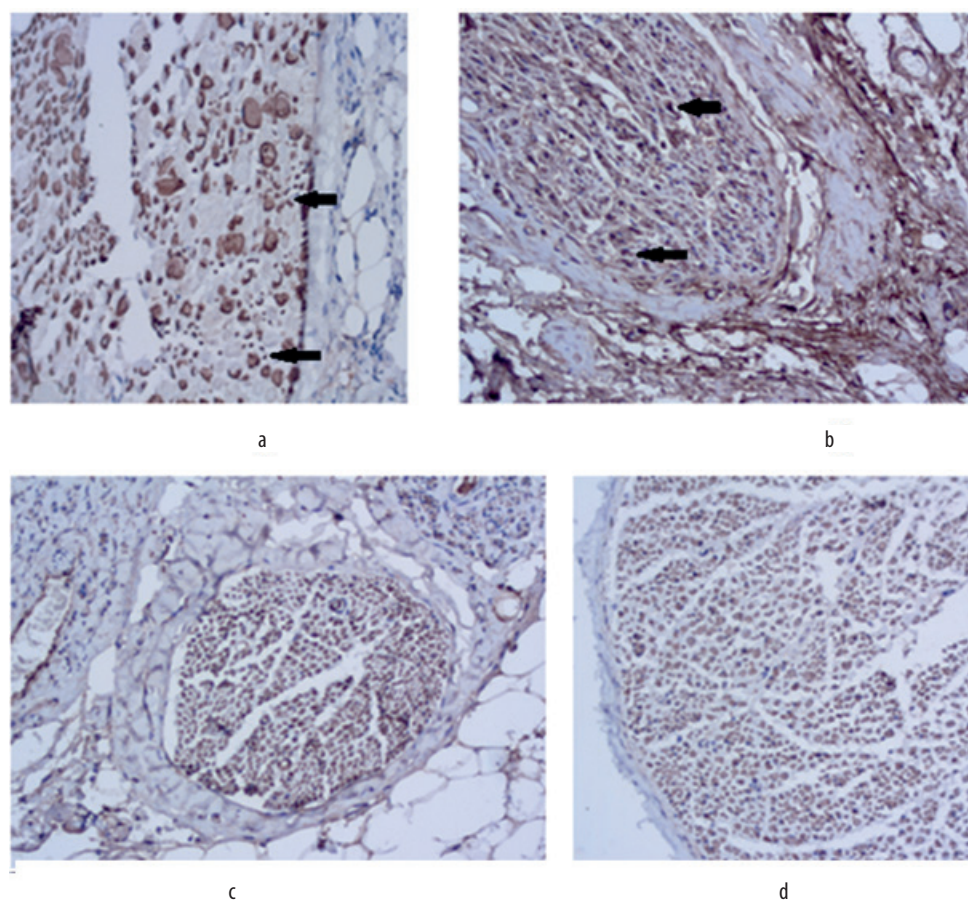
large, intensely hematoxylin-stained regrowth Schwann cells, which had no immunopositive staining, were detected. The ratio of GFAP-negative cells to GFAP-positive in the area of nerve regeneration was 10: 1.

When using laser irradiation of the green spectrum with a wavelength of 520 nm, the morphological picture generally corresponded to the previous group (see Fig. 2c). GFAP-positive Schwann cells diffusely located in the nerve thickness and formed plexuses of regenerated nerve fibers that regenerated. A large number of GFAP-negative Schwann cells that outnumbered GFAP-positive cells (approximately 10: 1) were also identified.

When using green spectrum laser irradiation with a wavelength of 560 nm, single large Schwann cells with an immunospecific color intensity of up to 2 points were located in the thickness of the nerve diffusely at a great distance from each other (Fig. 2d). The entanglement of their fibers around the regenerating nerve fibers was not noticeable. The total number of Schwann cells in the nerve fiber thickness was significantly lower than in the previous groups, and the proportion of GFAP-positive cells did not exceed 1-2%.

Thus, under the conditions of laser irradiation of the blue spectrum and the green spectrum with a wavelength of 520 nm, nerve regeneration was more active, which was manifested in pronounced proliferation of Schwann cells, their germination in nerve thickness and the formation of weaves of processes around nerve fibers. Approximately 10% of these cells were GFAP-positive. When using laser irradiation of the green spectrum with a wavelength of 560 nm, the severity of the glial reaction was much lower, and the number of GFAP-positive cells did not exceed 1-2%. Tissue distribution of another glial marker - S100 protein is presented in Fig. 2. In the peripheral nerve fiber, it is expressed in myelinated Schwann cells [5]. In the control, the expression of the marker is expressed in numerous cells and their processes, which are located in the thickness of the nerve fiber and perineurally with a color intensity of up to 2 points. Diffusely located single large cells with intensely (up to 3 points) stained cytoplasm (Fig. 2a).

When using blue spectrum laser irradiation (450-480 nm) in the nerve fiber thickness, the number of S100-positive cells and the overall color intensity were reduced



**Fig. 3.** Rat sciatic nerve before (a) and 90 days (b, c, d) after intersection with suturing 30 minutes after neurotomy; representative results of immunohistochemical study of NSE; additional staining with hematoxylin;  $\times 200$ .

*a* - sections of nerve fibers have an intense immunopositive color; there are numerous diffusely located glial cells (arrows); *b* - the use of blue spectrum laser (450-480 nm); dyed thin regenerating myelin fibers; a large number of large immunopositive cells with different color intensities (arrows); *c* - application of a green spectrum laser (520 nm); positive staining of thin myelin fibers and individual glial cells; *d* - application of green spectrum laser (560 nm); the overall color intensity and the number of immunopositive cells are significantly lower compared to other groups

compared to the control (Fig. 2b). In the area of nerve regeneration, the density of S100-positive cells was higher and amounted to 50% of the total number of glial cells. The intensity of their color varied from 1 to 3 points. Among others, there were large single S100-positive cells with intensely stained cytoplasm and processes.

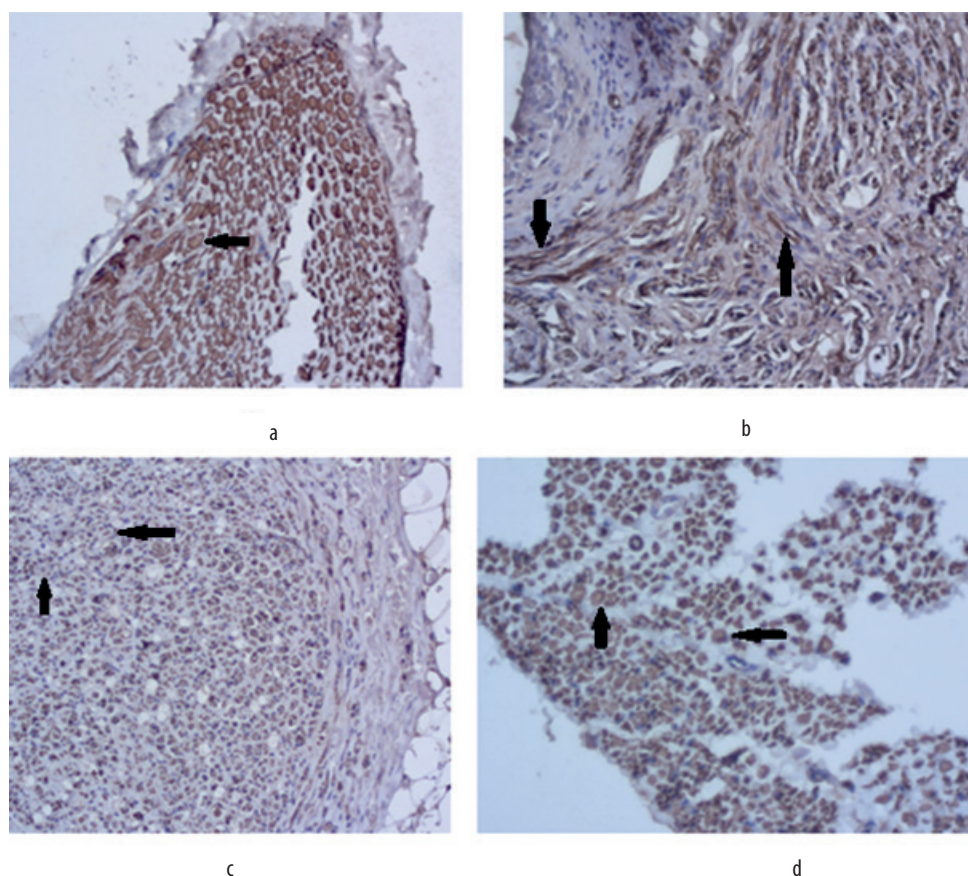
When using laser irradiation of the green spectrum with a wavelength of 520 nm, a very active immunopositive staining was observed, in the nerve thickness up to 50% of Schwann cells were S100-positive (see Fig. 2c). S100-positive cells with long processes have also been observed in perineuria. The intensity of their color varied from 1 to 3 points. The cells had different sizes, among the Schwann cells of the usual process shape, some cells had a round shape.

When using laser irradiation of the green spectrum with a wavelength of 560 nm, a decrease in the number of S100-positive cells to 15-20% of the total amount of glia was observed (see Fig. 2d). The cells were round in shape and were located in the thickness of the nerve between the regenerating nerve fibers and in the perineuria. The intensity of the specific color was up to 2 points.

Thus, the general patterns of the reaction of S100-positive glia in the regeneration of nerve fibers were a decrease in the total number of immunopositive cells, heterogeneity of color and loss of processes. To a lesser extent, such changes were manifested when using a blue spectrum laser, to a greater extent - when using a green spectrum laser with a wavelength of 560 nm.

The marker of differentiated neurons is NSE, the distribution of which in the control group is shown in Fig. 3a. Positive staining with an intensity of up to 3 points was detected along sections of nerve fiber, which corresponded to the cytoplasmic localization of this glycolytic enzyme [7]. Intensely stained bodies of glial cells located between nerve fibers were also found.

When using blue spectrum laser irradiation (450-480 nm) in the nerve thickness, the immunopositive color of low intensity (up to 1 point) was preserved by regenerated thin myelin fibers and numerous diffusely located glial cells with color intensity from 1 to 3 points. 3b). A similar pattern was observed with the use of green spectrum laser irradiation with a wavelength of 520 nm (Fig. 3c).



**Fig. 4.** The sciatic nerve of the rat before (a) and 90 days (b, c, d) after intersection with suturing 30 minutes after neurotomy; representative results of immunohistochemical study of NEFL; additional staining with hematoxylin;  $\times 200$ .

*a - high-intensity staining is distributed mainly on the periphery of myelin nerve fibers (arrow); b - the use of blue spectrum laser (450-480 nm); regenerated thin myelin fibers with intense peripheral coloration and enlightenment in the center (arrows); c - application of a green spectrum laser (520 nm); specific color is weaker than in previous groups; thin myelin fibers with color on the periphery and in the center of the fiber in the form of a dot or dash (arrow); d - application of green spectrum laser (560 nm); larger diameter nerve fibers with peripheral color (arrows)*



When using laser irradiation of the green spectrum with a wavelength of 560 nm, a decrease in the intensity of immunospecific staining and the number of NSE-positive cells compared to the previous groups. The intensity of the specific color ranged from 1 to 2 points.

Thus, thin myelin fibers that regenerated after neurotomy in the fiber thickness had a relatively weak NSE-positive color compared to the control. The weakest color was when using laser irradiation of the green spectrum with a wavelength of 560 nm.

The tissue distribution of NF-L is presented in Fig. 4. In the control, high-intensity immunopositive staining (up to 3 points) was uniformly expressed throughout the section of nerve fibers, especially on their periphery (Fig. 4a).

When using blue-spectrum laser irradiation (450-480 nm), NF-L expression was significantly pronounced, and the color intensity in the regenerated thin myelin fibers was up to 3 points (see Fig. 4b). Large ganglion cells with high color intensity were determined. Large ganglion cells with high color intensity were determined.

When using laser irradiation of the green spectrum with a wavelength of 520 nm, the intensity of immunospecific color did not exceed 2 points. An interesting morphological feature of nerve fibers was noteworthy - they had a specific color on the periphery and in the center in the form of a dot or a thin line (Fig. 4c).

When using laser irradiation of the green spectrum with a wavelength of 560 nm, the total intensity of the specific color was 2 points. Nerve fibers had a more intense color on the periphery than in the center.

Thus, the regenerating fine nerve fibers were generally less intense in color than in the control, but when the groups were compared, the best recovery in NF-L expression was found in the blue-spectrum laser group compared to green spectra.

## DISCUSSION

These data substantiate our previous results on the positive effect of laser radiation on the regeneration of the sciatic nerve after its surgical suturing [11].

It is known that after crossing and surgical treatment, axons grow from the proximal to the distal nerve stump, branch, some twist and may even grow in the opposite direction [14]. At the same time regeneration occurs gradually - by "steps". Thus, in the first week only 25% of axons cross the growth zone. Many axons branch out because they have access to more than 100 distal tubes formed by Schwann cells at the same time, so axons usually do not return to their innervation targets. Such "wandering" of axons is not subject to surgical control and, apparently, requires other approaches to the reunion of ruptured axons with the corresponding distal pathways. Within a month, all motoneurons regenerate their axons through the suture site and the distal nerve stump [15]. Moreover, electrical stimulation of the distal part of the nerve with a frequency of

20 Hz for an hour increases the number of axons that begin to regenerate and synchronizes the reinnervation of the distal stump.

The selectivity of motor axon regeneration during the first 3 weeks in the motor or sensory branches of the femoral nerve depends on the selective expression of Schwann cell growth factors [6, 16]. They play a crucial role, as they express modal-specific phenotypes associated with the stimulation of selective regeneration [3].

Our studies have shown a relationship between the best effect of blue spectrum and green spectrum radiation with a wavelength of 520 nm with pronounced proliferation of Schwann cells and their germination in nerve thickness with the formation of intertwining processes around regenerating nerve fibers. The lower efficiency of irradiation when using a green spectrum laser with a wavelength of 560 nm corresponded to a lower glial response with a low number of GFAP-positive cells. In GFAP (-) transgenic mice, axon regeneration after injury was significantly inhibited because mutant Schwann cells lost their ability to proliferate [17, 18].

Therefore, it can be assumed that laser irradiation of the nerve suturing zone in the first 10 days contributed to the results of nerve regeneration due to the activation of GFAP-positive Schwann nerve fiber cells.

It should be noted that not only exercise and electrical stimulation promote functional recovery and regeneration of damaged peripheral nerves, but also extracorporeal shock wave therapy increases the expression of GFAP and other neuroglial proteins [19, 20].

Regarding the role of S100-positive glia, our results showed a general decrease in its activity. The reason for this may be the loss of these cells of central innervation after nerve crossing for a long time [3]. Chronically deinnervated myelinated Schwann cells lose the phenotype that supports the growth of nerve fibers, and their number is reduced [6, 21, 22]. According to our data, morphologically, this was manifested by a decrease in the total number of S100-positive cells compared with control, heterogeneity of color and loss of processes. The difference in the action of laser radiation of different spectra showed that to a lesser extent such changes were manifested when using a blue spectrum laser, and more - when using a green spectrum laser with a wavelength of 560 nm. Therefore, it can be assumed that the blue spectrum of laser irradiation stimulated myelinated Schwann cells, preventing the effect of prolonged deinnervation [23, 24].

The results of determining the effect of laser radiation on NSE expression can be interpreted from the same positions. NSE-positive staining was significantly reduced compared to the control, with the worst results when using green spectrum laser irradiation with a wavelength of 560 nm.

Detection of neurofilaments by immunohistochemistry is highly informative and correlates well with electron microscopy data [25]. We showed that the intensity of NE-L-positive staining correlated with the res-

toration of sciatic nerve function, which was consistent with data from other studies [9].

According to the data obtained, the regenerated thin nerve fibers had a lower intensity of NE-L-positive staining than in the control. Comparison of the groups showed that the best effect on NF-L expression had blue spectrum laser irradiation. We also found a certain morphological feature of the recovery of nerve fibers, which in the process of regeneration had a higher intensity of specific color on the periphery of the fiber, which was consistent with the fact that axons first inhabit the peripheral parts of distal epineural tubes [1, 3].

Our results were consistent with data on enhanced regeneration of severely damaged peripheral nerves under the influence of laser phototherapy (photobiomodulation) [26]. It has been shown to have a stimulating effect not only on nerve regeneration, but also to prevent muscle atrophy. Forty-five days after sciatic nerve injury, rats regained motor function, which correlated with the duration of irradiation sessions.

## CONCLUSIONS

1. The study of the marker of non-myelin Schwann GFAP cells showed their pronounced activation with germination in the nerve thickness and the formation of weaves of processes around the regenerating nerve fibers. On the contrary, the number of S-100-positive cells decreased, the heterogeneity of their color and the loss of processes were determined.
2. The study of neuronal markers showed a general decrease in the intensity of NSE- and NF-L-positive staining of nerve fibers regenerated after neurotomy, which was less pronounced when irradiated with a laser with a wavelength of 450-480 nm and 520 nm.
3. In general, the use of laser radiation had a positive effect on the repair of nerve fibers after neurotomy. According to the immunohistochemical study of neuromarkers, the effect of laser irradiation of the blue spectrum was the most effective.

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#### CONFLICT OF INTEREST

The Authors declare no conflict of interest.

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# AGE ASSESSMENT OF THE DYNAMICS OF MORPHOLOGICAL REARRANGEMENT OF BONE TISSUE OF THE ARTICULAR PROCESSES OF THE HUMAN LOWER JAW DEPENDING ON THE LOSS OF THE MASTICATORY TEETH

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## ABSTRACT

**Aim:** To analyze morphometric changes in the structure of bone tissue of the mandibular articular processes and establish their densitometric dependence on the masticatory teeth loss in people of I-II periods of adulthood.

**Materials and methods:** We analyzed 136 digital CT recordings of human temporomandibular joints. The research subjects were divided into three groups based on the degree of dentition defect acquisition: the first – a limited defect, the second – a final defect, and the third – a preserved dentition (control); by age into two periods of adulthood of postnatal human ontogenesis. Digital statistical analysis of the bone density is presented as  $M \pm \sigma$  (mean and standard deviation). We compared the experimental groups with the control group using nonparametric statistical analysis.

**Results:** Changes in the vertical dimension of occlusion due to limited masticatory teeth loss acquire variable morphometric features, causing an interrelated process of bone atrophy of the cellular part and the trabecular layer of the mandibular processes. The density of bone tissue of the cortical layer of the articular-fossa quadrant (A-Fh/q) of the articular head of the mandibular process increases on the right with limited defects and decreases with final defects. Indicators of bone densitometry of A-Fh/q on the left is characterized by a decrease with limited defects for individuals of the I-st period of adulthood and an increase in the final defects in the II-nd on the left and right.

**Conclusions:** Multifactorial pathomorphological compensatory processes ensure bone density, but with a change in values on the right and a decrease on the left. Morphometric values of trabecular layers, the most vulnerable areas of the neck and base of the mandibular articular processes, indicate the reconstruction of their bone tissue with limited defects; in the first period of the adulthood, they decrease with a significant predominance on the left.

**KEY WORDS:** bone atrophy, lower jaw, articular processes, computed tomography

## INTRODUCTION

The most frequent visits to the dentist because of pain in the maxillofacial region, which occupy second place after dental pain, are disorders in the temporomandibular joints (TMJ). According to the analysis of epidemiological studies, the prevalence of TMJ pathology varies between 40-60% of the total human population. However, the number of patients receiving complex, highly specialized treatment is estimated only at 10-15%. This indicates a need for a more fundamental theoretical understanding of the etiology and diagnosis of this nosology by dentists, even at the early stages of destructive changes, which are reflected in changes in the bone density of the articular processes of the lower jaw, first of all [1-3]. After all, stagnant destructive, and inflammatory processes lead to fibrous or bone adhesion of the articular surfaces, which causes partial or complete disappearance of the articular gap, leads to limited opening of the mouth, and requires complex reconstructive operations [1, 2, 4, 5]. The development of X-ray diagnostic methods and digital analysis provided a minimally invasive diagnostic process, even with minor manifestations of pathological damage to the components of the complex TMJ disorder [6-8]. Using

the above possibilities, we paid attention to the morphological rearrangement of bone tissue and its cortical and trabecular layers, primarily depending on the loss of masticatory teeth with bounded or free-end edentulous spaces in the dentition of the lower jaw [9-11].

## AIM

To conduct an age-related analysis of the dynamics of morphometric variation of the trabecular layer of bone tissue of the articular processes of the lower jaw and to establish the densitometric dependence of their cortical and trabecular layers on the influence of multifactorial pathoetiological factors, in particular, the loss of the masticatory teeth.

## MATERIALS AND METHODS

From the available clinical database of 18689 studies of PLC "MEDICAL 3D DIAGNOSTICS CENTER" (legal entity identification number: 41907653, location: 79010, Lviv region, Lviv, Chernihivska Str., 18, Ukraine), we selected 136 CT records of the human TMJ study, which provided appropriate information content and corresponded to the goal of this work. The research material was selected following the agreement on scientific cooperation No.

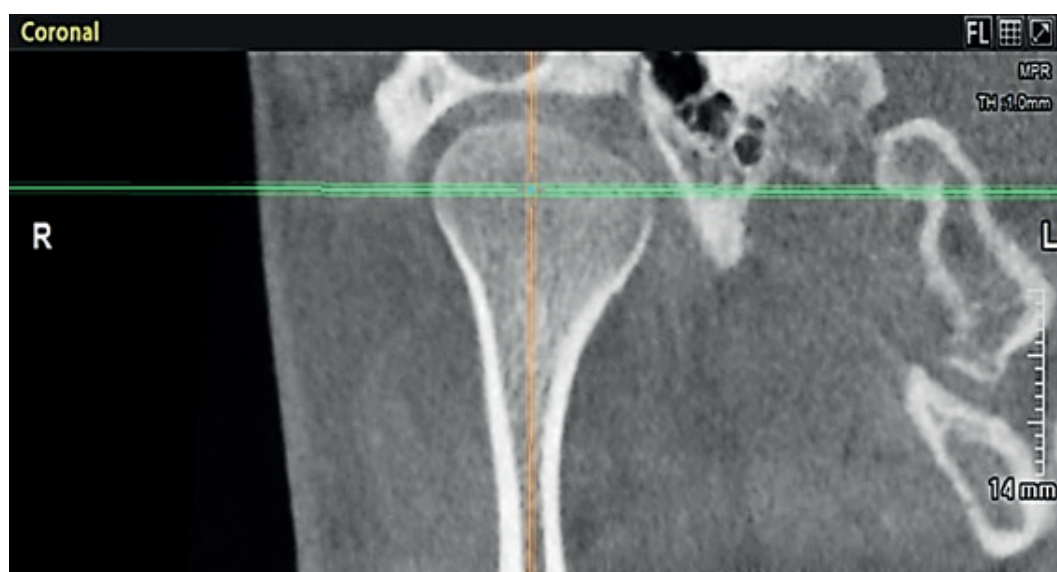
02 dated 02.10.2020 between Bukovinian State Medical University (58002, Chernivtsi, Teatralna Square, 2, Ukraine) and MEDICAL 3D DIAGNOSTICS CENTER. This is the availability of digital methods of morphological research, in particular, the method of densitometric analysis using extraoral scanning Vatech PaX-i3D Green CT (PHT-60 CFO) with an ultra-sensitive radiation detector, functions: orthopantomography, tomography, teleroentgenography, TMJ (open/closed mouth) and an additional MAR module, to reduce the number of artifacts from overlays and inclusions (Fig. 1) with Ez3D-I (5.1) software, it provided an opportunity to perform a quick, detailed analysis of the bone structure of the articular processes of the lower jaw on the left and right sides, in particular, its density in a minimally invasive and ergonomic way.

CT digital scans were analyzed using Hewlett-Packard Z4 G4 Workstation computer equipment with an Intel Xeon W-2104 central processor, Nvidia GeForce GTX

1660 GPU, 32 GB of RAM, and Windows 10 Pro for Workstations software (version 1903, product code 00391-70000-00000-AA381).

The method of statistical selection was used to distribute the study material by age for two periods (I-II) of adulthood of postnatal human ontogenesis (I-st period of adulthood - men aged 22-35 years, women aged 21-35 years; II-nd period - men aged 36-60 years, women aged 36-55 years) [12]. Depending on the pathoetiological factor, the selected material was distributed according to the degree of acquisition of a dentition defect of the lower jaw (LJ) by patients into three groups, namely: the first group - limited dentition defect, the second group is an existing final defect, the third group is individuals with preserved dentition, the control group (Table 1).

To determine bone density, we selected quadrants that were primarily subject to pathological changes (Fig. 2), in particular:



**Fig. 1.** Settings. In the coronal plane (investigated option window), the sagittal axis is located along the vertical axis of the articular process, centered perpendicular and in the middle of its macrostructure.

**Table 1.** Grouping data when studying qualitatively homogeneous aggregates – quantitative indicators that determine bone density in conventional grayscale units (CGU) of the articular processes of the lower jaw due to partial/complete loss of the lateral/masticatory teeth, n= 136.

Group name/age period		Number of observations	Articular processes of the lower jaw	
			A - right side	B - left side
First group: Limited dentition defect	I adulthood	26	13	13
	II adulthood	22	11	11
Second group: Final dentition defect	I adulthood	16	8	8
	II adulthood	24	12	12
Third group: Preserved dentition - control group	I adulthood	26	13	13
	II adulthood	22	11	11
Total number of objects under study	I adulthood	68	34	34
	II adulthood	68	34	34



- A-Fh/q - articular-fossa quadrant of the articular head of the mandibular process;
- A-Pn/q - anteroposterior quadrant of the neck of the mandibular process;
- A-Pb/q - anteroposterior quadrant of the base of the mandibular process;
- c/g – control group, quadrant of the mandibular angle.

When conducting medical research, it is often necessary to use statistical analysis methods of data presented in semi-quantitative, semi-qualitative, and qualitative forms, which forces us to direct our choice to use non-parametric evaluation criteria.

Digital statistical analysis of the bone density of the articular processes of the lower jaw, depending on the loss of the masticatory teeth, presented as  $M \pm \sigma$  (mean value and standard deviation). Using nonparametric statistical analysis methods, we compared the experimental groups with the control group using the Mann-Whitney U test.

Comparison of groups with each other was conducted using the multidimensional Kruskal–Wallis test as an alternative intergroup analysis of variance, which compares three or more samples to test null hypotheses according to which different samples were taken from the same distribution with similar medians. The obtained differences between the groups were considered reliable as the change in the density of bone tissue has a multifactorial patho-etiological dependence described in this paper.

All the studies were conducted after patients familiarized themselves with and signed informed consent to participate in research in compliance with the main provisions of the GCP (1996), the Council of Europe Convention on Human Rights and Biomedicine (dated 04.04.1997), the World Medical Association Declaration of Helsinki on ethical principles for conducting scientific medical research involving human subjects (1964-2013), order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009 № 616 dated 03.08.2012.

## RESULTS

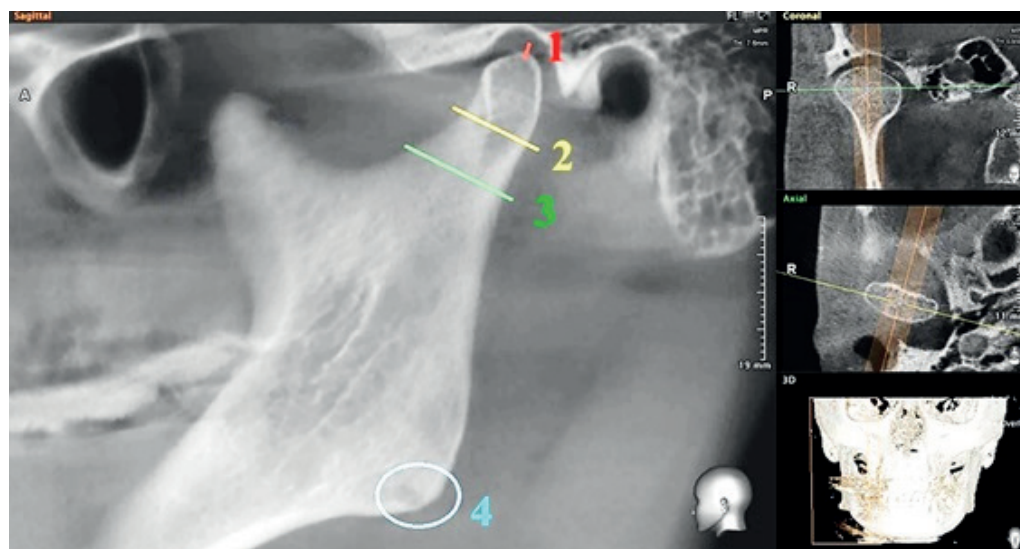
For dynamic assessment of the bone density, we identified "areas" that were primarily exposed to patho-etiological factors to change densitometric values in the direction of increasing and decreasing. Such studied quadrants are the vertex of the cortical layer (M/cort) of the articular head of the articular-fossa surface (A-Fh/q) and, accordingly, the trabecular (spongy) bone (SD/sp), which was measured subcortically to a length of one millimeter parallel to the axis.

Attention is paid to the places of attachment and the vector of the masticatory muscle force, which play a crucial consistent role in the series of irreversible pathological changes, with their morphometric analysis. Antero-posterior quadrant of the neck of the mandibular process (A-Pn/q) gives an idea of the restructuring of bone tissue based on the spongy matrix. Therefore, the constructed algorithm covers morphometric studies (M/mph) for measuring between cortical layers and determining the density of the spongy layer (SD/sp), followed by average values in tables for statistical processing and analysis (Table 2-5). The same algorithm was followed in the study of the anteroposterior quadrant of the base of the mandibular process (A-Pb/q).

It is generally accepted that the angle of the lower jaw has a stable value relative to its morphological rearrangement. For comparison and more comprehensive objectivity, we determined the density of the cortical layer at the edge of the lower jaw angle (c/g), along the length of a line of four millimeters, in the plane of the sagittal section.

No less and priority role is given to the morphometric study of the trabecular layer of bone tissue since the loss of the masticatory teeth leads to its atrophy and gives an understanding of the objectivity of bone tissue rearrangement depending on tooth loss as a vector patho-etiological factor.

Morphometric values of the most vulnerable areas



**Fig. 2.** Settings. In the coronal plane (investigated option window), the sagittal axis is located along the vertical axis of the articular process, centered perpendicular and in the middle of its macrostructure.



**Table 2.** Results of quantitative and qualitative indicators that determine the density (CGU) and morphometric values of bone tissue of the articular processes of the lower jaw on the right side of the I-st the period of adulthood in postnatal human ontogenesis, due to partial/complete loss of the lateral/masticatory teeth, n= 34.

Marking	Research areas	Control group (preserved dentition) M±σ	Limited dentition defect M±σ	Final dentition defect M±σ	P <sub>1</sub>	P <sub>2</sub>	P <sub>3</sub>
	n	13	13	8			
A-Fh/q	M/cort	1149±398.1	1225±312.8	1095±158.7	0.412	0.828	0.169
	SD/sp	668.7±227.4	590.6±244.5	737.8±319.8	0.457	0.515	0.169
A-Pn/q	SD/sp	849.6±260.1	708.2±302.0	616.8±235.6	0.209	0.083	0.347
	M/mph	4.438±1.274	4.438±1.570	4.850±1.174	0.878	0.328	0.717
A-Pb/q	SD/sp	882.1±195.3	910.4±329.3	658.7±160.5	0.457	0.017	0.021
	M/mph	4.992±0.867	4.515±1.852	4.913±1.374	0.191	0.664	0.492
c/g	cort.	2313±806.2	2490±615.8	2107±440.9	0.305	0.942	0.278

**Table 3.** Results of quantitative and qualitative indicators that determine the density (CGU) and morphometric values of bone tissue of the articular processes of the lower jaw on the left side of the I-st period of adulthood in postnatal human ontogenesis, due to partial/complete loss of the lateral/masticatory teeth, n= 34.

Marking	Research areas	Control group (preserved dentition) M±σ	Limited dentition defect M±σ	Final dentition defect M±σ	P <sub>1</sub>	P <sub>2</sub>	P <sub>3</sub>
	n	13	13	8			
A-Fh/q	M/cort	1062±337.8	1047±288.6	1139±164.9	0.939	0.515	0.664
	SD/sp	621.6±229.5	582.5±265.5	526.3±272.0	0.739	0.366	0.664
A-Pn/q	SD/sp	720.3±354.2	659.4±314.9	526.7±143.7	0.858	0.247	0.278
	M/mph	4.500±0.936	4.346±1.133	4.813±1.093	0.473	0.294	0.385
A-Pb/q	SD/sp	888.0±406.4	775.6±385.8	709.0±154.9	0.489	0.515	1.000
	M/mph	4.723±1.182	4.692±1.614	4.838±1.038	0.818	0.971	0.690
c/g	cort.	2227±667.4	2348±523.6	2151±319.1	0.293	0.800	0.311

**Table 4.** Results of quantitative and qualitative indicators that determine the density (CGU) and morphometric values of bone tissue of the articular processes of the lower jaw on the right side of the II-nd period of adulthood in postnatal human ontogenesis, due to partial/complete loss of the lateral/masticatory teeth, n= 34.

Marking	Research areas	Control group (preserved dentition) M±σ	Limited dentition defect M±σ	Final dentition defect M±σ	P <sub>1</sub>	P <sub>2</sub>	P <sub>3</sub>
	n	11	11	12			
A-Fh/q	M/cort	1148±185.7	1032±271.3	1184.1±330.2	0.251	0.580	0.243
	SD/sp	650.1±214.0	546.6±238.0	692.2±204.5	0.309	0.623	0.157
A-Pn/q	SD/sp	787.0±285.1	669.8±231.3	746.8±186.8	0.309	0.689	0.356
	M/mph	4.345±1.667	4.273±1.003	4.417±1.129	0.922	0.854	0.854
A-Pb/q	SD/sp	810.4±299.5	739.9±321.7	694.8±198.2	0.251	0.132	0.806
	M/mph	4.982±2.180	4.673±0.957	4.883±1.564	0.948	0.975	0.782
c/g	cort.	2122±562.3	1926±230.8	2028±349.0	0.491	0.902	0.296

**Table 5.** Results of quantitative and qualitative indicators that determine the density (CGU) and morphometric values of bone tissue of the articular processes of the lower jaw on the left side of the II-nd period of adulthood in postnatal human ontogenesis, due to partial/complete loss of the lateral/masticatory teeth, n= 44.

Marking	Research areas	Control group	Limited	Final dentition	P <sub>1</sub>	P <sub>2</sub>	P <sub>3</sub>
		(preserved dentition)	dentition defect	defect			
		M±σ	M±σ	M±σ			
n		11	11	12			
A-Fh/q	M/cort	988.8±255.5	926.4±179.5	1064±153.7	0.341	0.580	0.091
	SD/sp	558.2±281.2	461.2±128.1	619±257.2	0.094	0.902	0.085
A-Pn/q	SD/sp	609.0±325.5	501.4±119.8	673.8±218.7	0.844	0.356	0.043
	M/mph	4.482±1.492	4.764±1.177	4.358±1.355	0.512	0.782	0.460
A-Pb/q	SD/sp	748.4±385.1	542.9±178.8	691.4±260.8	0.168	0.758	0.140
	M/mph	4.855±1.569	5.236±1.510	5.067±1.624	0.325	0.806	0.926
c/g	cort.	2061±311.9	1873±252.0	2133±334.3	0.123	0.623	0.027

Notes Tables 1-5:

p<sub>1</sub>-comparison: Control group (preserved dentition) with a limited dentition defect;

p<sub>2</sub>-comparison: Control group (preserved dentition) with a final dentition defect;

p<sub>3</sub>-comparison: limited dentition defect with final dentition defect.

of the neck and base (A-Pn/q, A-Pb/q) of the articular processes of the lower jaw with limited dentition defects indicate the reconstruction of their bone tissue, in particular, in the I-st period of adulthood of postnatal human ontogenesis (PO) and they are characterized by a decrease with a significant predominance on the left side. With a change in the vector of muscle strength, there is a morphological restructuring of the height of the processes, namely, the distance from their base to the neck, in the negative direction due to the loss of occlusal ratios. A change in the vertical dimension of occlusion due to a limited loss of chewing teeth stipulates quick adaptation to new conditions of reducing pressure on the joints, causing an interrelated process of bone atrophy of both the cellular part and the trabecular layer of the mandibular processes.

With the final dentition defects of the lower jaw, chewing pressure is formed in the middle, pushing the jaws to the front in order to grind food. This distribution of pressure on the articular processes, in turn, causes a change in the angle of the lower jaw as a compensatory resistance to pathomorphological processes with a significant increase in their morphometric values in the A-Pn/q, A-Pb/q of the studied quadrants.

Synchronous pathomorphological, compensatory processes provide bone density, but with a change in values on the right side and a decrease on the left in both human age periods (Fig. 3).

Attention is drawn to the increasing bone density of the cortical layer of A-Fh/q of the studied quadrant of the right side, with limited dentition defects and a decrease in its values with final dentition defects. The synchronicity of the decrease in bone density on the left side of A-Fh/q is characterized by a sharp decrease in limited dentition defects of the I-st period of adulthood of the human PO and

its increase in the final dentition defects of the II-nd period of adulthood for both the left and right sides.

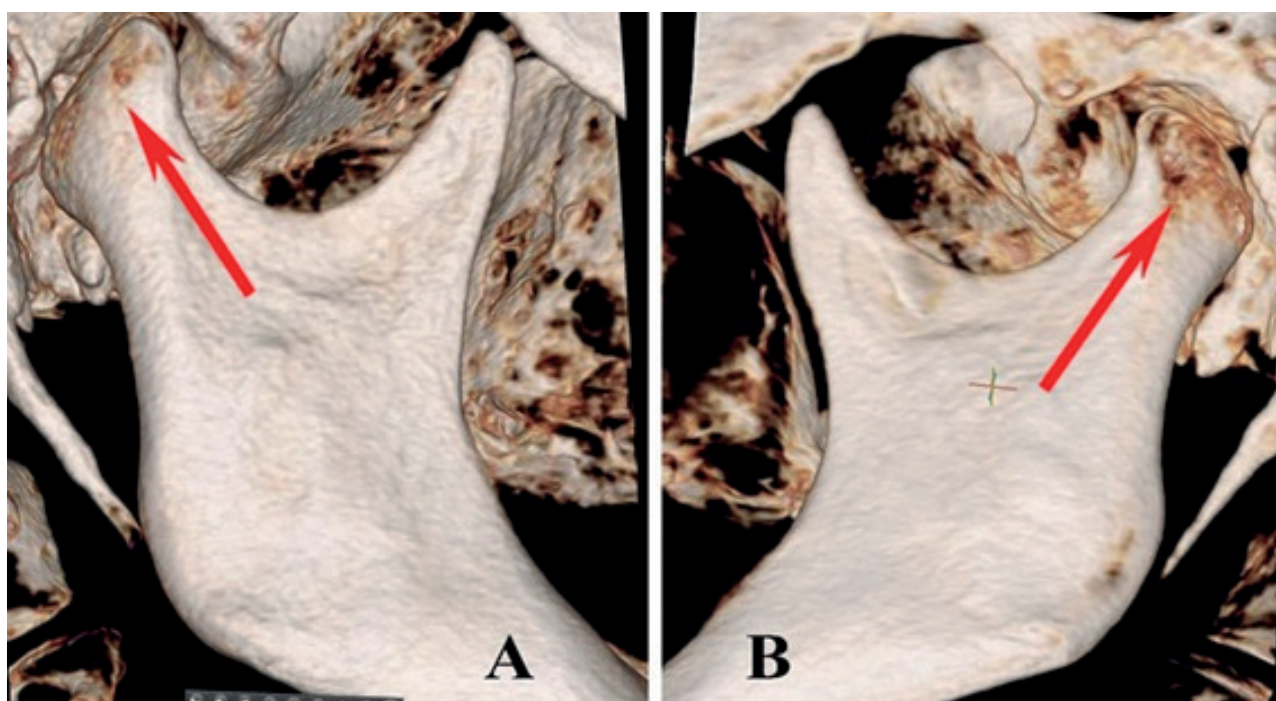
Comparison of the results of the constant density of the studied quadrant of the cortical layer of bone tissue of the lower jaw angle (c/g) in the I-st period of adulthood of PO is confirmed by a conditional pattern growth-decline. In II-nd period of adulthood of human PO, on the contrary, decline-growth of its density is on the left and right sides of the jaw.

Multifactorial pathoethological dependence does not make it possible to establish the reliability of differences between the comparison groups p<sub>1</sub>, p<sub>2</sub>, and p<sub>3</sub> (see Note below Table 1-5) with a constant expression p<0.5 since the change in bone density depends on the somatic state of the body, its coenzyme capacity, hormonal regulation and the time of manifestation of etiological factors, as described above.

This paper details individual values that reveal bone tissue's behavior (restructuring) caused by the loss of individual chewing teeth or their groups. They have significant informative value during the planning and conducting of reconstructive surgical interventions, particularly osteosynthesis.

## DISCUSSION

Attention is drawn to the morphometric and densitometric examination of TMJ using minimally invasive methods of CT in maxillofacial surgery for the manufacture of navigational surgical templates and patient-specific retainers using CAD/CAM technologies in patients with a mandibular head fracture, which enables improving the anatomical and functional results of their surgical treatment, namely, increasing the accuracy of restoring the anatomical shape of the head, reducing the frequency of occlusal disorders and secondary dis-



**Fig. 3.** 3D reconstruction model of the articular processes of the lower jaw: A) the right articular process of the LJ of the normal morphological structure of its cortical layer; B) the left articular process of the LJ with the manifestation of pronounced destructive changes in its cortical layer. X-ray positioning "closed mouth".

placements, as well as increasing the maximum range of movements of the lower jaw [13].

The authors [14] point out the importance of using not only the methods but also the areas (points) of bone tissue of the articular processes that will provide the most stabilizing and restoring results of TMJ integrity.

Updated results of clinical observations [15] confirm the importance of understanding the anatomical features of the articular processes in achieving a proper anatomical reduction of the lower jaw during surgical planning, which becomes the method of choice and reduces the time of surgery and morphological rehabilitation.

Loss of the bone density of the articular processes is a convenient platform for even a primary infection, with the subsequent development of septic lesions of the entire TMJ complex and their spread to adjacent areas [16-18].

The asymptomatic course of pathological processes such as osteopenia or osteoporosis of the bone tissue of the lower jaw processes in the early stages is available for diagnosis by CT methods, focusing on the values presented by us, even without bone sampling.

The unjustified ergonomics of methods [19, 20] determining the mineral saturation of micro- and macronutrients takes on a historical vector. After all, the minimal invasiveness of digital radiography in densitometric and morphometric research can offer reduced radiation doses and the advantages of image analysis, which increases sensitivity and reduces the error resulting from the subjective analysis.

Another important argument for the need to study

bone density, according to the author [21, 22], for most specialists working in medicine, may be helpful that the latter is an unknown, overly variable structure in the human body. According to the World Health Organization, bone mineral density disorders are the fourth most common globally – after cardiovascular diseases, cancer, and diabetes.

We know the works of Kulinchenko RV (2012-2016), which reflect the loss of the masticatory teeth as the influence of a pathoetiological factor on the morphological components of the TMJ, but, at the same time, do not detail the morphometric and densitometric definitions of the studied areas of the articular process of the lower jaw.

Therefore, we propose to take the results obtained as a basis of morphometric values and density – quantitative and qualitative characteristics of the bone tissue of the articular processes of the lower jaw since the sources available do not disclose similar studies, which makes it impossible to compare them.

## CONCLUSIONS

1. Changes in bone density of the articular processes of the lower jaw depend not only on the loss of the masticatory teeth but also on the functionality of the muscular system, particularly the masticatory muscles, and adaptation processes aimed at preparing and forming the oral lump.
2. The loss of chewing teeth, causing the pathology bounded edentulous spaces in the dentition, leads to atrophy, first of all, of the trabecular layer of bone tissue of the articular processes in the I-st

period of adulthood of postnatal human ontogenesis and growth of its density in the II-nd period of adulthood postnatal ontogenesis in final dentition defects.

3. The bone density of the cortical layer of the lower

jaw angle, which is considered to be conditionally "stable", undergoes densitometric variation depending on the time, the strength of action, and the spread of pathoetiological factors.

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**CONFLICT OF INTEREST**

The Authors declare no conflict of interest.

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# IMPLEMENTATION OF THE DECISION TREE METHOD IN EXPERT ANALYSIS OF THE MEDICAL ERRORS IN OBSTETRIC PRACTICE

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## ABSTRACT

**Aim:** To identify expert patterns in cases of improper medical care in obstetric practice based on the analysis of the materials of judicial and investigative cases initiated against obstetrician-gynaecologists in cases of improper performance of their professional duties, using the decision tree method.

**Materials and methods:** A retrospective review of all alleged medical malpractice cases (a total 350) between 2007 and 2016 handled at Ternopil Regional Bureau of Forensic Medical Examination, Chernivtsi Regional Bureau of Forensic Medical Examination and Zhytomir Regional Bureau of Forensic Medical Examination (Ukraine) was performed.

**Results:** Expert commissions confirmed various shortcomings and omissions in provision of medical care in 232 (72.0%) of the investigated cases. Obstetricians were involved in claims in 82 (23.4%) cases. Application of intelligent data processing technology "Data Mining" with the use of the decision tree method revealed that inadequacies with regard to the medical records (attribute usage 100%) were the most informative attribute in the expert assessment of inappropriate medical care in obstetrics. Defects in the provision of obstetric care with a probability ( $P = 0.71$ ) occur simultaneously both at pre-hospital and hospital levels and with a high probability ( $P = 0.83$ ) result in severe consequences.

**Conclusions:** The use of modern technologies for data analysis and processing contributes to the formulation of mathematically substantiated statements that significantly enhance the reliability of expert opinions in cases of forensic medical examination attached to dereliction of duties by the medical practitioners.

**KEY WORDS:** forensic medical examination, inappropriate medical care, medical malpractice case, decision tree

## INTRODUCTION

Analysis of medical care deficiencies in most scientific publications is usually based on well-known statistical data processing methods that provide absolute or relative numerical values of certain medical care defects.

However, in cases of non-obviousness, complexity and multifactorial nature of the system, when the strength of hidden information relationships among a large array of disaggregated data needs to be investigated, traditional methods of statistical processing of such data become insufficient [1]. Scientists have pointed out that applications where data mining tools are used in the fields of medicine are becoming more and more frequent [2-4]. Under such conditions, to solve the problems of expert assessment of the quality of medical care and predict defects in its provision, artificial intelligence technologies are applicable, in particular data processing and analysis technology Data Mining and one of its most popular methods - the decision tree method [5].

Due to many factors, both objective and subjective, including the increase in the level of passionarity of society, the growth of legal awareness and social activity of the public, the ability to access almost any information resource due to the widespread use of modern means

of communication, etc., a persistent public demand for raising quality standards of medical and diagnostic care provided to citizens is being formed. So, patients' rights are occupying a prominent place in health care [6-8].

As some researchers report, according to the specialties of medical practitioners, the most criminogenic in many countries are obstetrics and gynecology [9-11]. In Ukraine the number of medical malpractice litigations against obstetricians is huge too [12]. In such cases, representatives of law enforcement agencies initiate criminal cases, the investigation of which requires forensic medical examination. The expert opinion in the investigation of medical malpractice cases is of the utmost importance for examination and is one of the main sources of evidence in the case [6, 12]. At the same time, in practice, in view of the objective complexity of the examination of diagnostic and treatment work, which is due to the specifics of professional medical activity, the expert assessment of medical malpractice cases is rarely definitive, and in most cases is presumptive. This is due to the lack of objective criteria that could substantiate the scientific validation and, accordingly, increase the reliability of expert opinions in cases where medical practitioners are held liable for professional offences in health care [13].

## AIM

In this regard, the aim of this study was to identify expert patterns in cases of improper medical care in obstetric practice based on the analysis of the materials of judicial and investigative cases initiated against obstetrician-gynaecologists in cases of improper performance of their professional duties, using the decision tree method.

## MATERIALS AND METHODS

Materials of forensic medical examination for medical malpractice cases between 2007 and 2016 handled at Ternopil Regional Bureau of Forensic Medical Examination, Chernivtsi Regional Bureau of Forensic Medical Examination and Zhytomir Regional Bureau of Forensic Medical Examination (Ukraine) were reviewed. In total, 350 such cases were studied, as well as 5056 related ones, both medical documents (case histories, outpatient cards, expert opinions, post-mortem examination reports, etc.) and proceedings (originals of criminal cases, on-site inspection reports, medical staff interrogation files, materials of internal audits of the quality of medical care, etc.). For each medical malpractice case, 70 different indicators were studied: the type of defect (diagnostic, medical-tactical, organisational, deontological, in medical records); the nature of improper medical care (its insufficiency, untimeliness, incorrect provision of or failure to provide medical care); the stage of medical care at which the defect occurred; the speciality of the medical practitioner who committed improper professional actions; reasons for the defect (objective and subjective); its consequences; cause and effect relationship. Thus, the collected data bank amounted to 24,500 indicators, the statistical processing and visualization of which was performed using the MS Excel 2016 spreadsheet.

The decision tree method is a decision-making tool for statistical processing and analysis of a certain database using artificial intelligence technologies. The essence of the method is to compile a mathematical model that establishes the dependence of the so-called target variable (the attribute (factor), the influence of which is being studied) on many other independent variables (attributes), and predicts the probability of a certain value of such variable [2-5].

If the target variable takes discrete values (e.g., "yes" or "no"), then using the decision tree method, its dependence on many other independent variables is established and the forecasting problem is solved.

In its simplest form, a decision tree is a way of representing rules in a hierarchical, sequential structure. The basis of such a structure is the answers "yes" or "no" (programming language) to certain questions. In other words, the presence or absence of each of the 70 indicators mentioned above was noted in each case of the medical malpractice case studied. Their discrete values in the form of "yes" or "no" answers (mathematically denoted "1" or "0", respectively) were entered into a general map and formatted in the MS Excel 2016 spreadsheet. The data obtained in such way were further processed

mathematically by the C 4.5 algorithm specifically developed for the decision tree induction method, available in the licensed environment of the RStudio platform on the corresponding portal (<https://www.rstudio.com/>).

We have already covered in detail the theoretical foundations of the decision tree method, the technical details of creating an algorithm for the method, the mathematical problem of induction of the decision tree and its graphical model [13].

## RESULTS AND DISCUSSION

The process of creating a decision tree in cases of forensic examination of medical care defects in obstetric practice starts with the establishment of a dependent (target) variable, i.e., the main parameter; the relationship of that variable with others should be established, the strength of such relationship should be mathematically proven and the probability of the value of the variable itself should be calculated.

As we established before [14] out of 350 materials of investigative cases analysed, various shortcomings and omissions during the provision of medical care were ascertained by expert commissions in 232 (72.0%) cases. Among them, law enforcement agencies initiated 82 cases directly against obstetrician-gynaecologists (23.4% of all studied). The vast majority of criminal cases was due to complaints of citizens about the improper provision of obstetric care (80 cases or 97.6%), and only 2 criminal cases were initiated against gynaecologists. Thus, using the phrase "obstetrician-gynaecologists" further in the article, we meant doctors who are mainly engaged in obstetric practice.

To ensure the correct operation of the algorithm, the target variable (obstetrician-gynaecologists) should receive the appropriate abbreviation in English. For our example, we shall call it "obstr" (short for English "obstetricians"). Similarly, it is necessary to provide English names for other attributes with which the informative relationship of defects caused by obstetrician-gynaecologists in professional activity, is being investigated.

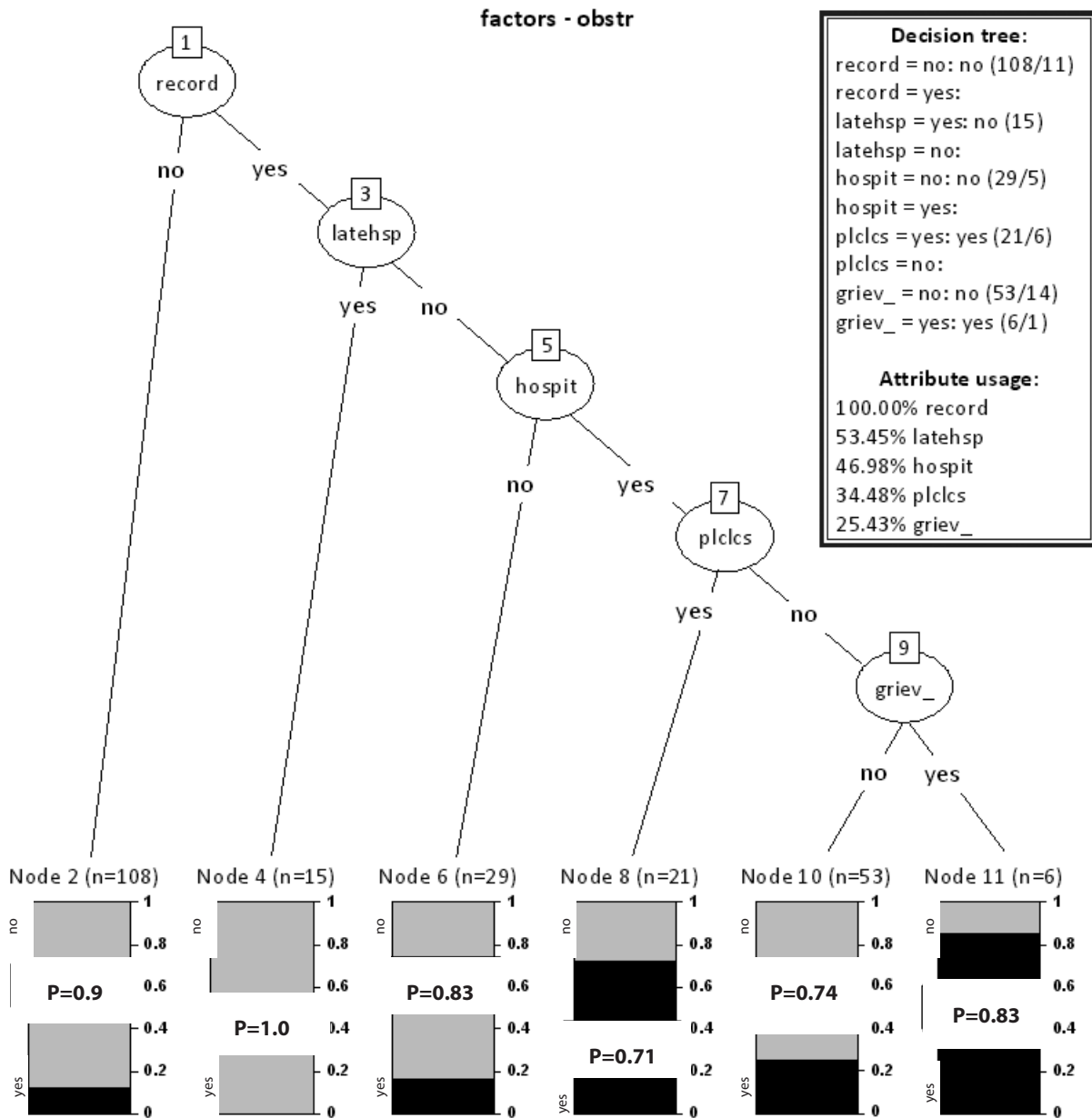
The tree to be modelled answers the question of what the predicted value of the target variable will be, given the known values of other attributes. The implementation of this task consists in finding such attributes that are the most informative in relation to the target variable selected for the study (i.e., for obstetrician-gynaecologists). The following attributes were selected by the C4.5 algorithm as most significant parameters (from the 70 indicators studied for each medical malpractice case) (Table 1).

It is from them that the algorithm selects certain attributes as internal nodes of the tree, along which its further gradual branching is carried out. When building a tree, it is necessary that the target variable "obstr" takes on a value of exactly one type ("yes" or "no"); those are the leaf nodes. Each leaf node is characterized by the probability of obtaining a specific value for the target variable, i.e., the probability of belonging to class "obstr: yes" or "obstr: no".

**Table 1.** Attributes for constructing a decision tree regarding to the target variable “obstr” (obstetrician-gynaecologists)

Attribute designation	Attribute name	Attribute designation	Attribute name
A1 (obstr)	obstetrician-gynaecologists	A17 (emrgn)	provision of inadequate medical care by ambulance personnel
A2 (ansth)	anaesthesists	A18 (plcls)	provision of inadequate medical care at outpatient stage
A3 (surg)	surgeons	A19 (hospit)	provision of inadequate medical care at hospital stage
A4 (pdtr)	paediatrician	A20 (direct)	direct cause and effect relationship
A5 (family)	family doctors	A21 (dif_dig)	medical care defect caused by diagnostic difficulties
A6 (traum)	traumatologists	A22 (atipic)	medical care defect due to atypical pathogenic mechanism
A7 (admsn)	admitting physicians	A23 (griev_)	improper provision of medical care led to serious consequences for the patient
A8 (diagn)	diagnostic pitfalls	A24 (comorb)	defect in medical care due to the presence of concomitant pathology
A9 (tactic)	medical-tactical defects	A25 (vidm)	adverse outcome due to the patient's refusal from hospitalization
A10 (istit)	organisational defects	A26 (latehsp)	adverse outcome due to late presentation of the patient
A11 (record)	defects in preparation of medical records	A27 (rapid)	adverse outcome due to the rapid progression of pathogenic mechanism
A12 (deont)	deontological errors	A28 (regum)	adverse outcome due to violation of the hospital regimen by the patient
A13 (unusuf_)	insufficient medical care	A29 (ridk)	defect in medical care due to the rarity of the pathology
A14 (untime_)	untimely medical care	A30 (unskill)	adverse outcome due to unskilled actions of medical personnel
A15 (improp_)	improper medical care	A31 (standr)	adverse outcome due to violation of the standards of medical care
A16 (care_abs_)	failure to provide medical care	A32 (Exitus)	medical care ended in a fatal outcome for the patient





**Fig 1.** Induced decision tree for the target variable “obstr” (obstetrician-gynaecologists).

Further, the construction of the decision tree consists of two stages: construction of the classification model (the decision tree itself) and its interpretation.

In fact, at the model building stage, a classification tree is built, where the path from its root to one of the nodes is a set of rules for a specific case and is used to answer the question “What is the probability of the target variable “obstr”?” (Fig. 1).

Namely: “What is the probability of the relationship of medical-tactical, diagnostic, organisational shortcomings during the provision of obstetric and gynaecological care, defects in the preparation of medical records, taking into account the characteristics of such inadequate medical care, the stages of its provision, negative consequences, objective and subjective factors that contributed to them.” The rule in our case is a logical construction,

represented as “if ..., then obstr: yes with the appropriate probability” or “if ..., then obstr: no with the appropriate probability”. This allows to conclude: “if a criminal case is initiated against an obstetrician-gynaecologist in connection with the improper performance by them of their professional duties, then ...” or “if a criminal case is initiated against an obstetrician-gynaecologist in connection with the improper performance by them of their professional duties, then ...”

In the constructed decision tree, the following main elements are distinguished:

- root of tree: the algorithm-defined attribute that has the strongest informative association (attribute usage 100%) with the target variable studied. In our case, it is “record” (defects in the preparation of medical records);

- internal tree nodes: other attributes selected from the database under study, in accordance with their information content in relation to the main factor (target variable). These attributes are called splitting attributes. For the constructed decision tree (see Fig. 1), such attributes are: "latehsp" (adverse outcome due to late presentation of the patient), "hospit" (provision of inadequate medical care at hospital stage), "plclcs" (provision of inadequate medical care at outpatient stage), "griev\_" (improper provision of medical care led to serious consequences for the patient);
- leaf node (or end node of the tree) is the value of the target variable "obstr", which suggests only two responses: "yes" or "no" – the so-called binary decision tree model (dichotomous classification). A leaf node is characterized by the probability of obtaining the target variable of a particular P value. The larger the P value, the higher the probability of a particular value (yes or no) of the main attribute under study.
- tree branch: sequence of response options (yes or no).

Each branch of the tree that comes from an internal node is marked with a splitting predicate. The latter may refer to only one splitting attribute of a given node. A characteristic feature of splitting predicates: each entry uses a unique path from the root of the tree to only one decision node. The combined information of splitting attributes and the splitting predicates at a node is called the splitting criterion. Selection of a specific attribute for splitting is the most important task of the decision tree derivation algorithm. The splitting criterion is formalised with certain mathematical expressions, with the help of which the informational entropy is analysed at each stage of the tree derivation, starting from the selection of a node and continuing to all final nodes. The best known of the existing splitting criteria are entropy and Gini index.

The decision tree construction process usually works in a top-down manner. During this process, the algorithm must find such a splitting criterion that can be used to split a set of data under study into subsets that would be associated with a certain internal node of the tree. Each such node must be marked with a certain attribute. There is a rule for attribute selection: it must split the input data set in such a way that the objects of the subsets resulting from such splitting are representatives of the same class. In order to identify the relationship between medical-tactical and diagnostic errors, defects in the preparation of medical records and organisational shortcomings during the provision of obstetric and gynaecological care with the features of such inadequate medical care, the stages of its provision, negative consequences, objective and subjective factors that contributed to them, etc., the algorithm processed 7424 separate data from 232 medical cases, in which defects in medical care were established by forensic expert commissions.

Along with the construction of a graphical model (the decision tree itself), the C4.5 algorithm also creates a so-called listing, which is a text output of a computer program written in the R programming language. The

listing provides a list of attributes selected by the attribute splitting criterion, indicating their numerical values (presented as a table in the upper right corner of Fig. 1).

Therefore, according to the splitting criterion, which calculates the informational entropy at each stage, all independent attributes are reviewed. Algorithm C4.5 selected the "record" attribute as the root of the tree: defects in filling out medical records as an attribute with the highest value of the splitting criterion among all the others.

It means that the closest informative relationship (attribute usage is 100%) between adverse medical activities in the field of obstetrics and the 32 attributes studied, the algorithm chose the "record" attribute (defects in the preparation of medical records) and defined it as the root node of the induced tree (Fig. 1). In addition to that node, the program highlighted 4 internal nodes (splitting attributes): "latehsp" (adverse outcome of treatment associated with objective reason – late presentation), "hospit" (provision of inadequate medical care at hospital stage), "plclcs" (provision of inadequate medical care at follow-up medical care stage), "griev\_" (adverse outcome of improper medical care in the form of death of obstetric patient, foetus or newborn, severe birth trauma, loss of reproductive function, etc.). Thus, among the data processed by the decision tree derivation method, characterizing the features of inappropriate medical activity in obstetric practice, informative relationship was found only with those four attributes, while in relation to other studied attributes, the database intellectual processing program established no informative relationships.

The "record" attribute (defects in the preparation of medical records) divides the entire set of studied "medical cases" into two subsets. In one of them, the "record" attribute has the value "no" (108 such cases), in the other one it has the value "yes" ( $15+29+21+53+6=124$  such cases). Thus, the analysis of the "no" branch of the "record" root node demonstrates that out of 108 cases of medical cases where no shortcomings in the preparation of medical records were found during the forensic medical examination, in 97 such cases with a probability of  $97/108$  ( $P = 0.90$ ) those criminal cases were not related to obstetrician-gynaecologists and were initiated by the judicial and investigative authorities against medical practitioners of other specialities. This mathematical statement should be understood as follows: there is a high probability ( $P = 0.90$ ) that there are no obstetrician-gynaecologists among those medical practitioners who do not make errors in compiling medical records. It means that the absence of shortcomings in medical records is typical not for them, but for representatives of other medical specialities.

Next, the subset formed by the "record=yes" branch is split by the splitting attribute "latehsp" (adverse outcome due to late presentation of the patient). That attribute, among all but "record", provided the maximum value of the splitting criterion among 124 cases for which "record=yes". In other words, among medical cases in which errors in the preparation of medical records were

stated (the value of the “record” attribute was “yes”), the attribute “latehsp” (late hospitalization) is most closely associated with the “record” attribute; the informative connection of “latehsp” with the studied target variable was 53.45%.

At the same time, according to the decision tree built by the algorithm and its listing (mathematical interpretation), the cases for which “record= yes” and “latehsp= yes” belong to class “obstr=no” with a probability of 15/15 ( $P = 1$ ) (Fig. 1). In other words, among the 15 cases of late presentation, not a single case was associated with obstetric or gynaecological pathology (“record = yes: latehsp = yes: no (15)”). It means that this statement should be interpreted as follows: among 232 “medical cases” in which various shortcomings in the provision of medical care were established by expert commissions and where there were omissions in the preparation of medical records, such an objective reason for a defect committed by doctors as late hospitalization, is not typical for obstetric practice with probability ( $P = 1.0$ )

Further analysis of the induced decision tree indicates the presence of a close informative relationship between the nodes “hospit” and “plclcs”. This indicates that among the “medical cases” with defects in medical records and where there was no untimely hospitalization of the patient, close informative relationship with the studied target variable (attribute usage 46.98%) demonstrates the shortcomings of medical care at the hospital stage. Under such conditions, allegations of improper performance of professional duties are made against obstetrician-gynaecologists with a probability of 15 cases out of 21 ( $P = 0.71$ ).

Special attention needs to be paid to the last node of the constructed tree “griev\_”, the semantic understanding of which should be stated taking into account predicate “hospit=yes-plclcs=no-griev\_—yes”. So, in cases where there were shortcomings in medical records, where

there was no late hospitalization, where improper medical care took place at the hospital stage and was not associated with omissions at polyclinic, in 5 cases out of 6 ( $P = 0.83$ ) obstetrician-gynaecologists cause serious bodily harm by their erroneous actions.

Thus, based on the exceptional importance for the investigation of not the presupposition (probability), but the reliability (authenticity) of expert conclusions [8], the arguments presented in the article may be useful for forensic evaluation of defects in medical and diagnostic activities. In addition, the splitting attributes established as a result of the application of the decision tree method can be considered risk criteria for the occurrence of various defects during the provision of obstetric and gynaecological care. The obtained data may be beneficial for health authorities in development of the necessary preventive measures aimed at preventing medical errors in obstetric practice, which, ultimately, will improve the quality of medical care for citizens.

## CONCLUSIONS

The use of the “Data Mining” intelligent data processing technology using the decision tree method showed that the most informative attribute in the expert evaluation of obstetric care provided with various defects is the shortcomings in the preparation of medical records (attribute usage 100%).

Defects in the provision of obstetric care with a probability ( $P = 0.71$ ) occur interrelatedly both at the outpatient and inpatient stages, and with a high probability ( $P = 0.83$ ) lead to serious consequences.

The use of technologies for data analysis and processing contributes to the formulation of mathematically substantiated statements that significantly enhance the reliability of expert opinions in cases of forensic medical examination attached to dereliction of duties by the medical practitioners.

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#### CONFLICT OF INTEREST

The Authors declare no conflict of interest.

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# FEATURES OF PRENATAL MORPHOGENESIS AND PECULARITIES OF THE UTRICULUS PROSTATICUS FETAL ANATOMY

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## ABSTRACT

**Aim:** To determine the peculiarities of the structural organization of the utriculus prostaticus (UP) in pre-fetuses and fetuses.

**Materials and methods:** The study of macroscopic features and microscopic peculiarities of the prostate gland and the prostatic part of the urethra was carried out on 46 sections of human pre-fetuses and fetuses aged from 9 weeks to birth (31,0-375,0 mm PCL). The work uses the method of microscopic study of serial histological and topographic-anatomical specimens of the prostate gland, as well as the method of the thin preparation of the prostate part of the urethra in fetuses of different ages and morphometry.

**Results:** In 58,0-66,0 mm PCL fetuses the paramesonephric ducts are reduced, except of their connected caudal part, which is a morphological substrate for the development of the UP. At 72,0-79,0 mm PCL fetuses, cavity is replaced by cellular mass. At the 85,0-120,0 mm PCL fetuses, the UP connects with the lumen of the urethra. The cavity of the UP intensively proliferates with cells. In fetuses of 125,0-135,0 mm PCL is present dense arrangement of glandular elements, which are surrounded by fibrous-muscular membrane. In fetuses of 150,0-160,0 mm PCL, in the caudal direction, the cavity of the UP gradually narrows, it forms invaginations, especially in the middle and lower parts, or is divided into separate, interconnected chambers. In fetuses of 170,0-185,0 mm PCL, UP has elongated-oval or rounded-oval shape. In the caudal direction, the UP is directed ventral to the colliculus seminalis and is located slightly anterior and superior to the ejaculatory ducts. In 8-month-old fetuses, the lumen of the UP is lined with a pseudostratified cubical epithelium, outside of which there is a tunica muscularis. Ejaculatory ducts lined with a two-layer cuboidal epithelium are placed on both sides of the UP. A 270,0 mm PCL fetus has no UP at the apex of the colliculus seminalis. In fetuses 315,0-335,0 mm PCL, the process of cavity formation spreads to new areas of glandular formations of the prostate gland and their final branches. Most of the glandular formations open into the prostatic part of the urethra directly below the UP and the distal parts of the ejaculatory ducts. Microscopic examination of frontal sections of the prostate gland of a fetus with a 360,0 mm PCL revealed a septum in the UP which divides the cavity of the UP into the right and left halves of a round-oval shape.

**Conclusions:** The formation of utriculus prostaticus occurs from the paramesonephric ducts in the 11th week of fetal development. At the beginning of the 4th month of intrauterine development, it gradually decreases in size. From the middle of the 5th month of prenatal development, the utriculus prostaticus lengthens, and starting from the fetus of 7 months, both its length and width increase. At the end of the fetal period, the utriculus prostaticus acquires a round-oval shape, its length increases from 0,5 to 4,3 mm during prenatal ontogeny.

**KEY WORDS:** prenatal morphogenesis, fetus, utriculus prostaticus, fetal anatomy, prostate gland

## INTRODUCTION

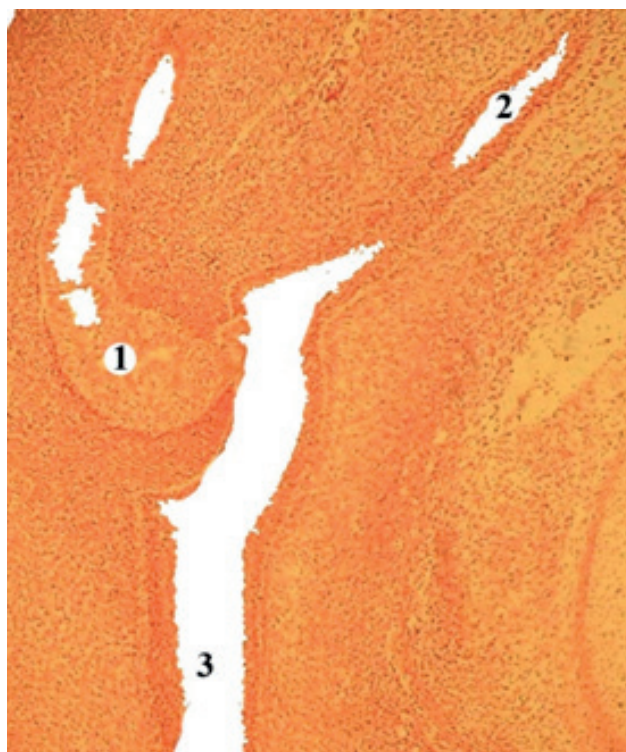
Diseases of the prostate gland are an actual problem in urology and andrology, and the most common among them are inflammatory processes, which affect up to 45 % of men of reproductive age. According to the scientific literature, the main role in the etiology of chronic prostatitis belongs to stagnation (disorders of the microcirculatory circulation) and infectious factors, which can cause the development of male infertility [1, 2].

Despite the large number of scientific studies on the morphology, function and pathology of the male and female sex organs, specially prostate gland in the prenatal period of human ontogenesis [3-7], much less attention has been paid to the macro- and microscopic structure of the colliculus seminalis, in particular the utriculus prostaticus in the fetal period of human development, which

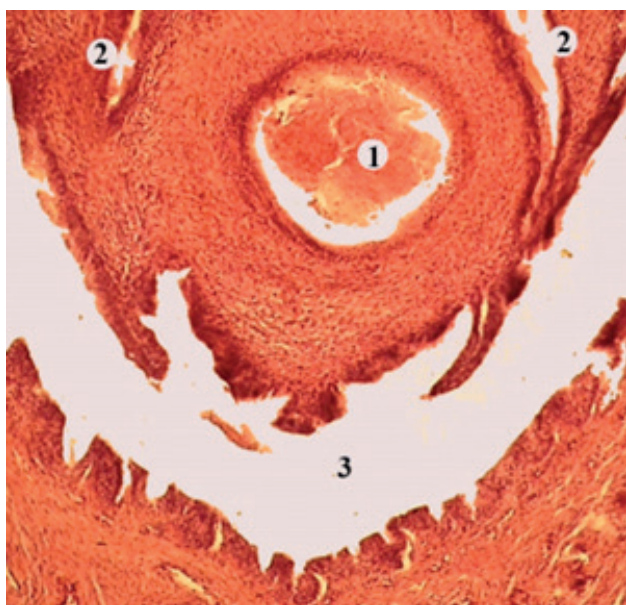
requires further scientific research. To date, the function of the utriculus prostaticus has not been clarified. However, in the sources of literature [8] there are reports of the presence of cells of the APUD system in the epithelium of utriculus prostaticus. Three cell populations were identified: 1 – serotonin-positive; 2 – serotonin-positive and argyrophil-positive; 3 – serotonin-positive, argyrophil-positive and argentophin-positive; at the same time, the largest population is the 2<sup>nd</sup> group of cells. The above cell populations are represented by 3 types of cells: open, closed and dendritic. Some authors associate the presence of intracellular serotonin inclusions in all cell populations with its influence on sexual function and the choice of a sexual partner. Freund K. [9] in an experiment on rats, with an increased concentration of serotonin in the blood, hyposexuality was noted, and with a small concentration, hy-



persexuality with the phenomena of homosexual behavior. This fact may indicate the possible involvement of the utriculus prostaticus in the hormonal regulation of male sexual activity. In this situation, data on the ontogenetic transformations of the utriculus prostaticus under normal



**Fig. 1.** Sagittal section of the urogenital complex of the fetus 58,0 mm PCL. Specimen. Staining by hematoxylin and eosin. X 80: 1 – utriculus prostaticus laying; 2 – paramesonephric duct; 3 – urogenital sinus.



**Fig. 2.** Frontal section of the fetal prostate gland 135,0 mm PCL. The area of the colliculus seminalis. Staining by hematoxylin and eosin. Specimen. X 80: 1 – the content of the utriculus prostaticus cavity; 2 – ejaculatory ducts; 3 – prostatic urethra.

conditions and in men of non-traditional sexual orientation, transsexuals and the possibility of its change under the influence of gonadotropic hormones are important from a practical point of view [4, 10, 11].

As a result of the analysis of scientific literature, we found fragmentary and contradictory information about the sources of development and morphological features of the utriculus prostaticus in different periods of human ontogenesis. In pre-fetuses of 41,0-44,0 mm parietal-caudal length (PCL), there is a partial reduction of Müller paramesonephric ducts, which is expressed by the reduction and obliteration of their lumen. Müller's ducts in male fetuses are gradually reduced, with the exception of their caudal connection, which is the morphological substrate for the formation of a utriculus prostaticus [12]. After birth, the utriculus prostaticus has the shape of a curved tube lined from the inside with prismatic epithelium. More or less developed muscle bundles sometimes occur in the lamina propria of the mucosa of the utriculus prostaticus. It is separated from the tissue of the colliculus seminalis of the utriculus prostaticus by a fibrous capsule, which includes cavernous vascular formations [13, 14]. The dimensions of the utriculus prostaticus are variable from 2,0 to 4,0 mm. Our study is a continuation of our earlier studies [2, 3, 5, 12-14].

#### AIM

The aim of the study was to determine the peculiarities of the structural organization of the utriculus prostaticus in pre-fetuses and fetuses.

#### MATERIALS AND METHODS

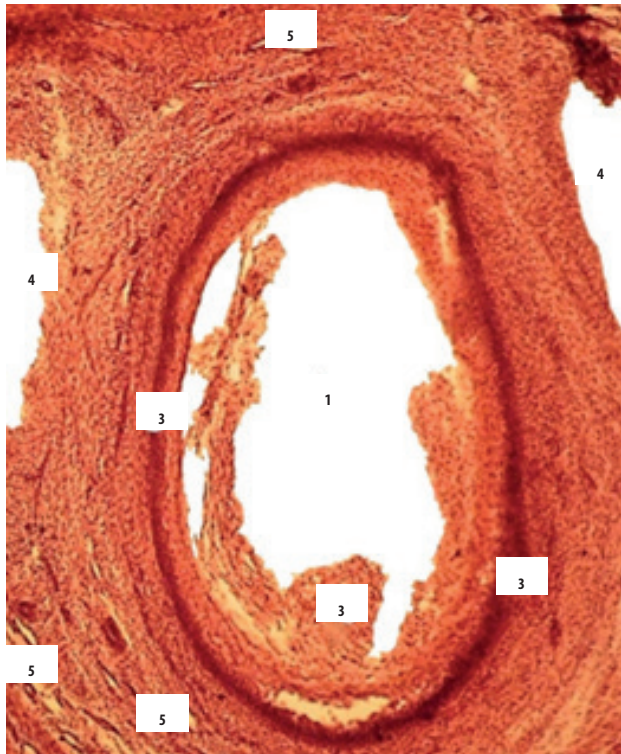
The study of macroscopic features and microscopic peculiarities of the prostate gland and the prostatic part of the urethra was carried out on 46 sections of human pre-fetuses and fetuses aged from 9 weeks to birth (31,0-375,0 mm PCL). The work uses the method of microscopic study of serial histological and topographic-anatomical specimens of the prostate gland, as well as the method of the thin preparation of the prostatic part of the urethra in fetuses of different ages and morphometry.

#### RESULTS

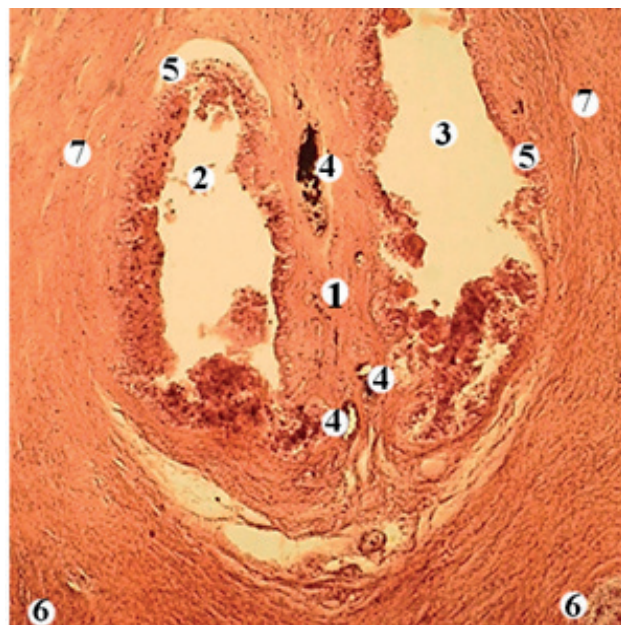
In 11-week-old male fetuses (58,0-66,0 mm PCL), the paramesonephric ducts are reduced, except of their connected caudal part, which is a morphological substrate for the development of the utriculus prostaticus, which does not yet have a connection with the urethra (Fig. 1). At the end of the prenatal period (72,0-79,0 mm PCL), an increase in the size of the utriculus prostaticus is determined mainly in the longitudinal direction, and its cavity almost disappears and is replaced by cellular mass.

At the beginning of the next period (85,0-120,0 mm PCL), the utriculus prostaticus slightly increases in the size and connects with the lumen of the urethra. The cavity of the utriculus prostaticus gradually decreases in size, which is due to the intensive proliferation of cells that line its cavity. The length of the utriculus prostaticus is 0,5-0,7

mm. In fetuses of 125,0-135,0 mm PCL, in comparison with fetuses of 85,0-120,0 mm PCL, there is visible more dense arrangement of glandular elements below the utri-



**Fig. 3.** Frontal section of the fetal prostate gland 265,0 mm PCL. Staining by hematoxylin and eosin. Specimen. X 35: 1 – the cavity of the utriculus prostaticus; 2 – the content of the utriculus prostaticus cavity; 3 – the wall of the utriculus prostaticus; 4 – ejaculatory ducts; 5 – excretory ducts of prostate glandular formations.



**Fig. 4.** Frontal section of the fetal prostate gland 360,0 mm PCL. Staining by hematoxylin and eosin. Specimen. X 35: 1 – septum of the utriculus prostaticus; 2 – right part of the utriculus prostaticus cavity; 3 – left part of the utriculus prostaticus cavity; 4 – septum vessels of the utriculus prostaticus; 5 – the wall of the utriculus prostaticus; 6 – glandular formations of the prostate; 7 – bundles of smooth muscles.

culus prostaticus and the ejaculatory ducts. The last one, together with the utriculus prostaticus, are surrounded by a general fibrous-muscular membrane. Glandular formations of the prostate gland almost reach the proximal parts of the ejaculatory ducts, and are located between them and the pars prostatica of uretrae masculinae. At this stage of development, the rejection of cells from its walls and the formation of cells were found in separate places of the cavity of the utriculus prostaticus (Fig. 2). The length of the utriculus prostaticus ranges from 0,55 to 0,75 mm.

From the middle of the 5th month of intrauterine development (fetuses 150,0-160,0 mm PCL), the utriculus prostaticus lengthens. The transverse size of the utriculus prostaticus increase only in upper part, where its size are largest. At the same time, in the caudal direction, the cavity of the utriculus prostaticus gradually narrows. The content of the utriculus prostaticus is homogeneous, weakly colored mass, among which barely visible cell nuclei are found. In some places, the cavity of the utriculus prostaticus forms invaginations, especially in the middle and lower parts, or is divided into separate, interconnected chambers. Around the utriculus prostaticus there are clusters of connective tissue elements, and on both sides of them there are ejaculatory ducts. Last ones and the utriculus prostaticus are surrounded by a general fibrous-muscular membrane.

In fetuses of 170,0-185,0 mm PCL, an increase in the length and transverse size of the utriculus prostaticus is observed, as a result of which it takes an elongated-oval or rounded-oval shape. The length of the utriculus prostaticus ranges from 0,7 to 1,6 mm. The upper end of the utriculus prostaticus is located slightly in front of the ejaculatory ducts and between them, reaching the base of the prostate gland near its posterior surface. In the caudal direction, the utriculus prostaticus is directed ventral to the colliculus seminalis and is located slightly anterior and superior to the ejaculatory ducts. The caudal sections of the utriculus prostaticus and the ejaculatory ducts are located in the area of the most convex part of the colliculus seminalis. From the tissue of the prostate gland, the ejaculatory ducts and the utriculus prostaticus are separated by circular connective tissue fibers. The process of cavity formation in the utriculus prostaticus spreads in the caudal direction.

At the end of the 6th month of intrauterine development (fetuses 225,0-230,0 mm PCL), the length of the utriculus prostaticus ranges from 2,0 to 2,5 mm. Starting with fetuses of 7 months, the length and width of the utriculus prostaticus increases, while its length is 2,4-3,1 mm.

The utriculus prostaticus in 8-month-old fetuses has a rounded-oval shape. The length of the utriculus prostaticus is  $3,8 \pm 0,23$  mm. The lumen of the utriculus prostaticus is lined with a pseudostratified cubical epithelium, outside of which there is a tunica muscularis. The last one consists of two layers: inner – circular and outer – longitudinal (Fig. 3). Among the fibers of the longitudinal layer of the utriculus prostaticus tunica muscularis, there are smooth muscle fibers of oblique and spiral di-



rection. Ejaculatory ducts lined with a two-layer cuboidal epithelium are placed on both sides of the utriculus prostaticus.

A 270,0 mm PCL fetus has no utriculus prostaticus at the apex of the colliculus seminalis.

Microscopic examination of a series of histological sections of the prostate gland in fetuses 315,0-335,0 mm PCL revealed that the process of cavity formation spreads to new areas of glandular formations of the prostate gland and their final branches. Most of the glandular formations open into the prostatic part of the urethra directly below the utriculus prostaticus and the distal parts of the ejaculatory ducts. At the same time, the glandular ducts that open on the colliculus seminalis above the ostium of the ejaculatory ducts have significantly smaller sizes and the number of branches compared to those located below the ostium of the ejaculatory ducts.

Microscopic examination of frontal sections of the prostate gland of a fetus with a 360,0 mm PCL revealed a septum in the utriculus prostaticus with a thickness of  $780 \pm 20$  mm. Vessels of different diameters are determined in the septum of the utriculus prostaticus (Fig. 4). The septum divides the cavity of the utriculus prostaticus into the right and left halves of a round-oval shape. At the same time, the length of the utriculus prostaticus is 4,6 mm.

At the end of the fetal period of human ontogenesis, the length of the utriculus prostaticus ranges from 3,4 mm to 4,3 mm.

## DISCUSSION

The modern development of andrology and urology requires morphologists to carry out complex studies of the regularities of the structure and formation of topographical-anatomical relationships of the male urogenital organs in the pre- and postnatal periods of human ontogenesis. The basis of the processes of morphogenesis of any organ in the human body system are intercellular interactions, that direct and determine the organotypic differentiation of cells and tissues during ontogenesis [12, 14, 15].

It is known that the prostate gland, as an unpaired glandular-muscular organ, secretes a mucous, that thins sperm and increases sperm motility, and as an endocrine organ, the prostate gland secretes prostaglandins into the blood, which regulate the synthesis of male sex hormones and the processes of spermatogenesis, stimulate the growth of nerves, contraction of smooth myocytes, etc. [16].

The problem of combining information about the peculiarities of the structural organization and function of the prostate gland into a single morpho-functional view about the object of research is one of the important ones for modern perinatal urology. This is especially demonstratively shown on the example of the back wall of the prostatic part of the urethra, where the mucous membrane forms a fold - the crista erethralis, in the middle of which is defined the colliculus seminalis, from which the

ejaculatory ducts open on both sides, and the utriculus prostaticus is located on the top.

The results of our research [12, 13, 16] prove, that the formation of the prostatic and intermediate parts of the urethra as derivatives of the urogenital sinus occurs in the 9th week of intrauterine development. In fetuses of 56,0-65,0 mm PCL, the caudal parts of the mesonephric ducts undergo intensive development, which is accompanied by the expansion of their lumen, the appearance of a circular layer of mesenchymal cells and the transformation of the epithelial lining, as a result of which the vas deferens, seminal vesicles and excretory ducts are formed prostate gland. At the beginning of the 11th week of intrauterine development, the beginning of the formation of glandular elements of the prostate gland is observed, which are formed as a result of the proliferation of the epithelium of the prostatic part of the urethra and have the appearance of continuous cell cords. The latter ones then turn into hollow tubules. At the same time, the glandular primordia structures of the posterior part of the prostate gland, which are found at the level of the openings of the mesonephric ducts, develop most intensively.

Three stages are distinguished in the prenatal development of the prostate gland: laying of the gland (8-12 weeks); formation (up to 25-27 weeks); the period of the primary formed prostate gland (from 28-29 weeks before birth). At the stage of formation of, there is an increase in the number and size of glands on the periphery of the prostate [14, 17].

At the same time, until recently, all the regularities of the chronological sequence of prenatal morphogenesis of the utriculus prostaticus, the sources of development and the formation of correlative relationships of the structures of the colliculus seminalis area in human fetuses and fetuses have not been established.

Thus, on the basis of the immunohistochemical study, some authors [16, 18] write that the utriculus prostaticus is not a derivative of the paramesonephric ducts, but it is formed from the dorsal wall of the urogenital sinus during the period when the regression of the caudal parts of the paramesonephric ducts took place, which contradicts Müller's theory that, the utriculus prostaticus is a rudiment of the paramesonephric ducts. Other researchers indicate that the utriculus prostaticus develops from the mesonephric ducts of Wolff [19].

However, our results regarding the development of pre-fetuses and fetuses the utriculus prostaticus from the caudal parts of the paramesonephric ducts are consistent with Muller's theory [20] and contradict the information of the above-mentioned authors.

## CONCLUSIONS

The formation of utriculus prostaticus occurs from the paramesonephric ducts in the 11<sup>th</sup> week of fetal development. At the beginning of the 4th month of intrauterine development, as a result of the intensive proliferation of cells that line the cavity of the utriculus prostaticus, it gradually decreases in size, and at the end of this month, in



some places of the cavity of the utriculus prostaticus, the rejection of cells from its walls and the formation of cells are observed. From the middle of the 5<sup>th</sup> month of prenatal development, the utriculus prostaticus lengthens, and

starting from the fetus of 7 months, both its length and width increase. At the end of the fetal period, the utriculus prostaticus acquires a round-oval shape, its length increases from 0,5 to 4,3 mm during prenatal ontogeny.

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### CONFLICT OF INTEREST

The Authors declare no conflict of interest.

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# OUTCOMES ANALYSIS OF SEPTOPLASTY IN CHILDREN

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## ABSTRACT

**Aim:** The aim of the study was to present the experience of a local hospital surgical department where septoplasty is performed on children suffering from its degeneration. **Materials and methods:** A retrospective cohort study with 100 patients aged between 3 and 18 years were taken. Both males and females out of 100 patients were followed up for 7 years. The patients were treated with using septoplasty as well as the related clinical procedures such as cauterization of the inferior turbinate. We performed clinical evaluation and nasal endoscopy of the cases in the postoperative period. The longest observation period was 7 years. **Results:** The male and female child enrolled in the study were 60 (60%) and 40 (40%), respectively. Out of this number of patients, 92 (92%) had inferior turbinate cauterization. In all the 100 cases, we did not notice any intraoperative complication. Also, all the cases were evaluated in 15th, 30th, and 60th days of observation. **Conclusions:** When performed correctly, septoplasty in children is a good clinical intervention as it allows the right growth and development of the craniofacial region and prevents abnormalities in psychic and somatic components in young patients. Moreover, this study confirms the previous studies that have demystified the point of view, that the setoplasty should only be recommended when the patients reach the ages of 17 and 18.

**KEY WORDS:** abnormalities, children, septoplasty, surgical procedure, retrospective cohort study

## INTRODUCTION

Deformed septum (abnormal septum formation, double cartilage), is a common problem in children [1]. Patients with this condition often suffer from respiratory problems and a runny nose. The normal septum is made up of bones and cartilage and is fully integrated with the mucous membrane [2]. When it is no longer in the middle, it deviates. This problem is congenital or acquired through injury or other rare causes. Septoplasty is a reconstructive surgery to repair a deformed septum in children and adults. Surgery is performed entirely on the nose, where the surgeon reconstructs or partially removes the septum. Surgery can be performed on their own or with other cerebral or nasal surgery [3]. In children, the cartilage is still growing, which means that with surgery, it is possible for it to be fully corrected and grow without further complications. Septoplasty is important as the most effective clinical method as it repairs the septum and completely reverses the common problems children face [4], for example, the most common symptoms of frequent sinus infections, noisy breathing during sleep, blood clots, and other face pains and frequent headaches [5].

In adults, septoplasty is a well-established surgical procedure that has been used for several years. However, it is nevertheless debated and debated when used with children. For example, some authors have objected to septoplasty before the patient reaches the age of 17 based on the assumption that early surgical intervention may adversely affect normal nasal growth. Some studies argue that when surgery done early enough, the septum and nose are generally given the opportunity for normal growth and development of other parts of the face. Launched in recent decades, septoplasty has undergone a number of technological changes, particularly

to reduce nasal congestion and the occurrence of complications after surgery [6]. There is some controversy in the literature on the effects of septoplasty in correcting septal defects in children and adolescents under 17 or 18 years of age. In fact, some studies have shown that early septoplasty is of great benefit to children in both the short and long term. In the early 2000's, Maniglia and colleagues undertook research to determine the possible and virtual effects of surgery on young children. In this study, researchers used a sample of 80 patients between the ages of 4 and 14, 65 of whom had undergone septoplasty and the rest had undergone rhinoplasty. After follow-up, the researchers found that only 13 patients experienced postoperative complications. In addition, it was found that postoperative complications were minor and had little effect on the growth and development of patients. Therefore, it was concluded that the benefits of surgery outweigh any possible complications.

In another study of Dispenza et al. [7] found that the degree of nasal obstruction was a complete indication and should be more important than the reference age of surgery. In particular, the authors suggest that nasal congestion during infancy may interfere with the growth of the skull angle. As a result, the problem affects maxillofacial growth and may cause malocclusion and jaw dislocation with deformities in the bones involved. Verwoerd et al. [8] have also shown that delays in the reorganization of the paralyzed septum are more likely to have adverse effects on organ systems that play a key role in both cognitive and somatic development in children such as sleep and voice processes. At the same time, researchers say that there should be adequate monitoring as an indicator for surgery. Some studies have shown that if done carefully, surgery cannot harm facial growth or promote paralysis of the nasal cavity.



**Fig. 1.** 12-year-old child with severe deviated septum.



**Fig. 2.** 10-year-old child with FAS and septal deviation.



Lee et al. (2017) states that septoplasty can be performed safely without affecting the growth of the face and nose and that delayed procedure causes craniofacial disturbances and facial asymmetry, which may affect the child's brain [9]. However, there are some studies that have found a possible link between surgery and malignant growth of the nasal dorsum, especially when the procedure is performed using an external method. There-

fore, the researcher states, that it is necessary to perform a thorough clinical examination in order to obtain an accurate diagnosis and appropriate surgical guidance before the procedure is performed in children [10]. As a result, it can be seen that most of previous studies, both clinical and anthropometric tests, show that septoplasty in children is a good clinical intervention as it allows for proper growth and development of the craniofacial region and



**Table 1.** Patient`s characteristics (n = 100).

Age at surgery (years)	Male (n=60)	Female (n=40)
2 - 5	2	1
6 - 10	10	6
11 - 15	28	16
16 - 18	20	17

**Table 2.** Procedures associated with septoplasty surgery.

Procedures	n (%)
Septoplasty	100 (100%)
FESS (fungl allergic sinusitis)	5
Antrochoanal polype	6
Cauterization	92 (92%)

prevents abnormalities in the psychic and somatic organs of younger patients. Therefore, it can be argued that the idea that surgery should be performed after a patient is 17 or 18 years old is unconfirmed [11].

At present, there is a need for further research to assess potential complications after surgery in children and to determine whether surgery should be recommended at an early age or delayed until patients reach the age of 18 years. Therefore, the purpose of surgery this study will include additional information on the growing volume of information about the effects of septoplasty and its postoperative impact.

### AIM

The aim of the study was to present the experience of a local hospital surgical department where septoplasty is performed on children suffering from degeneration of the nasal septum and to undermine the notion that surgery should be delayed until patients reach 18 years of age.

### MATERIALS AND METHODS

A retrospective cohort study was designed. In total, 100 patients aged between 3 and 18 years were taken. Both males and females out of 100 patients were followed up for 7 years, and those included in the study from January 2010 to April 2021. The patients were treated with using septoplasty (Fig. 1) as well as the related clinical procedures such as cauterization of the inferior turbinate, FESS for patients with allergic fungal sinusitis (Fig. 2) and antrochoanal polyps as considered necessary. Nevertheless, our main area of interest was the surgery itself. We performed clinical evaluation and nasal endoscopy of the cases in the postoperative period, namely on days 15, 30 and 60, and thereafter we evaluated them annually. The longest observation period was 7 years.

### RESULTS AND DISCUSSION

One hundred patients were treated with septoplasty surgical intervention. Table 1 shows the patient characteristics of the 100 cases used in the study. The mean age was 8 years. The male and female child enrolled in the study were 60 (60%) and 40 (40%), respectively.

Out of this number of patients, 92 (92%) had inferior turbinate cauterization. Table 2 shows the list of related procedures.

In all the 100 cases, we did not notice any intraoperative complication. Also, all the cases were evaluated in 15th, 30th, and 60th days of observation. Possible adhesions and reappearance of the deviations, infections, nasal deformities, and septal perforation were all observed. After the initial 60 days of observation, follow-up continued annually up to 7 years. We found no complications in all the cases except 3 cases with adhesion treated with local anesthesia.

The study confirms that performing septoplasty in children has no effect on the normal growth and development of the craniofacial region. In particular, the study's use of a large sample and follow-up period increased the validity and reliability of the process and results. Based on these results, it can be seen that septoplasty can effectively be done safely without affecting facial and nasal development in selected patients [12]. Moreover, there were no chances of developing the aforementioned deformities in older children because we found no relationship between age and the probability of postoperative problems [13].

This study shows that the degree of nasal obstruction is the absolute indication and is of more concern and importance than the age at which septoplasty is performed. It should be further noted that nasal blockade during infancy is likely to disrupt the normal development of the base of the skull. In this case, the problem might affect the patient's maxiofacial growth and might also cause malocclusion as well as protrusion of the jaw with deformities in the bones involved [14]. Any delay in restructuring of the deformed septum has high chances of bringing negative effects on the organ systems that have an important roles in both psychic and somatic development in children, such as sleep and voice processes [15]. At the same time, the researchers stated that there should be adequate monitoring as an indication for the surgery [16]. Moreover, it confirms the findings that, when performed conservatively, surgery cannot impair facial growth or stimulate deformities in the nasal cavity [17]. The surgery can be performed safely with no effect on the face and nasal development and the delay in the procedure causes craniofacial anomalies and facial asymmetries, which can psychologically affect the child. This study further supports the perception that it is necessary to carry out a thorough clinical examination for a the appropriate diagnosis as well as the right surgical indication before the process is done on children [18]. In fact, the study confirms previous findings that early intervention with septoplasty is beneficial because it corrects the problems early enough and allows organs to develop in the right manner, that would

otherwise be difficult in adults whose growth and development has rescinded [19-21].

Justicz et al in 2019 [22] said "Pediatric septoplasty may be safely performed without significantly affecting future nasal and facial growth. Septoplasty should be performed in patients with functional problems related to congenital anomalies or trauma, whereas a deviated septum causing NAO symptomatology also represents a reasonable and supported cause for early septoplasty in children as young as six years of age".

## CONCLUSIONS

When performed correctly, septoplasty in children is a good clinical intervention as it allows the right growth and development of the craniofacial region and prevents abnormalities in psychic and somatic components in young patients. Moreover, this study confirms the previous studies that have demystified the point of view, that the setoplasty should only be recommended when the patients reach the ages of 17 and 18.

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### CONFLICT OF INTEREST

The Author declare no conflict of interest.

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\* 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.

# ECHOCARDIOGRAPHIC METHODS FOR ASSESSING LEFT VENTRICULAR SYSTOLIC FUNCTION

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## ABSTRACT

Transthoracic echocardiography (TTE) is the recommended primary method of assessing cardiac function. The measurement of LVEF determines the strategy for treatment of patients, as well as influences their prognosis. 3D echocardiography has higher accuracy and reproducibility than 2D echocardiography; hence it is currently recommended for volume and LVEF measurements. New echocardiographic techniques: global longitudinal strain measured by speckle tracking and myocardial work allow earlier detection of myocardial abnormalities. In addition, they have greater sensitivity in detecting ischemia, fibrosis and left ventricular systolic dyssynchrony. In some myocardial pathologies, such as amyloidosis, hypertrophic cardiomyopathy or Chagas disease, we observe characteristic patterns of myocardial deformation (strain), which are their hallmarks. Myocardial work, on the other hand, allows assessment of contractility independent of the effect of afterload. The new echocardiographic techniques provide additional diagnostic tools for assessing left ventricular systolic function and information on prognosis, and hence their use can be expected to become more widespread in daily clinical practice.

**KEY WORDS:** strain, left ventricular ejection fraction, myocardial work

## INTRODUCTION

Transthoracic echocardiography (TTE) is the recommended primary method of assessing cardiac function [1]. Real-time imaging of the heart, lack of exposure to ionizing radiation, and the non-invasive nature of the test makes it the most important among available imaging methods in cardiology.

## AIM

The purpose of this article was to present echocardiographic methods for assessing left ventricular systolic function commonly used in daily clinical practice and new tools that allow more detailed diagnosis of myocardial pathology.

## REVIEW AND DISCUSSION

### LEFT VENTRICULAR EJECTION FRACTION

Calculation of left ventricular ejection fraction (LVEF) is an essential parameter to assess global systolic function, and its reduced values are associated with a worse prognosis [2]. The measurement of LVEF determines the strategy for pharmacological treatment of heart failure, as well as the eligibility for surgery in patients with mitral and aortic regurgitation in accordance with current guidelines of evidence-based medicine. Calculation of LVEF requires knowledge of both left ventricular volume in the diastolic and systolic phases of the heart. The volume of blood present in the left ventricle during the end-diastolic phase is called end-diastolic volume (EDV). We define the end-diastolic phase as the frame before the mitral valve leaflets' closure or the left ventricle's

largest dimension, which overlaps with the beginning of the QRS complex or the peak of the R-wave in the ECG. Similarly, the volume of blood that remained in the end-systolic phase in the left ventricular cavity is the end-systolic volume (ESV). It is measured when the aortic valve leaflets close or when the dimension of the left ventricle is at its smallest. This is before the mitral valve leaflets open in the four-chamber and two-chamber projection. The difference in these values determines the stroke volume (SV) of blood pumped through the aortic valve during a single cardiac cycle. Ejection fraction is that portion of diastolic volume (EDV) that is ejected during the systolic phase:

$$EF (\%) = SV/EDV \times 100\%, \text{ where } SV (ml) = EDV - ESV$$

We can assess ejection fraction using two-dimensional (2D) or three-dimensional (3D) echocardiography.

For 2D echocardiography, the American Society of Echocardiography recommends a two-plane disc summation method, known as the modified Simpson's rule for calculating LVEF [2]. The method involves dividing the left ventricular cavity into disks (usually 20) and then calculating their volumes, which are summed. The software of the echocardiography apparatus performs the calculation automatically after we have carefully determined the endocardial line adjacent to the left ventricular cavity. At the level of the mitral valve, we determine the points of attachment of the leaflets to the mitral annulus, between which a straight line is drawn. The length of the left ventricle is determined by the center of this line and the farthest point of the apex of the left ventricle. Optimal image acquisition with imaging of the endocardial bor-



der and measurements in both the apical four-chamber and two-chamber views is necessary. The most common drawbacks of this method remain the shortening of the left ventricular apex due to the passage of the ultrasound beam above and forward from the left ventricular apex. We then see a distorted left ventricle shape with a false, more rounded, and thicker apex, showing excessive contractility. As a result, the left ventricular axis is shorter, and the calculated volume is underestimated. Note that the correctly obtained image of the left ventricle resembles a "bullet" shape, and the apex of the heart is formed only by the left ventricle. Another weakness remains the lack of a visible endocardial border. It has been shown that the images obtained in a quarter of patients are sub-optimal due to the lack of a visible endocardial border [3]. To improve image quality, the penetration depth of the ultrasound beam should be reduced. In addition, it is possible to perform contrast echocardiography. The volumes obtained in this way can be larger, which correlates better with measurements obtained from magnetic resonance imaging [4]. However, this method is rarely used due to economic and reimbursement considerations. In addition, Simpson's method assumes that the left ventricle is a geometric figure formed on a matrix of measurements from two projections. As a result, there is a risk of underestimating the left ventricular volume if contractile abnormalities in wall areas other than those being analyzed are present. When interpreting the LVEF result, it is important to remember that its low value may be due to low ejection volume or EDV. In addition to myocardial contractility, LVEF value is also influenced by preload, primarily affecting EDV, and afterload regulating ESV. Hence, during the recording of the echocardiography examination, the value of arterial pressure should be noted. In heart failure with reduced ejection fraction (HFrEF), EDV and ESV are increased, so SV remains preserved despite the systolic dysfunction. In contrast, in so-called "small hearts," despite normal LVEF, SV may be low and insufficient to produce a gradient across a stenotic aortic valve. Therefore, in some clinical situations, such as valvular defects or heart failure with preserved ejection fraction (HFpEF), SV assessment remains important in interpreting the echocardiographic result, regardless of LVEF. It is recommended that left ventricular volume measurements should be related to the patient's body surface area (BSA). The software of echocardiographic machines calculates this index automatically after entering the patient's weight and height. The average BSA for people aged 20-79 is 1.73 m<sup>2</sup>, lower for women (1.6 m<sup>2</sup>) and higher for men (1.9 m<sup>2</sup>). The upper normal range for EDV is 74 ml/m<sup>2</sup> for men and 61 ml/m<sup>2</sup> for women. The corresponding ESV is 31 ml/m<sup>2</sup> for men and 24 ml/m<sup>2</sup> for women. Normal LVEF measured by the modified Simpson's method averages 63±5% and ranges from 53 to 73%. Caution should be exercised in interpreting the result in obese patients. Patients with BMI ≥30 kg/m<sup>2</sup> were excluded during the development of the standards, and there is a risk of underestimating the indexed parameters.

Measurement of LVEF determines the diagnosis of heart failure phenotype requiring treatment according to the according to current guidelines. We distinguish between:

- heart failure with reduced left ventricular ejection fraction (HFrEF), defined as a reduction in LVEF ≤40%,
- heart failure with mildly reduced left ventricular ejection fraction (HFmrEF) including patients with LVEF 41% to 49%,
- heart failure with preserved left ventricular ejection fraction, including patients with LVEF ≥50%.

#### VISUAL ASSESSMENT OF EJECTION FRACTION (EYEBALLING)

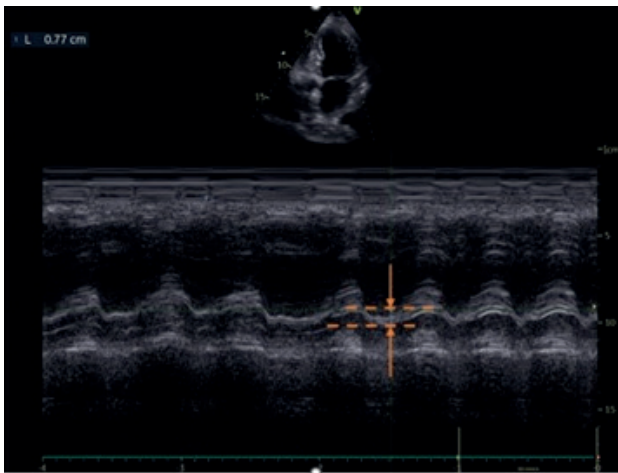
Visual assessment of LVEF remains common in daily clinical practice, even though it is not currently recommended. It is repeatedly used due to the insufficient quality of the images recorded, preventing satisfactory contouring of the endocardium. This approach has been shown to overestimate the ejection fraction value compared to calculations obtained by Simpson's method [5]. In addition, it is characterized by greater variability in results between assessors of up to 14% [6].

#### 3D ECHOCARDIOGRAPHY

The assessment of the volume of heart cavities based on 3D echocardiography has higher accuracy and reproducibility than 2D echocardiography; hence it is currently recommended for volume and LVEF measurements [7]. The accuracy of 3D imaging is comparable to that of MRI, but the calculated volumes are slightly smaller due to the delineation of the trabecular boundary. In addition, the differences in results depend on the quality of the recorded images, and when 3D methods are used, very good quality of recorded images is required. Image acquisition can be based on recording the volume of the left ventricle during a single cardiac cycle. Unfortunately, volume registration in place of a plane, as is the case with 2D echocardiography, requires more time. In practice, this involves a decrease in temporal resolution. In the case of significantly enlarged heart cavities, where the recorded volume is very large, ECG-gated volume recording over several cardiac cycles may be a solution. In a study comparing the assessment of left ventricular morphology and function in 20 patients with hypertrophic cardiomyopathy, Leticia et al. showed that 3D echocardiography had slightly better agreement with magnetic resonance imaging results than 2D echocardiography [8]. In addition, the analysis showed an underestimation of LVEF by 2D echocardiography. In patients after myocardial infarction and with left ventricular aneurysm, 3D echocardiography provides a comparable assessment of left ventricular volume and function to MRI and can be used to evaluate scar tissue [9].

#### MAPSE (MITRAL ANNULUS PLANE SYSTOLIC EXCURSION)

Measuring mitral annular excursion in the late systolic phase toward the LV apex is a rapid method for

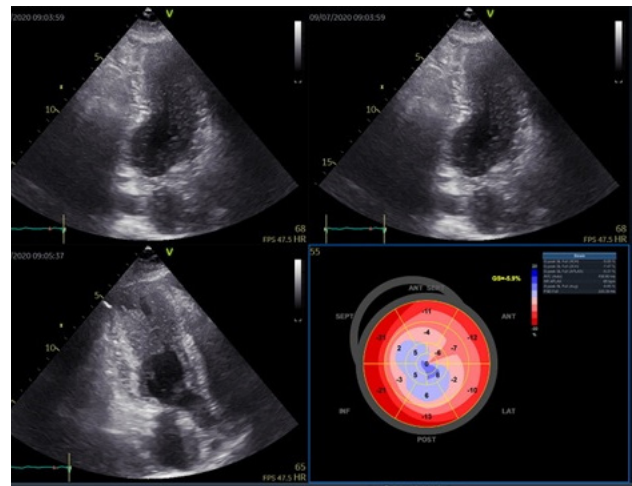


**Fig. 1.** MAPSE measurement: mitral annular excursion in systole and in diastole.

assessing left ventricular systolic function, especially when imaging conditions are difficult. Currently, it is rarely used in clinical practice since guidelines do not recommend it. However, it has been shown that the values of this parameter, measured by cardiac magnetic resonance imaging, correlate with the values of longitudinal strain [10]. An image of ring motion is obtained using M-mode set perpendicular to the plane of the ring in the apical four-chamber view (Fig. 1). Mean values range from 12 to 15 mm [11]. Values  $> 10$  mm correlate with LVEF  $> 55\%$ , while  $< 8$  mm is associated with LVEF  $< 50\%$ . In contrast, MAPSE  $< 7$  mm is associated with LVEF  $< 30\%$  [12]. It should be remembered that MAPSE reflects the contractile function of longitudinal fibers; hence this parameter cannot be used for regional wall motion abnormalities. Moreover, mitral annular calcification, myocardial hypertrophy or pericardial tamponade limit its interpretation.

#### LEFT VENTRICULAR STRAIN

Left ventricular strain describes the relative length change from the muscle fibers' baseline in a given direction. The mechanics of left ventricular contraction is a complex process that, in a nutshell, can be compared to the movement of a "rolled towel." The deformation of muscle fibers occurs in three directions: longitudinal - from the base to the apex of the left ventricle, radial - perpendicular to the long axis of the left ventricle and epicardium, reflecting the thickening of the myocardium, and circumferential - perpendicular to the other two directions. During the contraction phase of the left ventricle, muscle fibers shorten in the longitudinal and circular directions; hence we speak of negative strain values. In contrast, they elongate in the axial orientation, expressed by positive strain values. The norm for peak global longitudinal strain (GLPSS) of the left ventricle is  $> -18\%$ . Strain can be estimated by Doppler recording of myocardial velocities or speckle tracking. If the Doppler method is used, measurement of myocardial motion is possible only in a plane parallel to the ultrasound

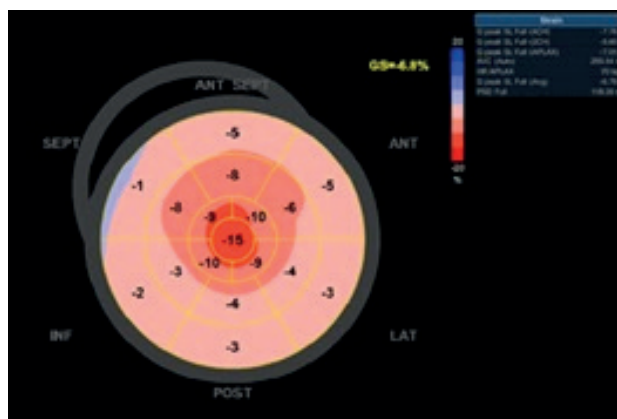


**Fig. 2.** GLS assessment by 2D speckle tracking in a patient with hypertrophic cardiomyopathy.

*Comment: the diagram shows a reduction in longitudinal strain values in the left ventricular apex and most apical segments.*

wave stream and requires high-frequency recording. It is much easier in clinical practice to use speckle tracking, which involves tracking a specific number of gray-scale points that are made up of about 20 to 40 pixels, called "kernels." The defined area is invariant, with a unique pattern that is tracked during the cardiac cycle by the corresponding software. Speckle tracking allows strain to be measured regardless of the inclination angle and reflects only the active contraction of the fibers. Hence, strain measurement eliminates the error of the "tethering effect," which is the passive movement of fibrous tissue through adjacent viable myocardium. Global longitudinal strain (GLS) measured in this way is an objective and clinically useful method for assessing global and left ventricular systolic function, which has been confirmed by including this method in current guidelines [13-15]. In addition, the strain has better repeatability of measurement results than LVEF. The results of GLS measurements by an experienced echocardiographer and novice cardiac trainees showed excellent correlation ( $r=0.98$ ) and a deviation of  $-1.0 \pm 13\%$  from the measured value. In contrast, for LVEF, the correlation coefficient of the results was lower ( $r=0.91$ ), and the deviation was  $7.3 \pm 16\%$  [16]. Nevertheless, it should be remembered that strain assessment is dependent on afterload. In addition to GLS information, strain analysis by speckle tracing can provide information regarding regional left ventricular dysfunction, allowing values to be obtained separately for each of the 17 left ventricular segments. In addition, it is also clinically useful to analyze the pattern of strain abnormalities. There are characteristic patterns to indicate the underlying disease of contractile dysfunction, e.g., amyloidosis, Chagas disease, aortic stenosis, etc. (Fig. 2-3).

In addition to strain, another parameter for assessing regional left ventricular contractility is the strain rate (SR). It denotes the change in a strain made per unit of time and is expressed in  $s^{-1}$ . SR equal to  $0.6/s$  means about 60% of muscle fibers strain in one second. The



**Fig. 3.** Evaluation of GLS by 2D speckle tracking presented as a graphical diagram in a patient with amyloidosis.

*Comment: characteristic significant reduction in GLS values in the basal and mid segments. Higher values are observed in the left ventricular apex, the so-called "apical sparing."*

range of normal values for SR is 1.3/s to 1.7/s. Calculating SR based on the strain obtained by speckle tracking is not recommended but only based on transformations of recorded myocardial velocities.

#### MYOCARDIAL WORK (MW)

It is a non-invasive measurement of the work the left ventricular muscle performs during isovolumic contraction and diastole, which considers afterload. Work is the product of a force and the displacement resulting from its action. An analogy was used to calculate myocardial work by considering the pressure in the left ventricle (or more precisely, the fiber tension, which is the force applied per unit area) and the relative strain of the muscle [17]. Due to the assumption that aortic pressure is equal to left ventricular systolic pressure, its estimated measurement is obtained from the measurement of systolic pressure on the brachial artery. Exceptional situations include aortic stenosis and left ventricular outflow tract stenosis, which contraindicates MW calculations by this method. The extent of myocardial work is presented by the area inside the pressure-strain loop (PSL) (Fig 4). MW is measured during systolic stroke work or mechanical contraction and isovolumetric diastole and is expressed in units of mmHg%. In analyzing the MW, we use the following parameters:

- global work index (GWI) - the total work the left ventricle does during mechanical contraction (from mitral valve opening to closure).
- global constructive work (GCW) - the work done by the left ventricle during the shortening of muscle fibers in the contraction phase and their lengthening during isovolumetric diastole.
- global wasted work (GWW) – the work done by the left ventricle during an unproductive contraction. It includes muscle lengthening during systole and shortening during isovolumetric diastole. Wasted work is observed during dyssynchrony of contraction, such as in LBBB, ischemia, and some myocardial diseases. It represents an additional metabolic

burden that can lead to reverse remodeling.

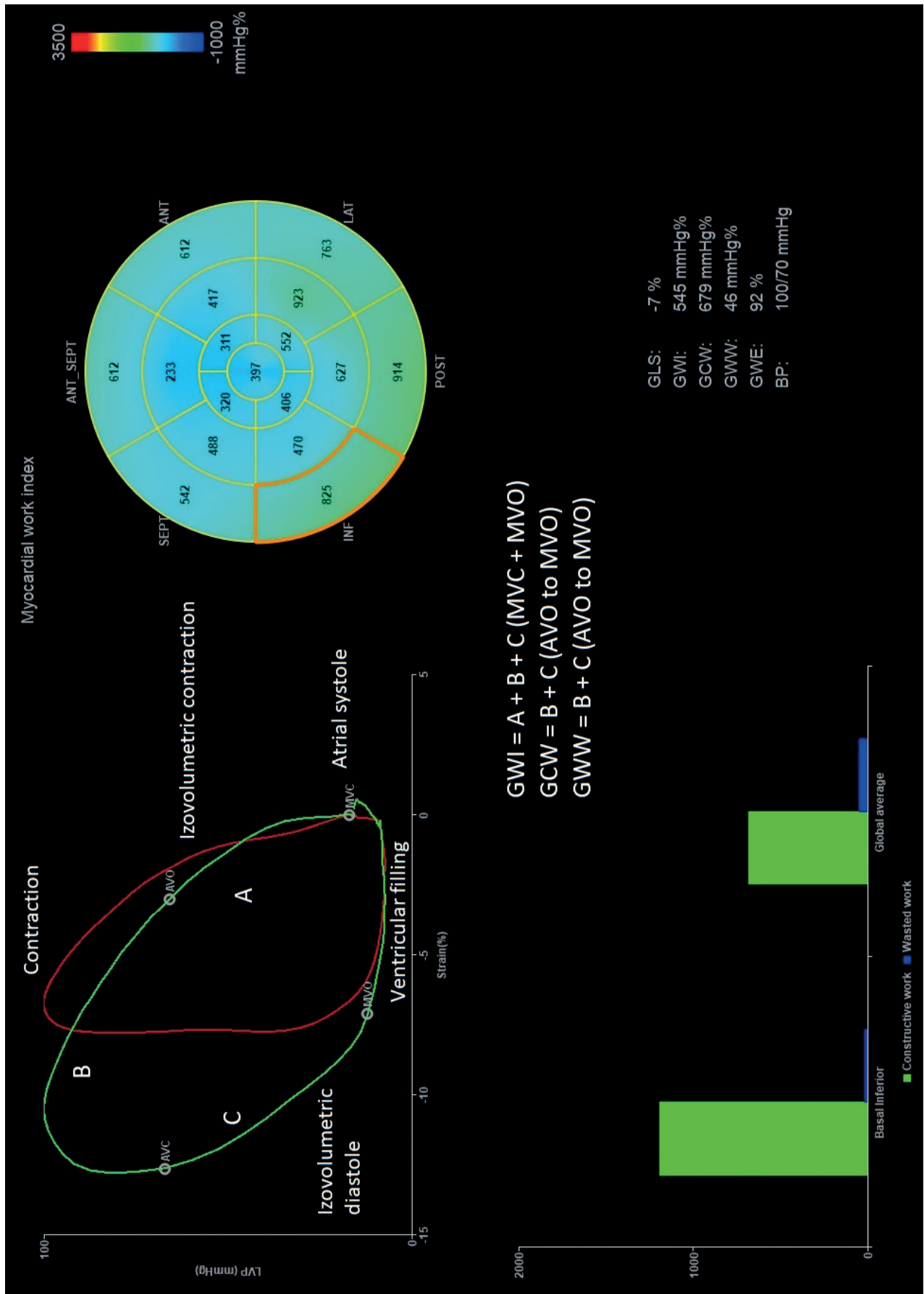
- global work efficiency (GWE) - global productive work, is the ratio of constructive work to the sum of constructive and wasted work, expressed in %:

$$GWE = GCW / (GCW + GWW)$$

The above parameters are calculated both in total for the left ventricle and its individual segments. The result is presented as a buffalo eye diagram with numerical values and on a colour scale. Red corresponds to high work areas, green to normal work, and blue indicates negative work. Negative work means that the segment is absorbing energy rather than providing energy to the heart as a pump. Hence, it denotes wasted work, consisting of fiber elongation during contraction or shortening during isovolumetric diastole. MW shows greater sensitivity in detecting impaired left ventricular efficiency with preserved normal contractility. In a healthy heart, all 17 segments of the left ventricle contract simultaneously, and wasted work represents a negligible amount. Since the estimated left ventricular systolic pressure does not consider the geometry of the ventricle and the thickness of the myocardial wall, myocardial work values should not be compared between patients but only with respect to individual segments of a given heart [17]. Reference values applicable to daily practice are shown in Table 1 [18]. MW was first described in patients qualified for cardiac resynchronization therapy (CRT) [17]. In dyssynchrony, the interventricular septum (IVS) is characterized by reduced work, while work is increased in the lateral wall area. In addition, higher WW values are found in the IVS range. After CRT implantation, the opposite effect is observed. The observed change in MW redistribution in the early period after CRT implantation was the strongest predictor of reverse remodeling alongside other parameters such as QRS complex morphology and duration and ischemic cardiomyopathy [19]. In patients with reduced LVEF  $\leq 35\%$ , GWW  $< 200$  mmHg% is associated with a lower likelihood of response to CRT and an increased risk of death [20]. MW also enables the detection of single or multivessel coronary artery disease with greater sensitivity than LVEF or GLS. Jingru et al. showed that GWE and GWW at the peak exercise on a treadmill stress test were predictors of significant de novo coronary artery disease in patients presenting with stenocardial complaints [21]. In patients with anterior wall STEMI, GCW was the best marker of improvement, and

**Table 1.** The range of reference values of the parameters determining the work of the heart muscle.

	Value	
	♂	♀
GWI [mmHg%]	1270 – 2428	1310 – 2538
GCW [mmHg%]	1650 – 2807	1543 – 2924
GWW [mmHg%]	94 – 271	74 – 278
GWE [%]	88 – 97	90 – 97



**Fig. 4.** PSL curve with marked phases of the cardiac cycle and time of opening and closing of the heart valves.

*Comment: GWl corresponds to the area under the curve from mitral valve closure (MVC) to mitral valve opening (MVO). GCW is the work from aortic valve opening (AVO) to MVO. The green curve corresponds to the global values, while the red curve represents the selected segment.*



lower values were associated with complications during hospitalization [22]. In heart failure, myocardial work indices help predict the prognosis of patients [23]. GWI correlates with NT-pro-BNP values and maximal oxygen consumption [24]. A reduced GWI <750 mmHg% was shown to be associated with higher mortality and more frequent hospitalization [25]. In patients with HFrEF, a significant increase in GCW and GWI was observed after the inclusion of sacubitril/valsartan (26). In patients with hypertrophic cardiomyopathy, GCW is reduced and correlates with the presence of fibrosis, as confirmed by magnetic resonance imaging. GCW is related to left ventricular muscle thickness and adverse prognosis of patients [27]. Papadoulus et al. showed that GCW corresponded with a significant reduction in LVESV after MitraClip implantation at 1-year follow-up [28]. Hence, it may be a marker of positive remodeling in patients with functional mitral regurgitation, enlarged left ventricle and reduced contractility. COVID-19 infection often results in myocardial damage and an increased risk of cardiovascular complications [29]. In patients hospitalized

for COVID-19, GWI was found to be independently associated with higher mortality, including among patients with normal LVEF [30].

## CONCLUSION

Left ventricular ejection fraction remains a parameter of significant prognostic importance. When assessing LVEF, one should choose methods of its evaluation with the highest accuracy and reproducibility, primarily based on 3D echocardiography. There is a growing body of data that assessment of myocardial strain and myocardial work allows earlier detection of myocardial abnormalities, diagnosis of specific diseases based on characteristic patterns of strain abnormalities, and provide prognostic information. Hence, it can be expected that the use of parameters assessing myocardial strain and work will become more widespread in daily clinical practice.

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# OBTAINING INFORMED CONSENT TO MEDICAL PROCEDURES

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## ABSTRACT

Informed patient consent to a medical procedure is a prerequisite for the treatment process to be legal. Actions taken for the good of a person are regulated by the Constitution of the Republic of Poland, international documents, and statutory law. The provisions of the Act on the Professions of Physician and Dentist or the Act on the Professions of Nurse and Midwife are significant here as well. Moreover, the issues of respect for the patient are tackled by the Act on the Patient's Rights and the Patient's Rights Ombudsman. As prescribed in the Medical Code of Ethics, the physician's mission is to protect human life and health, prevent diseases, treat the ill. It is a legal and deontological tool allowing selection of a medical procedure for the patient. Both law and medicine are predominated by the view that any action performed by the physician without the patient's consent is unlawful even if performed for a therapeutic purpose. The border of these two scientific fields is where a clash occurs between legally protected interests: life and health on the one hand, and the right to autonomy on the other. The provisions of Art. 192 of the Polish Penal Code protect the patient's right to self-determination in the scope of agreement to or rejection of therapeutic procedures, also in situations where their life or health are threatened. The paper aims to analyze possible issues related to consents to treatment of adults capable of expressing informed consents.

**KEY WORDS:** declaration of intent, informed consent, therapeutic procedures

## INTRODUCTION

The patient's informed consent to treatment is a unilateral statement of intent about treatment directed toward the provider of medical procedures. Its disposer – the patient – is entitled to revoke it at any time [1]. The effect of consent is to exclude the unlawfulness of a medical intervention (within the limits of law) while the patient assumes the risk of ordinary consequences associated with the service provided [2]. The patient's voluntary and informed consent is the foundation of the medical interventions performed. It is sometimes called the "cornerstone" of performing medical procedures [3]. Obtaining consent authorizes the physician to undertake medical procedures with respect to the patient. Internationally, such consent is specified in the Convention for the Protection of Human Rights and Dignity of the Human Being in the Field of the Application of Biology and Medicine of April 4, 1997 (Poland signed the Convention in 1999, however, it has not been ratified to date). The concept of consent is described in Chapter II, Article 5 of the document. According to it, "an intervention in the field of health may be carried out only after the person concerned has given free and informed consent. The person must be given adequate information in advance as to the purpose and nature of the intervention, as well as its consequences and risks. The person concerned may freely withdraw consent at any time" [4-6].

The issue of the necessity of obtaining consent to a medical procedure remains the subject of many studies available in the world literature [1-3, 5-28]. This fact is not surprising, given the practical importance of the duty in question and the consequences of its obser-

vance for both the patient and the physician performing this medical procedure. Thus, the necessity of obtaining consent to a medical procedure and the accompanying obligations constitute a real problem that doctors need to face in their professional practice. At the same time, it is the subject of judicial consideration in cases of so-called medical errors, being one of the most important prerequisites for court rulings.

## AIM

The paper aims to analyze possible issues related to consents to treatment of adults capable of expressing informed consents.

## REVIEW AND DISCUSSION

### SOURCES OF OBLIGATION TO OBTAIN CONSENT

The institution of consent to medical treatment has evolved over the past two centuries from a paternalistic model, in which the physician was a decision-maker in the treatment process, to the current model, based on the need to obtain consent from the patient for any medical intervention. At the root of the current position is respect for the individual's will, values, and beliefs [2, 11]. As a result of the transformation of the positions indicated, there has been an "empowerment" of the patient.

In terms of national legislation, the basic sources of the obligation to obtain consent for a medical procedure should be sought in the Act of Nov. 6, 2008 on the Patients' Rights and the Patients' Rights Ombudsman [29] and – with regard to physicians – in the Act of Dec. 5, 1996 on the Profession of Physician and Dentist [30]. In addition, this issue is regulated in the Code of Medical

Ethics [31]. The physician's duty to provide information is a mirror image of the patient's right to obtain it. Despite the separate legal regulation, the above-mentioned legal norms correlate with each other, dealing with the same issues, however, viewed either from the patient's side or from the physician's side.

#### EFFECTIVENESS OF PATIENT CONSENT

In the current state of the law, every medical procedure requires prior consent of the patient. The scheme for evaluating the action of the physician, based on legally effective consent, assumes that the patient, by consenting to a given procedure, assumes the risk of the procedure, while the physician, acting in accordance with the medical knowledge available at the time, is not liable for any complications. The illegality of the action is excluded – in other words, the physician acts legally [13,23]. In the absence of effective consent, the physician can be held both civilly [32] and criminally [33] liable, even if the physician's action is in accordance with current medical knowledge.

As a rule, consent to a procedure is given by the patient, i.e., the one whose personal rights are protected by the obligation to obtain it. The patient must be competent, i.e., capable of giving this consent knowingly and freely [2]. In principle, it is essential that the patient has full legal capacity, as well as that he or she is in a state in which it is possible to make an informed decision on the subject of treatment (problematic are situations in which the patient is under the influence of psychoactive substances, alcohol, or in a state in which his or her cognitive functions are impaired, for example, due to dementia). As jurisprudential practice shows, the above indication impinges not only on the assessment of the effectiveness of the expression of the act of will itself, which is the granting of consent to a medical procedure, but also on the manner and scope of transmission of information, preceding the decision about treatment. Indeed, the physician's task is to provide information to the patient in such a way that the patient can understand it to later decide about treatment [14, 18-19].

Effective consent to a treatment procedure must be the so-called explained consent, or in other words informed consent [7, 11, 14, 20, 24-25]. This means that only a properly instructed patient is able to give fully informed consent to treatment. As indicated by the Supreme Court in its judgment of Sept. 24, 2020 (ref. IV CSK 49/19, LEX No. 3057399), the provision of correct information makes it possible "to compensate, to a certain extent, for the deficit of the patient's medical knowledge in order to create an opportunity for a person to truly participate in the diagnostic and therapeutic process concerning their body."

The correct provision of information to the patient determines the legal validity of consent. This raises the question of the scope, content and manner of correctly communicated medical knowledge. In general, the normative answer to the above question is found primarily

in Article 9(2) of the Act of Nov. 6, 2008 on the Patients' Rights and the Patients' Rights Ombudsman [29], as well as in Article 31(1) of the Act of Dec. 5, 1996 on the Profession of Physician and Dentist [30]. However, when analyzing court decisions that assessed the duty to provide information prior to making a decision, it can be concluded that this scope is not always the same. It may differ depending on circumstances of an individual patient's case. In terms of the cited legal norms, the physician should provide information about the patient's health condition, diagnosis, proposed and possible diagnostic and therapeutic methods, foreseeable consequences of their application or abandonment, the results of treatment and prognosis, within the scope of health services provided to the person and in accordance with his or her rights. The legal norms indicated do not resolve the scope of the concept of "foreseeable consequences" of diagnostic and treatment methods.

#### INFORMING THE PATIENT OF THE FORESEEABLE CONSEQUENCES OF THE USE OR OMISSION OF TREATMENT

Based on the legal regulations in question, Polish jurisprudence differentiates the scope of information provided, depending on the type of medical intervention performed by the physician. The first differentiation of the scope of information provided was made under the previous Act of Oct. 28, 1950 on the Medical Profession [34]. The concepts formulated at that time, despite the expiration of the legal force of this law, have been taken over by jurisprudence in the current state of the law and continue to form the basis of court decisions.

Certainly, the consequences in question entail the desired, assumed, typical consequences, as well as the so-called side effects that are not covered by the intention of those taking medical action (both short-term and those that may last a long time, or even appear only sometime after the procedure). Among them, there are consequences that are foreseeable in a given factual situation, as well as those that are extraordinary, unexpected, including those that are unlikely. Moreover, the concept also extends to the consequences of abandoning the diagnostic and therapeutic methods in question. In either case, legally relevant information should include determination of the degree of probability of their occurrence in a particular patient. In a well-established line of jurisprudence, the Supreme Court indicates that it is the physician's duty to inform the patient about the "direct and ordinary consequences" of a given medical intervention (Supreme Court judgment of August 27, 1968, I CR 325/68, LEX no. 4641), and that "it cannot be demanded of the physician to warn the patient of all possible complications, especially those that occur extremely rarely. Such a warning could lead to unnecessary aggravation of the patient's well-being and to an unjustified refusal to consent to the procedure," and that "on the other hand, it is not required to instruct about all possible consequences that are normally impossible to foresee, unusual and unlikely" (Supreme Court judg-



ment of August 28, 1972, II CR 296/72, OSNCP 1973, no. 5, item 86). As the Supreme Court points out, "it is sufficient to specify in general terms the type of possible consequences of the procedure and to indicate whether they endanger the patient's life, or what impact (significance) they may have on the proper functioning of the body" (Supreme Court judgment of Sept. 28, 1999, I CKN 511/98, LEX no. 234833).

Based on the analysis of the cited judicial decisions, a general thesis emerges that the physician's duty is to provide information in full as a rule, from which extremely rare complications may be excluded. However, further analysis of the court rulings leads to more far-reaching conclusions. The jurisprudence makes a distinction between medical interventions undertaken, distinguishing between procedures performed to save life or health, i.e., for the so-called absolute indications; medical interventions for relative indications (e.g., aimed only at improving health, diagnostics, or when the doctor's action is not immediately necessary, and when surgery can give results similar to conservative treatment); and cosmetic surgery. This division directly translates into the required scope of information, preceding the patient's decision to consent to the procedure. As expressed by the Supreme Court, "the manner of instruction when taking consent to a procedure (surgery or examination) must depend on the type of procedure" (judgment of August 28, 1973, I CR 441/73, OSNC 1974/7-8/131).

Thus, in a situation where the patient's life-saving surgery is involved, the duty to provide information may be "limited to the indication of possible adverse consequences and complications, which are an ordinary, typical consequence of the procedure in question" (Supreme Court judgment of April 1, 2004, II CK 134/03 17, LEX No. 355344).

On the other hand, "in a situation where there are no absolute indications to perform a surgical procedure, the requirement of the patient's consent is preserved only if he or she is duly informed – in accordance with the circumstances of the case – about the specific treatment options, and especially about the fact that surgery is the only possible treatment" (Supreme Court decision of Nov. 14, 1972, I CR 463/72, LEX no. 2711441). In these cases, the duty to inform is viewed far more broadly than in situations qualified as lifesaving [26].

The requirement for the broadest information about the possible consequences of the procedure is formulated in relation to actions undertaken solely for aesthetic purposes. In such a situation, the patient should be "sufficiently informed in advance also about the specific, that is, any more or less foreseeable consequences of the intervention, not posing a higher-than-average risk to him or her" (Supreme Court judgment of Sept. 5, 1980, II CR 280/80, LEX no. 5138).

Moreover – as if in isolation from the above division – there is an obligation to inform the patient also about rare complications (in addition to detailed and comprehensive information on significant ordinary, typical com-

plications). "The information should (...) include those foreseeable possible consequences of the procedure, especially if they are consequences consisting in significant and material damage to health, which – as a side effect – although rare or very rare, cannot be excluded, and should specify the degree of probability of their occurrence" (Supreme Court judgment of 28.09.1999, II CKN 511/98, LEX No. 234833). The above means that the scope of the information provided must consider the patient's specific health situation.

The distinctions cited above (developed by the jurisprudence) are not justified by the content of the norms of current law. Their enumeration appeared in connection with the fact that the factual circumstances surrounding emergency and necessary medical interventions are different, and those in which time does not play such an important role. Nevertheless, this must not impinge on the dogmatic construction of the obligation to provide information. Moreover, making such distinctions introduces a margin of discretion for the physician, whose conduct in the event of a dispute is anyway subject to the court's evaluation, carried out with the consultation of an uninvolved and impartial expert witness. The physician is not always able to accurately assess the likelihood of negative consequences of the procedure. In the course of a trial, this is done *ex post*, when the course of events is already known, in particular, when it is known what consequences the implemented treatment has brought to the patient's life and health. Also, statistics on the incidence of complications in given procedures do not always provide a reliable answer on the frequency (or rarity) of a given complication. It is rightly argued that the risk of complications will be different in specialized centers, where given procedures are performed almost routinely (by a specialized team of professionals) compared to those where these medical procedures will be rare. In addition, the success of the procedure depends on many variables, such as the age of the patient, the existence of comorbidities, etc.

#### HOW TO PROVIDE THE PATIENT WITH INFORMATION ABOUT PLANNED TREATMENT

This raises the issue of how information should be conveyed, or rather, how the content conveyed should be adapted to the patient's perceptual capabilities. The starting point should be the statement that there is (and, in fact, should be) no objective pattern of a person being informed. In order for medical information to be comprehensible to the patient, the physician must adapt the manner and content of the conveyed information to the patient's capabilities, keeping in mind that patients may differ in their ability to think analytically, comprehend the words used (especially considering the high professionalism of medical language and the high level of emotion that often accompanies the transmission of health information) [11 -12,15-17, 28]. In other words, information should be individualized and specified each time. At the same time, an obligation is formulated that the

information provided should not negatively affect the patient's mental state. According to the Supreme Court, the physician in certain situations "may not give the patient the kind of information about possible surgical complications that could negatively affect the patient's psyche and thus increase the risk of surgery" (Supreme Court judgment of Jan. 11, 1974, II CR 732/73, LEX no. 4884). It is impossible to agree with this last indication, as it appears as a manifestation of the paternalistic attitude toward the patient as indicated in the introduction. If the axiological foundation of the institution in question is the patient's right to decide about his or her own fate, it should be forbidden to condone concealment (silence) of circumstances that may affect the patient's decision about treatment. In doing so, the physician must act with sensitivity and empathy [3]. Undoubtedly, providing the patient with information about the possible consequences of the procedure can (and often does) increase anxiety [8, 27]. Nevertheless, this should not impinge on the extent of the information provided.

Exceptionally, the legislator has provided for a limitation at the express request of the patient (Article 9(4) of Nov. 6, 2008 on the Patients' Rights and the Patients' Rights Ombudsman Article 31(3) of the Act of Dec. 5, 1996 on the Profession of Physician and Dentist) and in invoking the so-called therapeutic privilege (Article 9(6) of Nov. 6, 2008 on the Patients' Rights and the Patients' Rights Ombudsman, Article 31(4) of the Act of Dec. 5, 1996 on the Profession of Physician and Dentist) [29,30].

The above discussion leads to the conclusion that it is impossible to develop a pattern of correctly provided information, although, of course, some common starting point is adopted in practice. The doctrine and case law also raise the problem of the practice of obtaining the patient's consent, which is often wrong [2]. Regardless of the form of consent (oral, explicit or implied, final or written – required for surgical procedures or those with a higher risk for the patient), it must be preceded by the

provision of reliable information. Thus, the so-called blanket consents, included in, for example, a hospital admission form or at the first visit to a particular health care provider, are regarded as legally irrelevant. Moreover, it is considered only an aid to provide the patient with written information detailing possible complications of medical procedures. It seems that verbally informing the patient is more comprehensible to the patient, giving the physician the opportunity to monitor the understanding of the information provided on an ongoing basis [27]. Nevertheless, brochures, multimedia applications illustrating the course of treatment are being developed in world medicine. Sometimes standardized consent forms approved by the relevant authorities of countries are used as well. [10 -13, 17, 22]. They fulfill a supportive role, especially when it is possible to provide them to the patient well in advance. In order to assess the effectiveness of consent, it is important to consider the circumstances under which it is provided. The patient should be given time, according to the possibilities of the case, to make a decision or consult another doctor. In any case, the patient should not feel pressured, the decision should not be forced, or worse – made for him or her (the narrowing of possible treatment options can be interpreted in this way, after all).

## CONCLUSIONS

The problems cited above, related to the institution of consent to a medical procedure, indicate their practical applications in the daily work of medical personnel. The growing public awareness of rights and the possibility of asserting them in court proceedings leads to the conclusion that further familiarization of the issues in question is important for physicians and other entities participating in the organization of the health care system. Consent to a procedure is not just a formality but represents an opportunity for the patient to make an informed decision about his or her own health.

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# TRAUMATIC EVENTS AND MENTAL DISEASES: THE ROLE OF CERTAIN NEUROTRANSMITTERS, METALLOENZYMES AND HORMONES

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## ABSTRACT

**Aim:** To study the role of certain neurotransmitters (brain-derived neurotrophic factor (BDNF), 5-hydroxytryptamine (5-HT)), metalloenzymes (matrix metalloproteinase-9) (MMP-9) and hormones (ghrelin) in the pathogenesis of mental disorders associated with stress under the impact of traumatic events.

**Materials and methods:** We conducted a systematic search of major electronic medical databases published before October 1, 2022. Such keywords as (post-traumatic stress disorder OR PTSD), (Brain-derived neurotrophic factor OR BDNF), (matrix metalloproteinase-9 OR MMP-9), (serotonin OR 5-HT), ghrelin, melatonin identified relevant studies. All articles were reviewed, including original studies, systematic reviews and meta-analyses.

**Conclusions:** Unfortunately, the imbalance of neurotransmitter systems of the brain remains not fully understood under such a condition at this stage of world science development. Their role remains unclear both during the immediate exposure to the stress factor and in the remote period. Therefore, understanding the mechanisms underlying the systemic consequences of PTSD is crucial for the development of prediction models and timely rational therapy.

**KEY WORDS:** posttraumatic stress disorder (PTSD), neuroplasticity, oxidative stress, brain-derived neurotrophic factor (BDNF), 5-hydroxytryptamine (5-HT), matrix metalloproteinase-9 (MMP-9), melatonin.

## INTRODUCTION

Participation in battles, being in a combat zone, physical injuries, pandemics, loss of the loved ones, housing and work, becoming a hostage, refugee, complete uncertainty of one's situation combined with the inability to predict the future create dramatic social circumstances that have a significant psycho-traumatic effect on people and, as a result, the body's reaction from a general adaptation syndrome turns into a pathogenetic factor [1-3]. Special attention is needed for people with already existing psychological and mental disorders, or with such past diseases the burden of which has a direct impact on the current state of their functioning on the background of current events [4].

Traumatic events are common worldwide, but comprehensive population-based cross-national data on the epidemiology of post-traumatic stress disorder (PTSD) as a trauma-related psychiatric disorder are not sufficient. The peculiarity of this disorder is the tendency not only to not disappear over time but to become more pronounced, to appear suddenly against the background of general well-being. In addition, according to the scientific data, it is this disorder that determines the violation of regulatory mechanisms in the central nervous and neuroendocrine systems. It should be noted that the level of PTSD is primarily related to personal and situational

anxiety, psychopathological parameters, expressiveness of depression symptoms, and socio-demographic characteristics [2]. Epidemiological data on the incidence of PTSD vary significantly depending on various factors such as the nature of the psychological trauma, gender, age of the examined groups, socio-cultural characteristics, the level of education, etc. The international lifetime prevalence of PTSD is 3.9% in the general population and 5.6% among adult civilian injured individuals.

According to the results of large-scale epidemiological studies conducted in the USA and Australia, the incidence of PTSD is 9–15% among adults who have been exposed to traumatic events. In the USA, in the course of epidemiological studies, PTSD was found in 15% of male veterans and 9% of female veterans who had participated in combat operations [5].

Lim I.C.Z.Y. et al. conducted a systematic review of publications from January 1, 1945 to May 31, 2022, on the MEDLINE (PubMed), Web of Science, PsycINFO, and Embase platforms to study the prevalence of symptoms of depression, anxiety, and PTSD in both civilian and military populations exposed to war. Having conducted meta-analysis, they found that the combined prevalence of depression, anxiety, and PTSD in the general population that had experienced conflict or war averaged 28.9, 30.7, and 23.5%, respectively. The same researchers indi-



cated a significant difference in the levels of depression and anxiety, but not PTSD, between the civilian group and the military group, respectively (depression 34.7 vs. 21.1%,  $p < 0.001$ ; anxiety 38.6 vs. 16.2%,  $p < 0.001$ ; PTSD: 25.7 vs. 21.3%,  $p = 0.256$ ) [6]. Thus, this is another confirmation of the fact that PTSD problem affects not only military personnel who took part in combat operations, but the civilians as well.

The problem of the emergence and mass spread of acute stress disorder (ASD), adjustment disorders (AD) and PTSD development has become acute in Ukraine on the background of full-scale military operations. This is particularly peculiar to family members of military personnel, volunteers, witnesses, and participants in rescue operations. Refugees and civilians who found themselves in the area of hostilities make up a separate category: the average prevalence of PTSD can reach 30.6% according to the scientific data [1, 7]. We should not forget about children who are affected by emergencies in the same way as adults. As a result, it is more difficult for such children to socialize, adapt to new living conditions and learn. Scientific data show that 53.5% of children who have survived military operations have anxiety disorders; 76.7% have anxiety when separating from their parents; 5.9% of such children have PTSD. Thus, mental health during military conflicts is a problem that cannot be neglected, and appropriate assistance provided to risk groups can contribute to decrease in the prevalence of the above disorders.

In addition to the above mentioned, it is also important to consider that 85-88% of men and 78-80% of women with PTSD had concomitant psychiatric diagnoses according to the results of two large epidemiological studies conducted in the USA and Australia.

Despite the debilitating nature of PTSD, unfortunately, many people with the disorder do not seek treatment in time, and do so only after symptoms have been present for a long period of time. At the same time, the experience of trauma becomes central in a person's life, changing his or her lifestyle and functioning [8]. The reason is partly that the clinical-pathogenetic complex of PTSD is multi-staged. Negative psychological, social and other manifestations that depend on the direct impact of stress factors come to the fore. They are replaced by the new, "secondary" problems such as physical, psychological, emotional suffering, aggressiveness, addictive behavior, and various types of addictions. They are related to the clinical manifestations of PTSD itself rather than to stress factors. And only later, at the third stage of this clinical-pathogenetic complex, a detailed clinical picture of stress-induced pathology appears.

In the USA, where services are more accessible than in most countries, only about half of those with PTSD seek treatment, and only 58% of those who seek treatment receive help from a mental health professional. It should be noted that the number of treatment requests in high-income countries (53.5%) was approximately twice as high as in low-income (22.8%) and above-av-

erage (28.7%) countries. Victims develop fears, phobias, anxiety-depressive disorders, and psychosomatic disorders. In addition, various somatic symptoms occur on the background of PTSD much more often than in patients without this disorder. According to Morina N et al. (2018), social disadvantage, together with young age, female gender, loneliness, lack of education, low family income, and unemployment was associated with an increased risk of PTSD [8]. Available scientific literature provides relatively little information on the situation on this issue. Currently, relevant studies on PTSD prevalence in Ukraine are insufficient. However, the study conducted in 2016 involving 2,203 internally displaced persons from Donetsk and Luhansk regions found that 27.4% of participants (31.1% of women and 19.6% of men of total) suffered from PTSD, making the study of this disorder particularly relevant in today's Ukrainian realities.

### AIM

The aim was to study the role of certain neurotransmitters (brain-derived neurotrophic factor (BDNF), 5-hydroxytryptamine (5-HT)), metalloenzymes (matrix metalloproteinase-9) (MMP-9) and hormones (ghrelin) in the pathogenesis of mental disorders associated with stress under the impact of traumatic events.

### MATERIALS AND METHODS

We conducted a systematic search of major electronic medical databases such as PubMed, Scopus, Web of Science, and Google Scholar published before October, 1 2022. We reviewed the studies on serum levels of BDNF, MMP-9, serotonin, ghrelin and the feasibility of adding melatonin to standard treatment regimens as a possible therapeutic intervention in diseases associated with disorders of their secretion in patients with PTSD. Such keywords as (post-traumatic stress disorder OR PTSD), (Brain-derived neurotrophic factor OR BDNF), (matrix metalloproteinase-9 OR MMP-9), (serotonin OR 5-HT), ghrelin, melatonin identified relevant studies. All articles were reviewed, including original studies, systematic reviews, and meta-analyses. Studies with reported conflicts of interest and results presented in the popular media rather than in peer-reviewed journals were excluded.

### REVIEW AND DISCUSSION

The development of stress is based on the evolutionary mechanism of runaway or fight. The need for oxygen, glucose, fatty acids, minerals and vitamins participating in the formation of energy increases sharply at this stage. The brain stimulates the release of various hormones and neurotransmitters at the beginning of the stress factor action regardless of the type and strength of the stress [10]. Neurobiological factors involved in PTSD include the monoamine system activation, changes in the neuroendocrine system, and dysregulation of the hypothalamic-pituitary-adrenal axis [11]. In addition to neurotransmitters imbalance affecting mood and cognition, extreme oxidative stress and inflammation occur in case of PTSD.

PTSD neurobiology is not fully understood. In recent years, the concept of neuroplasticity of the central nervous system (CNS) has been formulated, i.e. an extraordinary property of nervous tissue for structural and functional reconstruction and restoration of lost neural connections in case of their damage [9]. The main players in the multilevel system of neuroplasticity processes regulation are neurotransmitters, in particular, brain-derived neurotrophic factor (BDNF) and serotonin - 5-hydroxytryptamine (5-HT) [10]. Martinowich, K et al have confirmed scientifically that BDNF-serotonin-ergic interaction occurs in case of anxiolytic disorders [12]. According to the scientific data, BDNF can influence neurotransmission and neuroplasticity through NMDA receptors. Neurotransmission and neuroplasticity are important for the extinction and consolidation of fear memories, thus becoming a trigger for the development of certain mental disorders [13].

There is a hypothesis that states that the increase in BDNF activity under the influence of external factors is a protective reaction of the body to stress, a compensatory reaction serving to increase the probability of an individual's survival, soften their reaction to fear and prevent PTSD development. Thus, the violation of endogenous BDNF activity increases sensitivity to stress and, as a result, vulnerability to stress-induced diseases [14]. This is supported by isolated scientific studies among US Army soldiers who fought in Iraq, suggesting that BDNF levels are likely to increase dramatically during the acute stress response. Unfortunately, data on the dynamics of this indicator in the period of remote consequences are limited. Sandra Domitrovic Spudic and co-authors investigated that veterans with PTSD had significantly lower plasma BDNF concentrations and worse cognitive performance [15]. The experimental data of Baranova KA and co-authors confirmed that insufficient expression of BDNF reflected a maladaptive response to severe stress and may be a basic component of both depression and PTSD development. On the basis of meta-analysis, Mojtabavi H et al. concluded that PTSD patients had higher BDNF levels compared to controls. In their study, they evaluated data from 20 carefully selected articles that collectively included data on 909 participants diagnosed with PTSD and 1,679 controls without PTSD [16]. In their experimental study, Sun H et al suggested that epigenetic signatures of BDNF genes may be associated with stress response, providing relevant information on the risk of developing psychopathologies [17]. The discovery of Bilc M I and co-authors indicates that susceptibility to stress is significantly increased under conditions of a single nucleotide polymorphism Val66Met of the BDNF gene, in particular in children, with a long-term effect on the regulation of emotions, as it increases the intracellular processing of the peptide and leads to a decrease in the secretion of BDNF [18]. An important finding by Dimitriadis, M, et al. (2019) is that the receptivity of the neurotrophic system can be permanently reduced ("dulled") by childhood trauma [19]. Diniz D.M. et al.

(2021) conducted experimental work on animal models to study the basic molecular mechanisms of depression in humans. They confirmed that the behavior of their subjects changed under the influence of regulation of BDNF expression. The testing results showed that the increase in BDNF expression in rats contributed to a positive behavioral result: an increase in their mobility and interaction, a decrease in the manifestations of loneliness, and an increase in the time they spent in the center of a new environment. Thus, these scientists considered increase in BDNF regulation as a potential target for new therapeutic approaches to improve depressive symptoms [20]. In this regard, several experimental studies have examined the effect of melatonin administration as a possible therapeutic intervention in case of diseases associated with disorders of BDNF secretion. In particular, some studies have shown that melatonin administration can significantly improve serum BDNF regulation levels [21]. Increase in the level of circulating melatonin in the body has been experimentally proven to affect inflammatory and neurotrophic factors, to have a positive effect on cognition, to control circadian rhythms, and to relieve schizophrenic symptoms, to have an antidepressant effect by exerting a protective action on the prefrontal area of the cerebral cortex and reducing neurotoxicity [21]. The exact physiological significance of melatonin high levels in the CNS is unknown, but it is likely to protect neurons and glia from oxidative stress and inflammation, as well as stimulate the formation of new neurons [23-25]. In addition, melatonin regulates the expression of genes that synthesize such antioxidant enzymes as glutathione peroxidase and superoxide dismutase.

While studying mental disorders related to stress, scientific researchers also considered possible dysregulation and resistance of the ghrelin system in patients with major depressive disorder (MDD) and PTSD [26]. Certainly, the phenomenon of central resistance to ghrelin in case of chronic stress requires intensive study in order to establish appropriate neurobiological correlates. Yong-Hong Li and co-authors indicated that low ghrelin levels contribute to a decrease in BDNF levels and impaired cognitive functions in case of depression [27]. The mechanisms by which stressors affect circulating ghrelin remain understudied. While some experimental studies suggest that ghrelin as a stress hormone exerts anxiolytic and antidepressant effects, reducing fear, anxiety and depression in rodents, others hold the opposite opinion [28]. Unfortunately, the scientific evidence that ghrelin modulates fear-, anxiety-, and depression-like behaviors is mostly experimental, and human studies are sparse and inconclusive. However, at this stage of science, ghrelin is clear to be much more than just a "hunger hormone". It is important to note that ghrelin can inhibit the expression and activation of matrix metalloproteinase-9 (MMP-9), which is involved in several key processes in the development of the nervous system, namely in the maturation of inhibitory neurons, the perineuronal network, and the development of a specialized structure of

the extracellular matrix, synaptic shortening and myelination [29, 30]. In addition, the expression of matrix metalloproteinases is known to have a close correlation with oxidative stress, namely the degree of its manifestation, which determines the relevance of studying the state of the prooxidative-antioxidative system and the activity of MMP-9 in the examined patients [31].

The serotonergic system of the brain is also important. It takes an active part in various forms of behavior, in particular, the regulation of aggression which plays an important role in learning processes, namely, memory consolidation, and sleep regulation. In addition to its important role in mental processes by affecting the CNS, 5-HT also affects peripheral tissues. Stresses that cause PTSD-like conditions increase 5-HT expression. PTSD patients exhibit some serotonergic abnormalities including an exaggerated response to stress and typical features of serotonergic alteration such as irritability, aggression, impulsivity, and suicidality [32]. Thus, dysregulation of the 5-HT-BDNF interaction may be the cause of

neuropsychiatric and behavioral abnormalities development.

## CONCLUSIONS

Thus, PTSD is a trauma- and stress-related disorder with dysregulated fear responses and neurobiological abnormalities, particularly at the neurotrophic and inflammatory levels. Unfortunately, the imbalance of neurotransmitter systems of the brain remains not fully understood at this stage of the world science development. Their role remains unclear both during the immediate exposure to the stress factor and in the remote period. Therefore, understanding the mechanisms underlying the systemic consequences of PTSD is crucial for the development of prediction models and timely rational therapy. Only when the specifics of these indicators dynamics in the context of stress is better understood, it will provide an opportunity for early diagnosis of psychiatric disorders related to stress and will become a target for new interventions in their pathogenesis

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#### CONFLICT OF INTEREST

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# METHODS FOR DIAGNOSING DENTAL CARIES LESIONS

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## ABSTRACT

Tooth decay (dental caries) commonly occurs throughout the world and is one of the most widespread infectious diseases of lifestyle, globally affecting all age groups; up to 90% schoolchildren and almost 100% adults in both developing and developed countries. When left untreated, it can lead to disease outbreaks resulting in adverse health and life-threatening conditions such as endocarditis or sepsis. Undoubtedly, basic measures are thus required in both dental and GP practice to ensure that dental caries are detected early. This article presents the various diagnostic methods used to identify these disease outbreaks.

**KEY WORDS:** dental caries, diagnostics

## INTRODUCTION

### DIAGNOSTICS OF DENTAL CARIES

Oral disease poses a serious burden to human health and is a serious issue facing the world's population. The most common types occurring are tooth decay, periodontal disease and oral cancer that are largely due to the presence of microorganisms that variously bear pathogenic potential. There is therefore a need for them to be quickly identified and to detect changes so that progression of such oral diseases becomes limited.

Any dysbiosis in oral microorganisms leads to profound morphological changes in oral tissue structure as compared to normal conditions. A major cause of periodontitis is the colonisation of subgingival plaque by pathogens such as *Porphyromonas gingivalis*, causing microbial dysbiosis. It is also observed that components of gingival fluid, such as infiltrating inflammatory cells and tissue degradation products, greatly vary between people with and without inflammation. Changes in the microbiome and components of saliva and tissues can thereby be used as markers in studies on oral diseases, whilst Raman Spectroscopy can be considered a promising diagnostic method for their detection [1].

Dental Caries is the most common diagnosis made in oral disease at all ages. This is a disease of affluence (lifestyle/civilisation) and occurs throughout the world. Its status can be assessed by the Decayed, Missing and Filled Teeth index (DMFT) used to characterise both the extent of its prevalence and treatment requirements arising from disease progression. Although dental caries is recognised to be a globally widespread disease, its epidemiology is different in many countries and depends to what extent preventative measures have been adopted to try to effectively combat this disease over recent decades.

Poland is one of the few European countries where it has not been possible to reduce the incidence of dental caries in children, despite WHO recommendations for 2000 aimed at reducing the incidence of caries in 6-year-old children down to 50%. Indeed, the WHO recommendation for 2015 was to reduce such incidence down to 30% in 6-year-olds, (ie. to have 70% of 6-year-old children free of dental caries) [2].

It has been statistically estimated that a 12-year-old in Poland has 3.5 teeth affected by dental caries and that 40% of 18-year-olds have experienced losses to their permanent dentition arising from dental caries complications [3].

A study by Milewska et al. found that 87.6% of 6-year-old children had dental caries, whilst an incidence of 98.08% has been reported in 12-year-old children, with rates of 17.1% found in their permanent dentition (Fig. 1) [4].

Dental caries lesions have been shown to occur in over 40% of children aged 3 years and in 90% of those aged 18 [5], as reported by the latest epidemiological studies conducted under a Polish Ministry of Health programme entitled 'Monitoring the oral health of Poland's population during 2016-2020'. It has been proved that dental caries lesions present in children's primary dentition are the strongest predictor of risk in their developing dental caries later in life. If dental caries occurs in children under 3 years of age, then there is also a high probability of permanent tooth disease [6].

Previous studies have indicated an alarmingly poor health condition of children's teeth in Poland. Such findings significantly contrast to the status observed, not only in the originally established EU countries, but also in those EU countries undergoing systemic transforma-

tion like Poland. The figure below shows the prevalence and severity of dental caries in 6-year-old children in Poland in relation to other selected countries [7].

A significant decrease has been observed in the aforementioned epidemiological parameters following the latest cross-sectional study on oral health in Germany, (DMSV-Fünfte Deutsche Mundgesundheitsstudie), performed in 2016. For example, between 1997 and 2016, the number of children without dental caries had doubled at the age of 12 years (from 41.8% to 81.3%), and the DMFT index in young adults had decreased by 30% to 4.9%. Furthermore, the DMFT for 13-14-year-olds dropped from 4.9% to 0.5%. It is also interesting to compare different social strata, where even though the better off achieve slightly more favourable results, improvements in oral health have been demonstrated in all social strata. A similar comparison has been seen between the regions of the former East Germany and West Germany. Oral health has almost been levelled within three decades. This thereby demonstrates how effective the preventive programs used in Germany are, and the usefulness of such a pro-health policy which promotes education, prevention and in rewarding patients when they are partially responsible for their own health [8].

One part of the pro-health German prevention system is to encourage patients to have twice yearly check-ups up to 18 years age and thence on once yearly. Patients meeting these criteria can not only count on having any pathological processes being thus detected early, but they can also benefit by being reimbursed if any treatment would be required.

A fundamental part of any dental examination of the oral cavity is in diagnosing dental caries. The most common method used is a medical examination, with a probe, under adequate lighting and with the benefit of a dentist's personal experience (dentist's eye). This is a simple and quick method for determining whether teeth are healthy which does not incur any large financial outlays, but are subject to inherent disadvantages in such procedures. A frequently used manoeuvre to support any diagnosis is X-ray diagnostics that increases the sensitivity and specificity of this procedure, however the patient is inevitably exposed to ionising radiation and in bearing the increasing costs such examinations. The price for the patient ranges, depending on the method, from a dozen to about 100 PLN, whereas purchasing the diagnostic instrument would cost from 30,000 to 250,000 PLN.

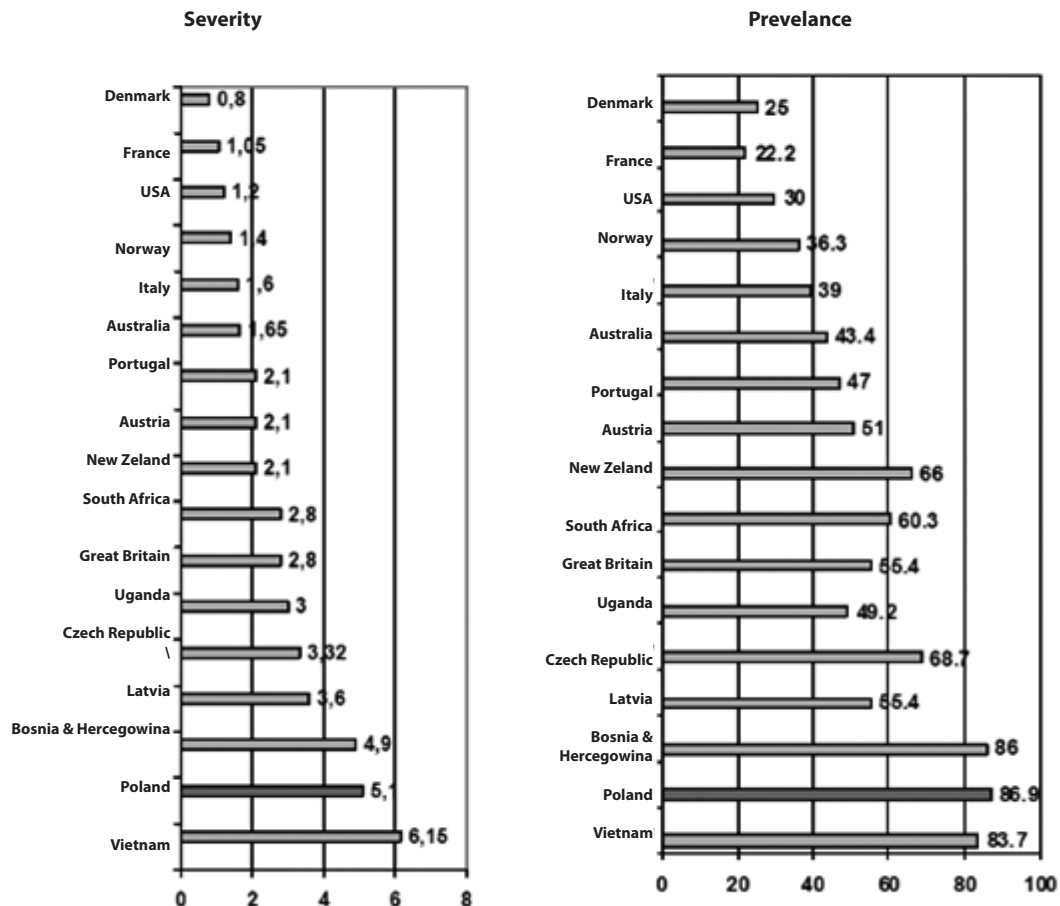
Although this is the working equipment now used as standard-practice for the majority of dentists, it may still represent a limitation at smaller dental centres. Computed tomography examinations are much more expensive. Although they are not part of the standard diagnostic process for detecting dental caries, they are used in dental surgeries that possess more advanced procedures. Such services cost the patient from about 250 PLN, whilst buying the diagnostic instrument would cost several hundred thousand PLN.

An alternative to radiological examination is to use the techniques of transluminescence and fluorescence, for example that are present on-board the KaVo Diagnocam instrument. Exposure to X-rays, can thus be avoided which allows pregnant women to have their teeth diagnosed by these means. The higher cost of the Diagnocam procedure appears to be offset by its non-invasive nature and it can also be validated during checking. A problem is however that false positives and incorrect conclusions can arise due to a lack of operator experience. There are also additional costs that must be considered for patients and, of course, doctors. The instrument costs around 30,000 PLN and not forgetting that it requires installation into dental units. These facts would thereby indicate an association between higher expenditure on diagnostics with increased effectiveness in the early detection of dental caries. However, this is only one of the aspects that determine how successful the outcomes are of prevention policy. In Poland, dental health care was and still is largely in the private sector, which means that the burden of paying for treatment rests with the patient. In Germany, a large part of available dental health services is free of charge to the patient and therefore the payer is the state. It is hardly surprising then, that the government (ie. payer) and health care regulator are interested in reducing the cost of treatment, thereby also increasing the role of pro-health prevention as being the cheapest form of treatment. Transferring this responsibility to patients in a system in which they themselves have to fully pay for it is, in authors' opinion, a very difficult task and explains why the set goals in reducing dental caries in Poland has proved unsuccessful.

Dental Caries is a localised pathological process caused by exogenous factors leading to decalcification of hard tooth tissue layers, followed by proteolytic decomposition of the thus exposed soft tissues. In Poland, it is diagnosed in over 85% of preschool children, including about 54% of 3-year-olds. The main contributing factors are an improper diet, lack of hygiene and an excess of microorganisms residing in the oral cavity, particularly *Streptococcus mutans* and *Streptococcus sobrinus* [9, 10]. These oral streptococci act on any available sucrose and produce tooth plaques containing water-soluble and water-insoluble extracellular polysaccharides called glucans (dextran and mutan) [11, 12]. When these bacteria enter the bloodstream, they can reach distant organs causing, *inter alia*, disease outbreaks. By such means, infections often arise in the joints, kidneys or heart as well as recurrent colds, pharyngitis and a slowing down of the healing process [13-15].

Research efforts should thus be focused on methods of prevention, including early detection of the first demineralization lesions. The most popular methods that can be employed at any clinic are the visual-contact method, X-ray image analysis and measuring tissue fluorescence [16].

Dental caries can be detected, usually at its certain stages of progression by basic diagnostic methods, such



**Fig. 1.** The severity and prevalence of dental caries in 6-year-old children in Poland compared to other selected countries.

as intraoral examination with a mirror and probe, along with radiography. An early diagnosis enables remineralization treatment to be given without the need for mechanical intervention to the tooth tissues. In order to avoid invasive treatment, attempts have been made to use various physical phenomena for diagnostic purposes. These methods are based on light absorption and conduction, conductivity and electrical resistance, fluorescence or reflections of ultrasonic waves [17].

### AIM

To review methods and techniques currently available for the early detection of dental caries outbreaks.

## REVIEW AND DISCUSSION

### OPTICAL METHODS

#### BASIC DIAGNOSTIC TOOLS

The oldest, but so far the most popular method for diagnosing dental caries is by visual inspection of the condition in tooth tissue. This is performed according to ICDAS II criteria (International Caries Detection and Assessment System) [18]. However, diagnosing dental caries using a probe and a mirror is not without its draw-

backs. It is a subjective procedure based on the experience and skills of the examiner. Diagnosis can be greatly facilitated with the aid of magnifying glasses or a microscope, which are able to magnify the viewed area by up to 20 times. It is however difficult to determine the extent to which the condition has developed within time and to plan an effective method of management/treatment or remineralisation. This method only detects fairly advanced lesions. It is also worth noting that even small white spots can reflect surface instability which, when probed, can lead to the destruction of the enamel structure and prevent non-invasive treatment [16].

#### TRANSLUMINESCENCE

This method increases the effectiveness of intraoral examination. Illuminating the tooth with cold light using the fiber optic technique enables the sensitivity of intraoral examination to become closer to the X-ray method, however its specificity remains at a lower level [19].

#### X-RAY DIAGNOSTICS

X-ray diagnostics, especially those digital, allow diagnostic capabilities to be significantly extended and

the use of digital image processing makes dental examinations more effective. In order to detect dental caries, intraoral bitewing and adjacent X-rays are taken as well as extraoral panoramic radiographs. Many authors however question the effectiveness of the latter. Even though taking X-rays increases the effectiveness of dental caries detection, it is still an ineffective tool for occlusal surfaces as it only shows advanced defects, nevertheless it is more useful for investigating proximal surfaces [20, 21].

The initial demineralisation as seen as a white spots are however imperceptible on an X-ray image [22]. When diagnostics are performed by both a probe and X-rays then the sensitivity and specificity are respectively 49% and 87% [23], which means that about half of the early lesions are undetectable and that dental caries was found in 13% of healthy teeth. In addition, ionising radiation adversely affects the human body. Because both methods have insufficient sensitivity and specificity, they are unable to describe/estimate how the dynamic process of re- and demineralisation develops [24]. This process cannot therefore be quantified by such means.

#### *ELECTRICAL CONDUCTIVITY*

Another diagnostic method is based on electrical conductivity (EC). Any material, including biological, possesses specific properties that define the flow of current. When the impedance of test tissue with a healthy standard is compared, then deviations from the norm can be detected. The porosity of the enamel increases in dental caries, resulting in increased amounts of fluid and electrolytes within this tissue which is reflected by increased conductivity but decreased resistance, thereby enabling dental caries to be diagnosed.

The first EC method is based on an ECM-electronic cars monitor using alternating current at a constant frequency of 23 Hz. The electrode applied to the tooth is in the shape of a probe / dipper, whilst the other is held by the patient. It is possible to test the point resistance or the impedance of the entire surface. Despite promising experimental results, physical factors such as tooth temperature [25], tissue thickness and hydration may affect the quality of the obtained data [26]. There are also doubts in assessing the advancement of lesions; it is not known whether total or partial surface porosity is being measured, whether the depth of defects is important nor whether their morphological complexity affects electrical conductivity. The ECM technique however gives hope that the effectiveness of dental caries diagnostics could be increased, but this requires further laboratory and clinical testing (Fig. 2).

Another instrumental technique that uses EC is EIC-Electrical Impedance Spectroscopy where an output series of current frequencies are scanned, that allows capacitance and impedance to be measured. This procedure enables a more accurate analysis of data and diagnosis of both the presence and the extent of dental caries lesions to be made [28].

#### *LIGHT SCATTERING*

A different analytical concept used for diagnosing dental caries is based on light scattering. Densely packed hydroxyapatite prisms, from which healthy enamel is built, create an almost translucent structure. Demineralisation becomes manifest as porosity forms, which causes spaces filled with air to occur that possess a completely different refractive index. Into these places, photons scatter (changing direction, without losing energy), and are seen as white spots. FOTI-fiber optic transillumination enhances this effect by using high-intensity white light, transmitted to the tooth via an optical fiber. Radiated light scattering disturbances are visible as shadows (Fig. 3 a-b).

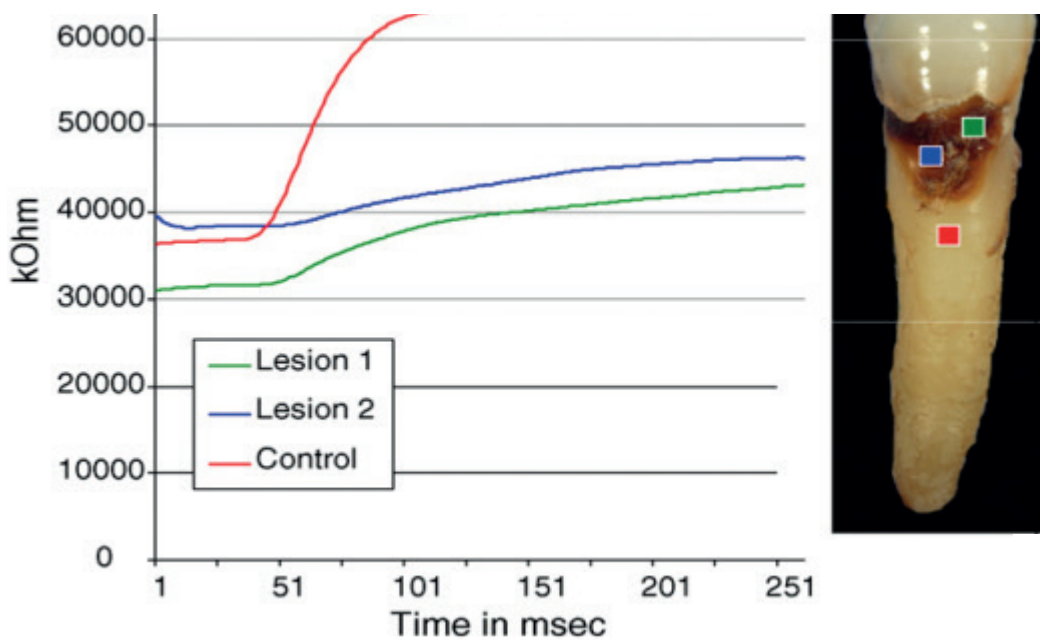
This method is simple and relatively inexpensive, however assessing the results is subjective and there are insufficient studies that confirm its effectiveness, along with there being no way to record the results. DIFOTI, (Digital Imaging FOTI) allows diagnostic images to be recorded by computer, that permits the progress of dental caries to be compared and evaluated. There are however still no objective tools for evaluating images, and a subjective assessment needs to be carried out by the investigator.

#### *FLUORESCENCE*

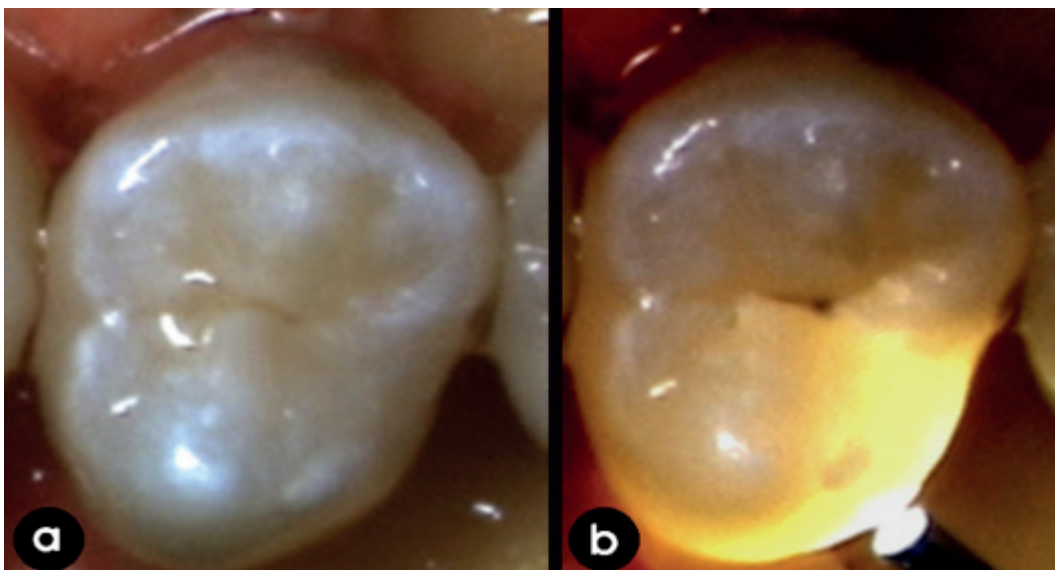
Fluorescence occurs when light is emitted from an excited atom or molecule. This emitted light has a longer wavelength than the excitation light, arising from the principle of the conservation of energy. In applied dentistry, Quantitative Light-induced Fluorescence (OLF) uses visible light with a wavelength of 370nm, lying within the blue part of its spectrum. The resulting fluorescence is recorded by an intraoral camera at a 540nm wavelength range. The filtered radiation gives red and, above all, green light, which is characteristic of enamel. Demineralisation reduces the amount of fluorescence, which is calculated by the appropriate on-board software. The decreased fluorescence is highly correlated with enamel demineralisation, as confirmed by previous studies. Teeth fluoresce as a result of the enamel-dentine connection (EDJ), which contains fluorophores. A decreased intensity of fluorescence when decalcification occurs is due to the increased porosity of the enamel, because the light falling on the EDJ is scattered earlier and thus causes less excitation of the fluorophore molecules. Furthermore, the resulting radiation is once again scattered away, which in turn reduces the fluorescence [29]. An advantage of this technique is that images can be saved, thereby allowing comparisons to be made at subsequent follow-up visits and that the progress of dental caries can be objectively monitored/evaluated.

Specialised on-board software allows the surface of the examined tooth to be analysed and a 5% fluorescence reduction is qualified as evidence of demineralisation. By setting a 5% threshold, the computer recalculates the total healthy and demineralised area (as pixels) into deltaQ values and calculates the %deltaF fluores-





**Fig. 2.** An example of the ECM (electronic dental caries monitor) when used for diagnosing dental caries [27].



**Fig. 3.** An example of FOTI used for diagnosing caries: (a) a tooth image without signs of caries and (b), the same tooth illuminated by white light demonstrating a visible dental caries focus seen as a shadow [27].

cence loss. These two variables can be easily and objectively compared and serve as a good diagnostic tool (Fig. 4 a-b) [30].

#### LASER FLUORESCENCE

The DD-Diagnodent is an instrument that uses laser emitting light at a wavelength of 655nm lying within the visible light range. It does not allow any image analysis, but provides numerical values that describe an examined tooth surface. Fluorescence in this case is generated by porphyrins which are metabolites of cariogenic bacteria (Fig. 5). Despite some promising research outcomes, there is a tendency for false-positive results to be made, (due to the presence of plaque and calculus) [31],

which would thus raise questions as to the validity of using this diagnostic method in everyday practice [32].

The DIAGNOcam (KaVo) technology is based on irradiating teeth through gum tissue, bone or tooth roots using infrared radiation, (at a wavelength of 780 nm), which is scattered by dental caries tooth tissue.

Its efficacy is not dependent on how much teeth are cleaned from plaque or tartar and it is therefore more reliable than DD [25]. This test is also non-invasive and is body neutral as there is no emission of any ionising radiation so making it suitable for pregnant women. The method permits diagnosis of dental caries foci and it can detect secondary caries on all tooth surfaces, particularly on the occlusal and proximal surfaces of teeth. Ad-

ditionally, it is more accurate than X-raying interdental surfaces [16].

#### OTHER OPTICAL METHODS

There are also several other methods for diagnosing dental caries that are still being researched and experimentally developed. These include, inter alia, optical coherent tomography-optical tomography, (OCT) using partially coherent light emitted by, for example, a superluminescent diode and also near infrared imaging spectroscopy (NIRS); i.e. imaging with a laser emitting near infrared light. They enable a micrometer level of resolution to be achieved and penetrate into the tissues, scattering the light. The spectrum of scattered light allows an analysis that gives hope as a potentially viable method of detecting early dental caries lesions [34].

#### ULTRASOUND

Ultrasonography is based on sound waves penetrating through gases, liquids and solids and the scattering and reflections at the boundaries lying between them. Tissue images are created by collecting and analysing the reflected sound waves. So as the sound waves can reach the tooth surface, they must pass through a 'coupling' medium which in dentistry is water or glycerin. A small number of studies have demonstrated the effectiveness of this method, for example when an ultrasonic dental caries detector (UCD) is used [35, 36]. This holds promise, but does not yet confirm the effectiveness of the US method for diagnosing of dental caries lesions.

#### OTHER METHODS

Other diagnostic methods, such as Terahertz Pulse Imaging (TPI) or Time-Correlated Single-Photon Counting Fluorescence Lifetime Imaging (TCSPC-FLiM) are at present under preliminary development and are therefore not alternatives yet to the methods described above. Amongst the aforementioned methods described, optical techniques are the most promising. Tissue fluorescence analysis has already seen practical use in the form of the Diagnostent device by KAVO. As previously stated, studies have confirmed its effectiveness as a diagnostic tool, but however also suggest a tendency to give false positives.

#### SPECTROSCOPIC STUDIES OF TEETH

The technique of Raman spectroscopy is a latest attempt to find another technological application in dentistry in order to increase the effectiveness for making early detection and diagnoses of dental caries possible and to try to eliminate the errors/drawbacks inherent in previous methods. Raman spectroscopy is a type of scattering spectroscopy, based on a theory developed in 1925 by Kramers and Heisenberg; 'quantum-mechanical scattering theory'. The Indian physicist Chandrasekhar Venkata Raman then lent support to experimentally confirm this theory in 1928 but also in the process, discovered a new phenomenon related to the scattering of light. Thus, a new type of spectroscopy was created for which he re-

ceived the Nobel Prize in Physics in 1930 [37]. Raman microspectroscopy is a technique based on the Raman effect of measuring scattered radiation (Raman scattering, i.e. the inelastic scattering of photons). The spectrum of scattered light always demonstrates a strong line corresponding to the wavelength of the incident radiation and there are also weak satellite bands present that are symmetrically located on both sides. The strong line corresponds to Rayleigh scattering, whilst the weak bands are due to Raman scattering. The weak bands shifted away from the excitation line towards longer wavelengths are termed the 'Stokes bands', whilst those shifted towards shorter wavelengths, 'anti-Stokes bands'. For a given substance, the position of the bands is constant and independent of the frequency of the incident beam, thereby constituting a unique 'chemical fingerprint' of a sample. The intensity of the Raman bands is however much lower, as much as 10<sup>3</sup>-10<sup>4</sup> times, than that of the Rayleigh band. Furthermore, the intensity of the anti-Stokes Raman band is much lower than the Stokes band, and so Raman spectrometry, in most practice, measures Stokes bands more often [38]. Raman scattering occurs during the interaction of electromagnetic radiation with a molecule. Electromagnetic radiation has corpuscular and wave properties (particle-wave duality) and therefore the origin of Raman scattering can be described in two ways. The first is based on the classical theory of electromagnetic radiation (wave description), and the second is based on quantum theory (corpuscular description).

The classical theory of Raman scattering describes interactions between the electron cloud of a molecule and electromagnetic radiation that cause inelastic light scattering. The Raman effect is observed when there are changes in the polarizability of a molecule, which is defined as the ability of an electron cloud to move relative to atomic nuclei in an electric field. The radiation-induced vibrating dipole moment is proportional to the polarizability of the molecule. Whilst classical wave theory describes the basic mechanism of inelastic scattering, it does not explain the changes in the position and intensity of the scattering bands of the Raman spectrum. Quantum mechanics can explain these changes based on graphs of energy levels. Molecules at the basic vibrational mode (zero level  $v=0$ ) absorb energy, thus going into an excited state. When they relax, the radiation scatters and the molecule either returns to its initial state, by Rayleigh scattering, or to one of the higher energy vibrational levels by Stokes Raman scattering. Changes in the intensity of the bands occur due to the quantitative differences of the molecules in the excited and lowered energy states. At thermal equilibrium, the molecule population behaves according to the Boltzmann dispersion state and is mostly at the fundamental energy level. Statistically, there are more molecules occupying the lowest energy levels and are thus capable of transitioning to the virtual (apparent/excited) state from the ground state, compared to those from the excited state. Thus, the Stokes band is more intense than the anti-Stokes band and it is the latter that is most

often used in analysing Raman scattering spectra [39]. Many diagnostic methods are used to analyse biological material, some of which include Raman spectroscopy. Such methods enable studies with a spatial resolution of 0.6-1  $\mu\text{m}$  and obtaining such high spatial capacity allows microstructural levels to be analysed for which infrared absorption spectroscopy is unsuited; this being another spectroscopy based on vibrational levels. In contrast to the latter, Raman spectroscopy has negligible sensitivity to the hydration state of the examined tissues. At present, the latest Raman method systems enable most biological tissues to be studied using a laser operating in the visible or near infrared range of the analytical setup. Using the latter, this allows fluorescence-related effects to be eliminated in the obtained Raman spectra that interfere in the analysis of spectral bands [40]. Both Infrared spectroscopy and Raman spectroscopy allow changes in chemical structure to be captured as well as those arising from mechanical damage or genetic defects. The high resolution of the instrumentation, (of the order of 1  $\mu\text{m}$ ), can facilitate the collecting of information on chemical processes such as remineralization.

Such spectra are recorded images of radiation broken down into individual frequencies, wavelengths or energies and are most often graphically presented by the intensity of the Raman band as a function of frequency. Although the recorded spectra should be composed of many narrow lines corresponding to dispersed energy quanta, in reality they are not in the form of lines, but in bands of different intensity and width. These band forms are due to the imperfections of the instruments recording them, as well as to the different widths of the energy states (Fig. 6) [41].

The main parameters characterising a given band when used for studying the structures of particles, molecules or crystals are:

- frequency, corresponding to the maximum height of the tested band contour;
- intensity, being the height of the band contour as measured from the background level;
- half width, being the width of the band contour, determined at the middle of its height;
- integral intensity, being the area bounded by the band contour of the band and the background.



**Fig. 4.** QLF. (source: Inspector Research Systems BV) - a) tooth in daylight, b) tooth highlighted.



**Fig. 5.** The Diagnodent system (source: DD KaVo Dental GmbH).

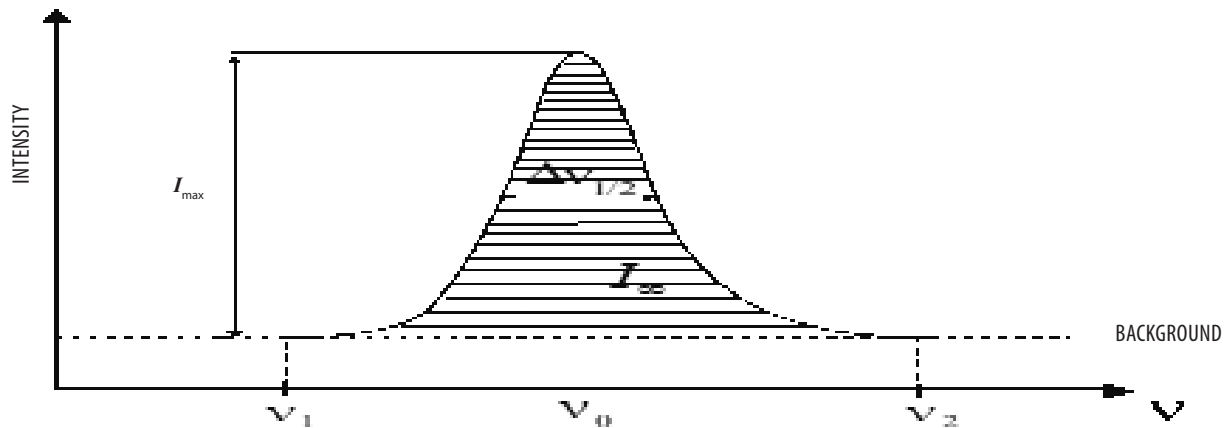


Fig. 6. A spectral band with descriptive parameters [41].



Fig. 7. Micro Raman system in Via (source: Renishaw).

#### THE INSTRUMENTAL SYSTEM FOR STUDYING RAMAN LIGHT SCATTERING

The classical study of Raman light scattering is performed by a spectroscope. In the case considered, a micro-Raman system is used equipped with the following elements:

- Excitation sources in the form of a laser.
- An optical system tasked with illuminating the sample, supplying excitation light and collecting the scattered radiation.
- A diffraction grating

- A diffuse radiation detector in the form of a CCD camera (charge coupled device).
- A signal recording and system control system (computer + specialised software) (Fig. 7).

Measurements with high spatial resolution at the micrometer level are made possible thanks to the confocal microscope on-board the instrument coupled with a measuring system, that allows the excitation light (laser) beam to be focused onto the test material, as well as collecting scattered light from a very small volume; in the order of several cubic micrometers.



### SPECTROSCOPY IN THE ANALYSIS OF ENAMEL

Thanks to Raman studies and infrared absorption, it is possible to characterise molecular tissue components, such as primary and secondary amides, calcium ions and carbonates, where the results serve as a framework for evaluating pathological changes within the tooth and its surface. Analysing selected Raman bands is particularly useful for distinguishing between healthy and pathologically altered teeth. Even subtle changes in the molecular structure of dental caries material (tissue) cause detectable changes in vibration states, as reflected in the spectral appearance of new bands, a changed location or changes in the intensity of those bands responsible for specific vibration states.

The recorded spectra show changes in the intensity of the bands in places associated with dental caries where there is increased background (increased intensity of Rayleigh scattering), a lack of structural order in the enamel damaged by caries, changed anisotropy of polarizability at the site of caries and increased carbonate to phosphate bands ratios at the lesion sites. Using many of these indicators, (like carbonate to phosphate band ratio intensities), confers on them the potential to be spectroscopic markers. Modern diagnostic methods must be harmless, easy to use, repeatable, capable of being archived and compared and inexpensive. Raman spectroscopy (RS) aspires to such criteria.

Although the first studies using Raman spectroscopy for dental examinations had already been done the 1960s, this technique was not extensively described in the scientific literature until almost the end of the 20th century; mainly due to the complexity and unwieldiness of spectrometers and fluorescence interference [42-53]. It was not until the NIR-FTR technique (near-infrared Fourier transform) had been developed, which eliminated the dominating background fluorescence, that interest in using RS revived for diagnosing dental caries at the end of the 20th century.

Raman spectroscopy enables vibrational spectra to be obtained of mineral structures by analysing the light scattered by a monochromatic laser. Molecular vibration bands can thereby be obtained of biological materials such as tooth enamel. When the positions of Raman bands are known that are characteristic for individual chemical groups, Raman spectra can be used for chemical identification and quantitative analysis [46]. It is therefore expected that Raman spectroscopy will not only be a tool to confirm the presence of caries but, above all, it will permit qualitative assessment of enamel and allow any early interventions to be made together with evaluating how effective preventive measures had been [55-57].

The present scientific literature describes the usefulness of Raman spectroscopy for detecting dental caries on the interproximal surfaces of molars and premolars that are difficult to clean [58, 59]. This paper presents the concept of using the above technique to assess the quality of enamel in the area of orthodontic brackets. However, the presence of orthodontic brackets and, above

all, any additional elements such as elastic chains, springs, hooks, additional intra- and extra-aural appliances makes it difficult to maintain oral hygiene. This is a new look at the diagnostic possibilities of PSR, and gives hope for avoiding any complications during orthodontic treatment.

### CONCLUSIONS

The driver behind the progress that has been achieved in medicine is the development of modern technologies.

New diagnostic capabilities has allowed a better understanding of disease mechanisms, to detect health threats earlier than before and treat them more effectively. The situation is similar in dentistry. Dental caries is nowadays still an unresolved problem, even though dental caries was described in ancient times, (mentioned in the writings of both Aristotle and Hippocrates) [60], and cavities had been found in homo-sapiens teeth since the time of Australopithecus. It is now so widespread that it deserves to be labelled a disease of affluence (lifestyle/civilization). According to the WHO, the DMFT index for 12-year-olds is 1.2-4.4 in developed countries whilst this is 9-13.9 for 35-44-year-olds [61].

In recent decades, the growing role of focal diseases in cardiology has become increasingly noticed.

Currently, mainstream orthodontic treatment for both children, adolescents and adults can lead to decalcification as a result of inadequate tooth cleaning, which initially manifested as white spot lesions (WSL). Numerous studies have pointed out the threat from WSL: Lovrov et al. at 25% [59], Panherz, Mühler at 29% [62] and Jost-Brinkmann at 17.5% [63]), whilst according to some the risk is even at 60.9% [64] or 72.9% [65]. Despite this wide range of results, it can be clearly stated that the risk of WSL is high and poses a serious health and aesthetic problem. The increased risk of dental caries requires the use of specialised prophylactic, diagnostic and therapeutic measures to ensure treatment safety, such as using preparations containing fluorine compounds, chlorhexidine, cetylpyridinium chloride or selenium.

Thanks to the high sensitivity of the new methods, it can be possible to intervene at early stages of demineralization and stop or even reverse the dental caries process. Preliminary results suggest that, in the future, it will become necessary to supplement diagnostic tools or even change procedural standards to thereby increase the effectiveness of detecting pathological changes. This would so allow principles of prophylactic treatment to be developed in patient care and possibly force through legislative changes [66].

Despite the promising outcomes of studies using the aforementioned diagnostic tools, objectively determining which one might prove to be the new diagnostic 'gold standard' remains elusive. Making any objective comparison on the effectiveness of the above methods is not possible at present, because most such studies were conducted in-vitro and any evaluation of results have, as yet, still not been standardised, thereby making a meta-analysis impossible to perform [27].

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# AUTISM SPECTRUM DISORDER AND SCHIZOPHRENIA – SIMILARITIES BETWEEN TWO DISORDERS WITH A CASE REPORT OF A PATIENT WITH DUAL DIAGNOSIS

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## ABSTRACT

This paper presents the genetic, molecular and neuroanatomical similarities between autism spectrum disorder (ASD) and schizophrenia using the case report of a 34-year-old female patient with a previous diagnosis of schizophrenia as an example. As a result of repeat hospitalization, expanded history, psychological testing and verification of persistent symptoms of psychopathology, a cooccurring diagnosis of autism spectrum disorder was made.

**KEY WORDS:** autism spectrum disorders, schizophrenia, neurodevelopmental disorders, iron triangle theory

## INTRODUCTION

In recent years, medicine has seen an increased interest in neurodevelopmental disorders. The consequence of which are numerous studies conducted on, among other things: the genetic, molecular, and structural base of the autism spectrum. Numerous similarities have been shown between the pathophysiology, symptoms or treatment of neurodevelopmental diseases and other psychiatric conditions. In the internationally valid ICD-11 classification of diseases, autism spectrum disorder (ASD) is referred to by code 6A02 [1]. In contrast, in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) classification of mental illnesses issued by the American Psychiatric Association, the term "holistic developmental disorder" has been dropped in favor of "autism spectrum disorder" compared to the previously applicable classification [2].

The diagnostic parameter for determining the severity of symptoms and daily functioning is a threetier classification. It takes into account consistent abnormalities in social communication and interaction, as well as limited repetitive patterns of behaviour, interest and activity. A prerequisite for meeting the diagnostic criteria is the presence of symptoms since early childhood. It is important to remember, however, that symptoms may or may not manifest themselves fully until social expectations exceed the child's limited capabilities [3].

## AIM

The aim of the study was to present a case report of the patient with dual diagnosis and to discuss similarities between ASD and schizophrenia.

## CASE REPORT

A thirty-four-year-old woman was receiving psychiatric treatment since she was 18 years old for adjustment disorder and since she was 25 years old for a diagnosis of paranoid schizophrenia. Since her last discharge from the psychiatric ward, she remained under medical supervision at the Mental Health Outpatient Clinic, where pharmacotherapy was administered: paroxetine, perazine and arypiprazole. According to her history - she took the prescribed medications irregularly, with significant interruptions in their use, which was most likely the reason for the exacerbation of her symptoms.

She came to the hospital emergency room due to an increase in psychotic symptoms: a sense of wobbliness, threat and agitation, additionally she reported insomnia. She was admitted to the psychiatry department. For the initial examination, during the hospitalization, the patient appeared without resistance, took the indicated seat and willingly entered into conversation with the examiner. She correctly provided personal information, the place where she was and the current date. She considered the reason for reporting to the hospital to be a feeling of confusion, as well as distraction, adding that she dreamed of love and marriage. During the examination she introduced numerous, multithreaded monologues, during which she talked about her ended, one-year marriage to a Pakistani man she had met over the Internet. She admitted that she had experienced psychological as well as physical abuse from her ex-husband. During the course of the interview, she remarked several times that she did not understand some of the questions, while asking for clarification "preferably in a way that she could



answer in the affirmative or negative." In an attempt to deepen the interview in the direction of manufacturing symptoms, she confirmed delusions of xenophobia and persecutory delusions ("sometimes I'm afraid someone will beat me up, like a certain couple I knew"). She reported problems with sleep, especially sleep maintenance. She described her appetite as great. During the examination, the patient's attention was drawn to the fact that she used full personal details with exact residential addresses including postal codes of the people about whom she spoke. In addition, she often cited the dates of specific past events. It should be added that she repeated the gestures and body movements of the examiner several times.

According to the interview, the patient's parents had been divorced for more than twenty years. The woman lived with her mother and her second husband. She had no siblings. She started her education on time, studied on average and did not repeat grades. She complained of problems making friends and experienced criticism and discrimination from peers for no apparent reason. She graduated with a bachelor's degree in two majors: history and pedagogy.

At the time of the study, the woman remained fully oriented, with no accompanying disorders of consciousness. Contact was significantly hampered by multitalking, multifaceted and excessively detailed statements. Both mood and drive remained level. Affect was described as pale, with its poor modulation. Possible delusional content required further verification. However, she denied hallucinations, thoughts and suicidal tendencies. The patient's criticism also remained ambiguous.

During hospitalization, the interview about the woman was extended with her parents. The father's attention was drawn to the woman's repetition of a given word several times, illogical statements, and a previously unseen need to take notes. In addition, he pointed to his daughter's infantile, naive behavior, accompanying from early childhood. The patient's mother also noted stereotypically repetitive phrases, which, according to her, had been occurring since high school. In addition, she claimed that the woman had isolated herself from her friends since childhood. Since high school, she noticed her daughter's problems with concentration and learning. She also added that she had never mastered the ability to handle basic household chores like laundry, cooking and cleaning. In addition, she noted her daughter's motor skills, which she described as corresponding to those of a 5-year-old child, but pointed out that she wrote English language essays at a level that stood out significantly from the class. The mother confirmed xobic and persecutory delusions, in addition to which her daughter was said to be accompanied by bizarre behavior in which she would spin in a circle while listening to music.

Somatic comorbidities of the patient included polycystic ovary syndrome. In the past, the patient had undergone surgery to remove her appendix and twice to

remove kidney stones. She had also been operated on for bowel obstruction. She denied head trauma with loss of consciousness, as well as diseases such as epilepsy, hepatitis and tuberculosis. She also denied smoking cigarettes, abuse of alcohol and other psychoactive substances. The woman made no suicide attempts and denied selfharm. Her family also had no record of mental illness or suicide.

During hospitalization, basic laboratory tests were ordered, the results of which remained within the age-appropriate norm. In addition, due to the suspected presence of neurodevelopmental disorders, a psychological consultation was coordinated, during which tests were conducted to determine the level of intellectual functioning. In the Weschler Intelligence Scale, the scores for the verbal, nonverbal and complete components remained at 78 points, verbal comprehension corresponded to 77 points, the level of perceptual organization showed 75 points, while the area of memory and resistance to distractors gave a score of 85 points. Based on the results presented, it was concluded that the patient functioned with 85% probability on the borderline of normal and mental retardation, as the functions tested were developed at a very low to average level. The patient scored best in the task measuring learning ability, while she scored worst during the task measuring visual perception and perceptual speed. In the area of factor scores, the woman functioned most poorly, as she was on the borderline of normal mental retardation, in verbal reasoning and perceptual organization. Memory and resistance to distractors were at below average levels. No difference was observed in the quotient of the verbal and nonverbal scales, which suggested a similar level of the patient's coping with verbal and nonverbal material. The result of the Benton Visual Memory Test suggested that fresh visual memory and perception were within the normal range for age. The result of the Connecting the Dots Test indicated a marked impairment in psychomotor speed and visual-spatial efficiency. The Roschach Test performed suggested features of stereotypy, rigidity, as well as underrated intellectual productivity. Moreover, the patient's interest in people and their lives was shown to be inhibited. The results made it possible to formulate conclusions about the intellectual functioning of the woman on the borderline between normal and mentally retarded. It should be noted that the psychogram of the test is not harmonious. Very similar results of the above test were also obtained by the patient during hospitalization taking place nine years earlier.

During her 29-day stay in the ward, pharmacotherapy with aripiprazole and perazine was continued, and agomelatine was additionally prescribed. Improvements in affect modulation and reduced disorganization were achieved. Over time, the patient was more willing to participate in therapeutic activities organized within the unit. Improvement was also observed in the quality and quantity of sleep. The woman continued to

speak in excessive detail and in multiple topics, but the topics taken up were discussed by her in a logical manner, accompanied by excessive, even fanatical interest.

The patient was discharged from the hospital in a good condition, with dual diagnosis (ASD and schizophrenia), with recommendation for periodic follow-up at the Mental Health Clinic.

## DISCUSSION

In the medical history of the 34-year-old female patient presented above, there were symptoms indicating a diagnosis of schizophrenia as well as ASD. The verbal stereotypy that accompanied the patient throughout her stay in the ward could be interpreted as a symptom of both schizophrenia and ASD. Excessive detail and multithreading, after verifying the authenticity of the content and ruling out its delusional nature, indicate a characteristics of ASD. It should also be noted the non-harmoniousness of tests determining the intelligence quotient, the patient's narrow, at times exaggerated interests, and the reduced level of fine motor functioning, which also supports the validity of the above diagnosis. The most important thing from the point of view of the diagnosis of neuro-developmental disorders seems to be the presence of symptoms of a possible disorder from the early childhood of the patient, which was also fulfilled in this case.

## GENETIC AND MOLECULAR SIMILARITIES BETWEEN ASD AND SCHIZOPHRENIA

Studies increasingly point to similarities between ASD and schizophrenia [4,5]. One example is reports from Japan, where the genetic material of patients with a diagnosis of schizophrenia and those on the autism spectrum, including a control group, was compared in terms of copy-number variants (CNVs). CNVs were found to be clinically significant in the region of 29 loci, which was common to both disorders. CNVs were reported in 8% of participants from both study groups, which significantly exceeded the occurrence of CNVs in the control group. In addition, phenotypic analysis showed an association between clinically significant CNVs and intellectual disability. Gene set analysis suggested significant overlap between biological pathways in both disorders, considering the importance of oxidative stress response, lipid metabolism and genomic integrity. In addition, genes have been identified: 22q11.2 or 3q29 - characteristic of both disease entities [6].

## IRON TRIANGLE THEORY

Noteworthy is the "iron triangle phenomenon," described in 2013 by Shorter and Watchel [8]. The phenomenon involves the cooccurrence of schizophrenia (usually manifested in childhood), the autism spectrum and catatonia. The "iron triangle" theory is based on the observation of a historical case series, which showed that all three diagnoses were routinely attributed to children and adolescents. The pattern in question sug-

gests the possibility of a common cause for each clinical entity. Cases where all three of the diagnoses discussed were observed have also been reported in contemporary literature [9].

## SIMILARITIES IN NEUROIMAGING BETWEEN SCHIZOPHRENIA AND ASD

Neuroimaging differences still do not form the basis for psychiatric diagnosis, but progress has nevertheless been made in characterizing the neuronal and structural dissimilarities corresponding to each disorder [17]. Studies indicate similar dimensions of the given neuroanatomical structures of the brains of patients suffering from ASD as well as those on the autism spectrum. The similarities include reduced volume in the cerebellum, the anterior cingulate gyrus, and increased size in the brain's ventricular system [18,19,20]. The literature points to changes within the functional networks that are responsible for processing complex cognitive features, which may condition similar dissimilarities in the dimensions of specific structures [17]. In addition, changes in the connectivity of neuronal networks common to ASD and schizophrenia have been observed. These included the balance network, frontoparietal network and default mode network (DMN) [20]. Other components common to the described disorders were distributed in frontal-parietal and limbic networks. Variations in thickness and area were observed within the same network, although not infrequently with different directionality of impulse propagation [21].

## SIMILARITIES IN THE PHARMACOTHERAPY OF ASD AND SCHIZOPHRENIA

A common group of substances used in the above disorders are antipsychotic drugs (LPPs). Both classical and atypical neuroleptics have been used to treat the irritability and aggression found in ASD. The first studies were conducted on haloperidol, which exhibits strong antagonistic effects against dopamine receptors. A reduction in aggression, psychomotor agitation and irritability was observed as a result of the substance, but dyskinesias, as well as dystonias, were reported after long-term use [29]. The introduction of selected atypical neuroleptics - risperidone and aripiprazole - into the pharmacotherapy of ASD proved to be a breakthrough, as they were the only drugs in this group to receive registration from the US Food and Drug Administration (FDA). Studies have shown that the use of risperidone had an impact on achieving improvements in overall functioning, aggressive behavior, emotional behavior and sensory hypersensitivity [30]. A newer drug with proven efficacy in ASD is aripiprazole, due to a different mechanism of action involving partial agonism to dopamine receptors, the substance causes less severe extrapyramidal symptoms than risperidone, although it is not without other side effects such as weight gain, fatigue, drowsiness, gastrointestinal abnormalities, and psychomotor restlessness [31].

## SIMILARITIES AND DIFFERENCES IN OTHER STUDIES

One of the leading etiologies of neurodevelopmental disorders as well as schizophrenia concerns pathology in the area of molecular components of postsynaptic density protein (PSD). A protein belonging to the aforementioned class - PSD-95 - is a major regulator of synaptic maturation. Expression of PSD-95 determines the interaction, stabilization and movement of N-methyl-d-aspartic acid receptors (NMDARs) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxo-azolo-propionic acid receptors (AMPA) to the postsynaptic membrane. There is evidence linking the cognitive and learning deficits observed in ASD and schizophrenia to abnormalities in PSD-95, involving significant differences in protein content and dysfunction. Moreover, the main function of PSD-95 is to participate in critical neurodevelopmental moments. In the future, further research on the aforementioned pathology may be a target in the pharmacotherapy of ASD and schizophrenia [7].

Fantozzi described an example is a 16-year-old Caucasian patient with no previous psychiatric treatment [10]. From early childhood, he presented symptoms characteristic of neurodevelopmental disorders, such as isolation, disturbed relationships with peers, and inflexible, stereotypical behaviour. In addition, the aforementioned disorders were accompanied by symptoms such as hyperactivity and impulsivity, inattention with persistent difficulties in organizing tasks, emotional dysregulation with excessive reactivity and irritability. The specificity of symptoms for neurodevelopmental disorders is confirmed by the level of intellectual functioning, which remained on the borderline between normal and mentally retarded. Note the patient's year-long history of marijuana use and facial trauma with multiple fractures in the facial bones. Several months after the aforementioned event, the patient presented with acute restless legs syndrome, as well as accompanying persecutory delusions, isolation, behavioral disorganization, disorientation, agitation and reversal of sleep and wakefulness rhythms. The third component of the psychopathologies presented are abnormalities characteristic of catatonia, such as incoherence, mutism, negativism, lack of facial expression, monotonous gazing at a selected point, failure to make eye contact and repetitive behavior [10].

There are theories that indicate that altered peer relationships occurring in association with ASD can become a substrate for the development of schizotypal personality disorder [11, 12]. Catatonia, schizophrenia and ASD, on the other hand, were for a long time considered variants of a single disorder [13-15]. It is now known that the pathophysiology for the aforementioned disease entities remains largely common. However, further research

is needed to determine the exact degree of correlation between the conditions in question [16].

Maternal immune activation (MIA) is induced by stimulation of inflammatory pathways, which leads to an increase in the levels of cytokines and inflammatory chemokines. The molecules cross the placental barrier and then the blood-brain barrier, which is not indifferent to the neural development of the fetus. MIA and other immune abnormalities are key etiological factors in neurodevelopmental disorders such as autism, schizophrenia, depression and attention deficit hyperactivity disorder. Epidemiological studies continue to investigate the relationship between maternal infection and high levels of cytokines in pregnant women and the likelihood of developing disorders [22]. Moreover, the literature reports a positive correlation between maternal pro-inflammatory molecules [IL-1a, IL-6, IL-8, interferon gamma (IFN-g), tumor necrosis factor (TNF-a), granulocyte-macrophage colony-stimulating factor (GM-CSF), C-reactive protein (CRP)] and an increased likelihood of ASD or schizophrenia [22]. Other studies point to dysfunction in neuronal connections produced by the amygdala [23, 24], frontal-limbic networks of the white matter [25], and cognitive abnormalities in the pediatric population [23-25].

Of particular note is the SARS-CoV-2 virus, which also conditions the development of MIA by activating proinflammatory cytokines [26]. Due to the relatively short period of time since the first recorded virus infection (2019), it has not been possible at this time to conduct studies that could determine the neurodevelopmental consequences in the offspring of mothers with MIA. Nevertheless, based on similar infections, a theory has been suggested that supposes a significant link between the occurrence of COVID-19 and neurodevelopmental diseases [27, 28].

## CONCLUSIONS

- Autism spectrum disorders share common features with schizophrenic disorders.
- Common abnormalities in CNVs and PSD-95 found in both disorders.
- Neuroimaging studies have noted similarities in the dimensions of specific brain structures.
- Common to ASD and schizophrenia are abnormalities in neuronal networks.
- One theory explaining the common features of the disorders is the iron triangle theory.
- Antipsychotic drugs such as risperidone and aripiprazole have gained registration in both diseases presented.

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# FIRST EXPERIENCE WITH OCCLUTECH PLD OCCLUDER TO CLOSE PARAVALVULAR LEAKS PROSTHETICS OF THE MITRAL VALVE. CASE REPORT

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## ABSTRACT

This clinical case presents the results of using the Occlutech PLD occluder for transcatheter closure of a paravalvular leak (PVL) via a transapical approach in the remote period after mitral valve prosthetics. According to our results and to the literature, the procedure for closing the PVL of the mitral valve from a transapical approach using a special Occlutech PLD occluder is characterized by relative safety for patients, clinical effectiveness in terms of eliminating or reducing the degree of regurgitation and related symptoms.

**KEY WORDS:** paravalvular leak, occluder, transcatheter leak closure, mitral valve.

## INTRODUCTION

The regurgitation of blood flow characterizes paravalvular leaks (PVL) through the gap between the surrounding myocardium and the structure of the prosthetic heart valve. Although PVL occurs rarely, it is considered a severe complication after valve replacement, as its occurrence increases morbidity and mortality [1,2]. The presence of a large PVL can lead to the development of heart failure due to excessive regurgitation, while leaks of small diameter can often cause hemolysis [3].

In general, PVL are found in 5-17% of patients undergoing prosthetic heart valves [4]. The majority of PVL is characterized by a benign course, however, clinically significant regurgitation and associated symptoms may be observed in 1-5% of cases [5].

At the same time, as reported in their study, Ionescu A. et al. PVL is more common after mitral valve replacement compared to aortic valve replacement [6]. In addition, after a number of examinations of defects with the prosthetic mitral valves, the authors showed that PVL develops more often as a late complication of valve replacement [6, 7].

Later, De Cicco et al. in the analysis of a series of patients cases who developed clinically significant PVL after mitral valve prosthetics, it was established that the risk factors of these PVL were calcification of the annulus, older age, the presence of endocarditis, an increase in the size of the atria [8], and renal failure [9-15].

A recent British study found that the median time from mitral valve replacement surgery to percutaneous closure of the PVL was 4.7 years. Based on the obtained data, the authors suggested that the late development of PVL may be associated with the decay of tissues or the late destruction of the suture material [16].

Today, due to the increasing experience of using various devices for the closure of PVL, percutaneous interventions are preferred, since open surgical operations can be associated with significant risk and mortality [17-21].

Moreover, surgical repair of the valve annulus, especially the mitral valve, is often ineffective: in the presence of loose tissue, fibrosis, and calcification from a previous infection, the affected annulus cannot be easily corrected, and the sutures do not remain stable, often leading to clinically significant paravalvular regurgitation [22].

Regarding the percutaneous correction of this paravalvular defect, given the anatomy of the mitral annulus, most PVLs have a crescent shape, and, as reported by Goktekin O et al., the Occlutech PLD occluder, produced in a rectangular shape, is well suited for their effective closure [23].

This clinical case actually presents the results of using the Occlutech PLD occluder for transcatheter closure of a paravalvular leak in the remote period after mitral valve prosthetics.

## CASE REPORT

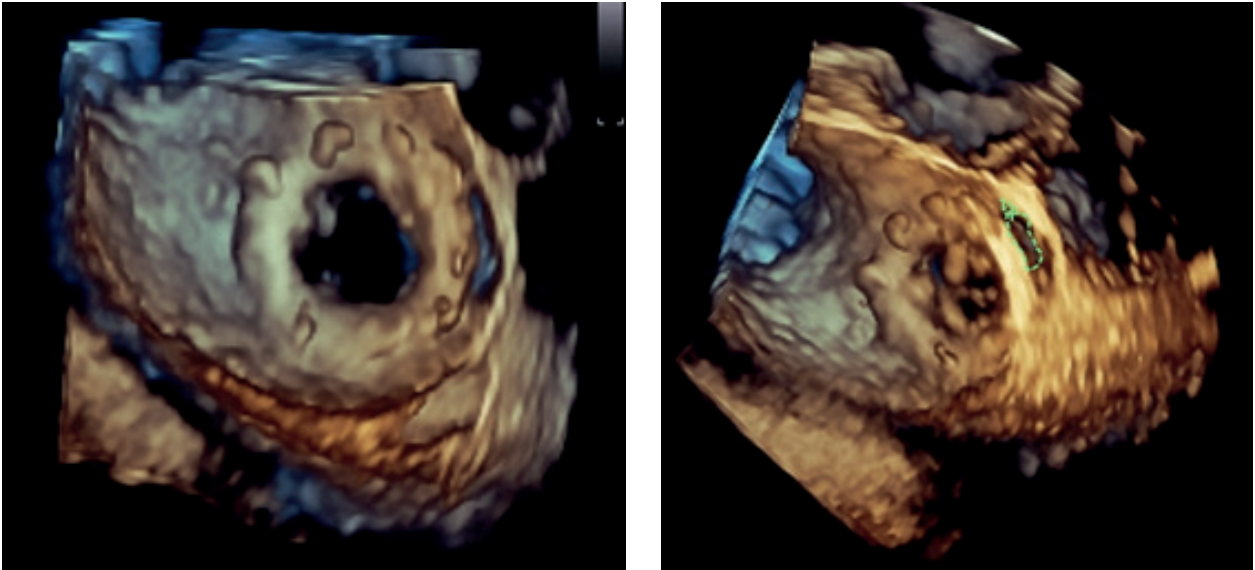
On November 26, 2020, a 68-year-old woman was admitted to the clinic of the State Institution "Ukrainian Health Ministry Heart Institute" with complaints of pronounced shortness of breath, a significant limitation of physical activity, and frequent cough with a small amount of sputum, pronounced weakness. These symptoms appeared within the last three months.

It is known from the anamnesis that in 2010, the patient underwent bioprosthesis of mitral valve (BPMV). At the time of admission: BP – 135/85 mm Hg., heart rate - 74 beats/min. On the ECG (November 26, 2020): sinus rhythm, without features. Echo-CG data (Novem-

ber 26, 2020): End-systolic volume - 24 ml, end-diastolic volume - 60 ml, left ventricular ejection fraction - 60%, systolic pressure in the pulmonary artery - 32 mm Hg., segmental contractility is preserved. Left atrium: diameter 5.4 cm, V max = 99 cm<sup>3</sup>, index 63 ml/m<sup>2</sup>, pronounced dilatation. The left ventricle, right atrium, and right ventricle are within normal limits. Mitral valve - prosthesis, maximum pressure gradient 8 mm Hg, paraprosthetic regurgitation ++(+). Aortic, tricuspid, and

pulmonary artery valves without features. According to the data of 3D-transesophageal echocardiography (3D-TEE) (November 26, 2020), a paraprosthetic mitral valve leak measuring 4.0\*5.0 mm was detected at 2:30 p.m., regurgitation ++(+), sharply eccentric along the atrial septum (Fig. 1).

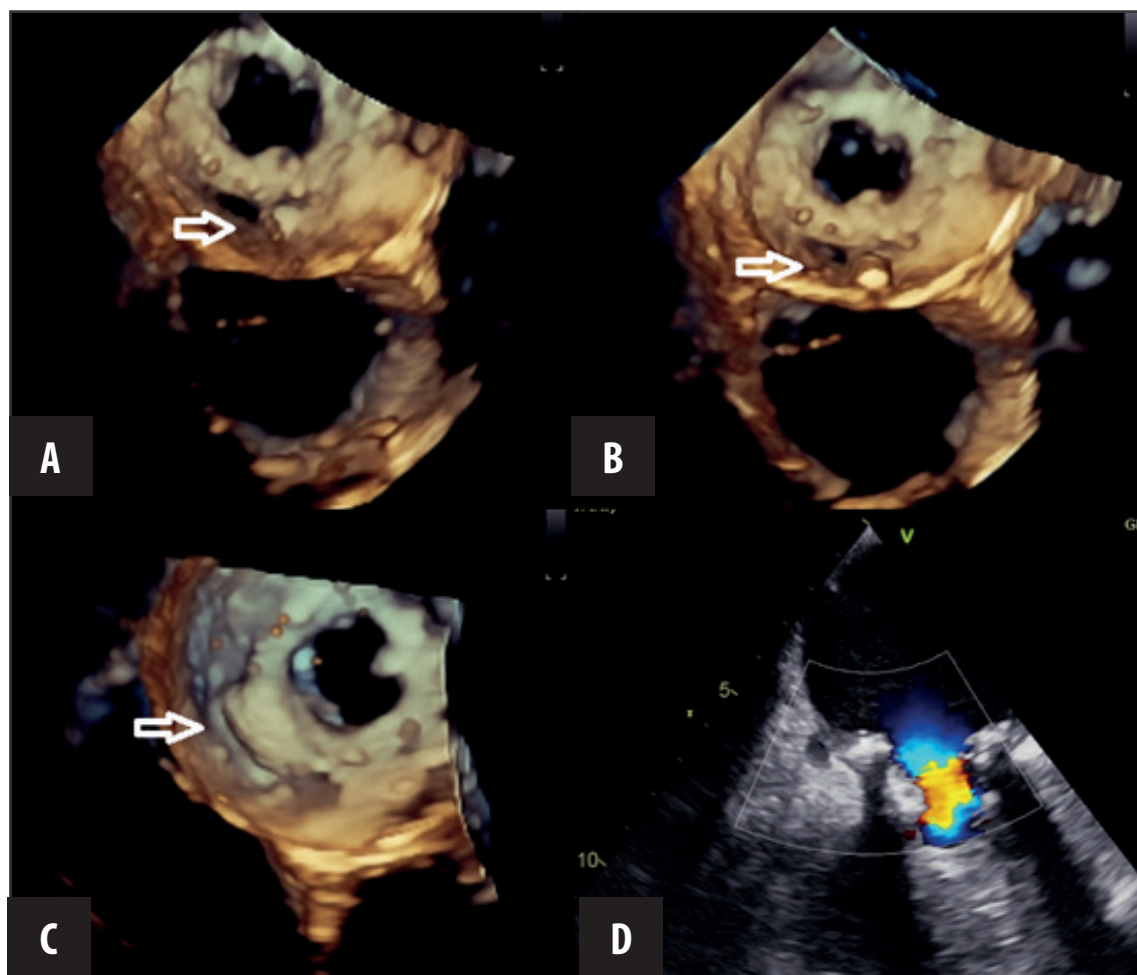
Clinical blood test (November 26, 2020): leukocytes - 12.7 \* 10<sup>9</sup>/l, erythrocytes - 4.14 \* 10<sup>12</sup>/l, hemoglobin - 108 g/l, platelets - 178 \* 10<sup>9</sup>/l, erythrocyte sedimen-



**Fig. 1.** 3D-transesophageal echocardiography (3D-TEE): paraprosthetic mitral valve leak measuring 4.0\*5.0 mm at 2:30 p.m.



**Fig. 2.** The top of the heart is exposed along the V intercostal space



**Fig. 3.** 3D-transesophageal echocardiography (3D-TEE): A) a hydrophilic conductor introduced through a paravalvular leak into the left atrium; B) a system of delivery to the left atrium through a paravalvular leak is established; C) deployed rectangular Occlutech® PLD paravalvular occluder; D) absence of regurgitation due to paravalvular leak.

tation rate – 6 mm/hour. Leukocyte formula: rod-nuclear granulocytes - 2%, segment-nuclear granulocytes - 83%, lymphocytes - 8%, monocytes - 7%.

Biochemical blood test (November 26, 2020): ALT - 27 IU/l, AST - 70 IU/l, total bilirubin - 12.4  $\mu$ mol/l, urea - 6.6 mmol/l, creatinine - 72  $\mu$ mol/l, total protein – 59.2 g/l, albumin – 36.1 g/l, glucose – 5.6 g/l.

Coagulogram (November 26, 2020): prothrombin time - 11.9 s, prothrombin index - 87.1%, INR - 1.11, aPTT - 30.2 s, D-fibrinogen - 3.28 g/l.

On the basis of examination data, and instrumental and laboratory studies, a diagnosis was established: the patient underwent bioprosthesis of the mitral valve (in 2010).

Paraprosthesis insufficiency of the mitral valve of the III degree. Hypertensive disease I-II degrees., 2nd stage, risk 4. Heart failure IIA.

Taking into account the history of cardiac surgery and the location and shape of the paravalvular leak, a decision was made to perform the intervention via a transcatheter transapical approach.

To close the PVL, we used the Occlutech® PLD paravalvular occluder (Occlutech GmbH, Jena, Germany).

Closure of paravalvular leak (November 30, 2020). The procedure was performed under general endotra-

cheal anesthesia. The top of the heart is exposed along the V intercostal space (Fig. 2).

At the top of the heart are two U-shaped seams with linings. Cannulation of the left ventricle through the apex of the heart using a 10F introducer was performed under visual control. A hydrophilic 0.035" Terumo Radifocus Guide Wire M (Terumo Medical Corp, Somerset, NJ) was advanced from the left ventricle into the left atrium through the paravalvular leak, situated 2:30 p.m. Through Amplatzer Left 3, 4f catheter (Fig. 3A). Control of the procedure was carried out through 3D-TEE and fluoroscopy. After placing the Amplatzer Left catheter inside the left atrium, the delivery system is established (Fig. 3B). A 10.0\*4.0 mm rectangular Occlutech® PLD paravalvular occluder was successfully deployed through the defect using the delivery system (Fig. 3C). With the help of 3D-TEE, the correct position of the occluder, the normal functioning of the mitral valve bioprosthesis, and the absence of regurgitation due to the paravalvular leak were confirmed (Fig. 3D). Later, the apex of the left ventricle was closed with purse-string sutures. The total procedure time was 168 minutes and the fluoroscopic time was 41 minutes. Note that during this procedure the patient was hemodynamically



stable, and no complications were observed during the procedure.

After the procedure, the patient was transferred to the intensive care unit (ICU). The early postoperative period was uneventful. After 2 days, the patient was transferred from the intensive care unit to the cardiology department for further treatment and observation. According to the results of Echo-CG on the 2nd and 9th day after the operation, paraprosthetic regurgitation on the mitral valve was not detected.

## DISCUSSION

The given clinical case demonstrates an example of the occurrence of a clinically significant paravalvular leak 10 years after mitral valve prosthetics, which is consistent with the work of Calvert PA et al., who emphasize that this complication most often occurs late [16].

Due to significant regurgitation due to the leak, this patient had clinical signs of mitral insufficiency, manifested by shortness of breath and significant limitation of physical activity.

In addition, according to the data from the clinical blood test, it is possible to notice the development of anemia, which can be caused by the hemolysis of red blood cells when passing through the leak.

Due to the presence of significant clinical symptoms, it was recommended to close this paravalvular leak using an occluder.

Characteristics of an ideal occluder include the possibility of reverse folding, ease of delivery, good conformation, and reliable fixation.

The Occlutech PLD occluder can meet the above characteristics. The Occlutech PLD occluder is a two-disc device that is rectangular in shape, with one disc slightly larger than the other.

The discs are connected to each other by a round or elliptical waist.

Recently, this occluder received approval for compliance with the main EU directives as a device specially designed for PVL closure [24].

When analyzing a number of different approaches (antegrade transfemoral (transeptal), retrograde transfemoral (arterial), and transapical) during a PVL mitral valve tran-

scatheter closure procedure, it is important to choose the method that will most comfortably place the occluder.

In this clinical case, a transapical approach was chosen due to the sharply eccentric location of the leak along the atrial septum at 2:30 p.m.

Overall, in a small series of 17 high-risk patients, Taramasso M et al. reported that PVL closure of the mitral valve through a transapical approach was characterized by good early postoperative results [25].

Thus, according to the study, the success of the PVL closure procedure was 94%, and the 30-day mortality rate was 0%.

Similar results were also obtained in another study, which included 43 patients.

In particular, the technical success rate of deploying the occluder by transapical access for mitral regurgitation was 89% [26].

Also, in a retrospective cohort study, Zorinas A. et al. analyzed 19 cases of paravalvular leak closure by transapical access using the Occlutech PLD occluder. According to the authors, in 18 (95%) patients, elimination or reduction to a lesser degree of paravalvular regurgitation was achieved. During the observation period, no stroke or myocardial infarction was detected among the patients [27].

As for the clinical effectiveness of the transcatheter PCF closure procedure, according to Millan X et al. successful PVL closure was associated with a lower rate of cardiac mortality (odds ratio [OR], 0.08; 95% confidence interval [CI], 0.01-0.90) and with improvement in functional class compared with failed interventions (OR, 9.95; 95% CI, 2.10-66.73) [28].

Moreover, Panaich SS sang. reported that successful PCF closure was characterized by a decrease in the degree of anemia, a lower need for blood transfusion, and a lower level of hemolysis markers [29].

## CONCLUSIONS

According to our results and according to the literature, the procedure for closing the PVL of the mitral valve from a transapical approach using a special Occlutech PLD occluder is characterized by relative safety for patients, clinical effectiveness in terms of eliminating or reducing the degree of regurgitation and related symptoms.

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