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P.I. SHATILOV AS A PUBLIC ACTOR, SCIENTIST, FIGHTER WITH EPIDEMIC DISEASES: TO THE CENTENARY OF DEATH

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Abstract

Prerequisites. The relevance of the study is caused by the fact that the personality of P. Shatilov does not have a sufficient scientific reflection in the literature from the standpoint and with the use of methods of studying medical local lore. In particular, historical research methods are neglected, however, they can be used to study the work of P. Shatilov in Kharkov in more detail during the epidemics that engulfed the city in 1919–1921. Today, when the whole world suffers from coronavirus infection, it is extremely important to give an example of medical struggle in emergencies, the victories of P. Shatilov not only as a physician but also as a citizen, because such examples instill responsibility to society. **Task** was to provide an updated biographical study of P. Shatilov for the centenary of his death, taking into account the methods of historical research, which had not previously been used in works of this kind. After all, medical personnel require a wider use of methods than previously represented biographical studies on the figure of P. Shatilov. To reproduce the biography of a scientist on a historical background, highlighting not only personal data, but also depicting the era in which the scientist lived and worked. **Materials and methods.** The results of similar studies have indicated that it is necessary to rely on conceptually important general scientific epistemological principles: historicism, objectivity, a combination of both logic and historicity, systematicity. The same methods were used in this study. The methodological basis of this type of research is a specific group of approaches and methods that are used for systematic analysis of the general historical process and medical personalia as an integral part of historical and medical knowledge. The biographical approach, thanks to which the historical reality is considered in time and space, widely covers the problem in a large historical context is a leading one. Phenomenological and paradigmatic approaches provide the necessary scientific tools to reproduce the atmosphere of the time period, reconstruct the preconditions for the formation of worldviews of P. Shatilov, clarify the sources of influence on personality development, the formation of views and beliefs of the scientist, generalization of views and beliefs and his impact on the development of medical science. The high share of this innovative and traditional form of research is provided upon the condition of following the principle of historicism, objectivity of coverage of facts, adequacy in the use of all sources of information, as well as avoiding idealization of the provisions and ideas of the past, giving them a dogmatic status. **Results.** As a result of a comprehensive study, a medical personalia of P. Shatilov was created, which is based on the application of a comprehensive methodological approach. This is what distinguishes this study from previously created ones and provides an example to researchers for studying topics related to personalities. **Conclusions.** P. Shatilov's work in Kharkiv in recent years has been marked by difficulties in combating the plagues that have engulfed the city. However, the scientist tried to introduce a systematic action to combat plagues, based on the principles of contemporary scientific knowledge.

Keywords: "All-Russian League for the Fight against Tuberculosis", typhus, epidemics, P. Shatilov, tuberculosis, Kharkiv, cholera.

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The life, activity and scientific achievements of Petr Ivanovich Shatilov were briefly covered in several purely medical publications [1; 2]. This is usually a reference to his name or general biographical information. There are also annoying mistakes in reputable publications, which are full of unsubstantiated and ill-considered approach to the study of the topic. Thus, in the "Crimean Therapeutic Journal" for 2010 in the second issue of the second volume there is an article stating that "P.I. Shatilov's student was a graduate of the Medical Faculty of Kiev University of St. Vladimir – Fedor Mechislavovich Openhovsky" [3]. Such conclusions should be made too carefully, because it is known that the scientific career of P. Shatilov began with the invitation of F. Openhovsky to work in the clinic. At that time, F. Openhovsky already had some experience and his own baggage of research. In addition, in 1913, when P. Shatilov had just returned from Paris, prof. Openhovsky was already elected as a chairman of the therapeutic section of the Kharkiv Medical Society, he developed as an outstanding doctor, teacher, scientist (1884 – defense of a doctoral dissertation), and in 1914 after the death of F. Openhovsky, it was P. Shatilov who delivered a speech on behalf of Fedor Mechislavovich's students [4]. Therefore, such a mistake is unacceptable, because when talking about the scientific school, the succession of generations, you cannot carelessly treat such facts, because the article written in a leading therapeutic journal will be quoted by descendants and will make the wrong impression, and then such errors will "travel" from one edition to another. And here we clearly see a narrow approach to the study of the personality, because a true historian always checks the factual material, involves several sources, compares, is critical of certain theses, and when being in doubt – always checks the information. Unfortunately, the study of medical personnel by medical researchers is not marked by such thorough approaches, so the scientific community receives such annoying mistakes. By the way, in the mentioned article, the date of F. Openhovsky's birth is also confused – he "rejuvenated" for three years, the year 1856 is indicated instead of the required 1853. What is this – negligence, a typographical error? And is such case the only one?

It should be noted that the personality of a scientist is not subject to comprehensive study, because from the standpoint of medical local lore, the personality should be considered taking into account historical time, realities, social and

economic, political events that influenced a person's life, formed his worldview. Fragmentary research, simple mentions between the lines, low-quality studies cannot fully reproduce the personalia of a healthcare professional, as can be done using the methods of general scientific and specific historical knowledge. Neglecting historical research methods impoverishes the individual, does not make it exhaustive and turns it into purely reference information. Giving life, major milestones, scientific achievements – this is a typical cliché of such works.

However, the contribution of those who developed P. Shatilov's personalia should not be underestimated, because it is still a means of popularizing the personality not only in medical circles, but also a representation for the general public of Kharkiv. An interesting experience in this regard is Max Rosenfeld's video from the series "History of Medicine in Faces", where Max Rosenfeld publishes information about Kharkiv doctors on the network channel [5]. However, such videos only draw attention to the personal, but do not provide the comprehensive information about the formation of views, the historical time when a person lived, his public position.

The aim of the work is to create a medical personalia of P. Shatilov using complex methods of scientific research. This will allow to qualitatively reproduce his life and work, to analyze the achievements in medical science of that time.

P. Shatilov is a bright representative of Kharkiv therapists who created his own scientific school. He was born in 1869 in the Kursk province and began his studies at the Voronezh Gymnasium, after which he continued his education in the city of Kutaisi, and in 1890, he entered the medical faculty of the Imperial Kharkiv University. In 1895, Petr Shatilov graduated from high school with the title of "doctor with distinction" [6]. Even then, he took an active public position, because, not yet having a medical degree, he actively helped to overcome cholera in the Cossack settlement, which began there in 1892.

After studying, the curious student Petr Shatilov at the invitation of F.M. Openhovsky remained a full-time resident of the therapeutic clinic, then he was transferred to the position of assistant, and in 1902 the young scientist defended his doctoral dissertation "On the doctrine of the forms of pulse curves" [7]. He went up the corporate ladder quickly: in 1904 he was a private associate professor, reading the subject "Clinical Research Methods", and in 1910 he was a professor at the Department of Internal Medicine

Diagnostics. From 1906 to 1908, Shatilov was in Europe, where he worked in the physiological and pathological laboratory of Paris, studied metabolic processes, became acquainted with current research on immunity, bacteriological innovations, mastered new diagnostic methods, visited Bern, Zurich, Berlin for scientific purposes.

Returning to his homeland, P. Shatilov became actively involved in the fight against tuberculosis and in 1911 became one of the organizers of the "All-Russian League for the Fight against Tuberculosis" [6, p. 422]. The problem of tuberculosis throughout Ukraine has arisen on a huge scale. At the same time, the Kharkiv province was noted as a pioneer – statistics showed that in the early twentieth century, 63% of patients were from this province [8, p. 141]. This is not surprising, because Kharkiv was actively developing at that time, the development of the city as an industrial center attracted people from different parts of the country in search of work, so the city suffered from overcrowding, poor hygiene, terrible sanitation, saying nothing about epidemic prosperity. Mostly tuberculosis was diagnosed among workers and peasants, exhausted by hard physical labor, deprived of normal living conditions, suffering from chronic malnutrition. Data were disappointing in other provinces as well, where the incidence rate was rising. Therefore, P. Shatilov immediately understood – the situation requires a systematic, balanced approach and the creation of a single coordinating center in the fight against tuberculosis. Thus, after Russia's accession to the International League against Tuberculosis in 1909, the scientist decided to promote the establishment of the corresponding center in Ukraine, which began operating on May 18, 1918 in Kharkov and eight more centers were opened in other cities of Ukraine. Shatilov helped to attract public funds, because there was a lack of state funding – the League created outpatient clinics, anti-tuberculosis sanatoriums, conducted sanitary and educational work. In particular, on December 6, 1912, at the initiative of the League, a free outpatient clinic with its own X-ray room was opened in Kharkiv on Sq. Voznesenskaya, 12 (now – Feuerbach) for patients with tuberculosis [9].

P. Shatilov began to form his own scientific school, introduced his students to new research. However, the imperial authorities, having started repressions against the professor, interfered with the normal work of the professor and due to the pressure of the Minister of Education Lev Kasso, Shatilov was forced to leave the city for a while.

He was the first in the Russian Empire in 1912 to introduce successful typhoid vaccinations, and for this, he was blamed by the incompetent leadership, because he did not have official permission to use the vaccine.

The scientist returned here after a brilliant speech at the international congress in Paris, where the results of his research were recognized by the world's leading physicians. In his first report, he introduced the scientific community to the typhoid vaccine, talked about anaphylactic shock, general and local reactions of the body to the vaccine, the minimum effective dose and so on. In the second report, P. Shatilov spoke about the individual approach to the patient during the diagnosis and treatment of diseases.

Shatilov returned to Kharkiv as a world-renowned scientist, so, in January, 1913, he headed the therapeutic clinic of the Kharkiv Imperial University [10]. In 1914, Petr Shatilov became the head of the faculty therapeutic clinic of the Women's Medical Institute.

In 1918 P. Shatilov was elected as a professor of the department of faculty therapy of the medical faculty of IHU. Already at that time, he revived the work, holding this position until his death. Within three years, the department began to develop issues of tuberculosis, pneumonia, cardiovascular system, epidemiology and immunology of typhus. P. Shatilov was demanding of staff and students, however, they loved the professor. It is known that some of the students who had problems with housing were settled by Shatilov in his country house until they found a room [11].

The change of authority in the city was perceived positively by P. Shatilov, as he was first and foremost a doctor and performed his public duty. Therefore, in 1918 he and M. Melnikov-Razvedenkov participated in the creation of the journal "Medical Affairs", which was to become and became a mouthpiece of the medical science of those times, because "Kharkiv Medical Journal" in 1917 ceased to exist and the medical community was left without a leading professional publication [12]. The first issue was published on December 1, 1918, where Petr Shatilov first edited the department of internal medicine in the journal, and then became the editor-in-chief of the publication.

Topical articles of doctors from different parts of the country were published here, reviews of the works of foreign scientists were conducted, and own analytical articles were published, which were absolutely necessary, as medical science

began to develop rapidly, requiring not only practical experience but also scientific basis.

Unfortunately, Shatilov's life ended prematurely. Examining patients with typhus in prison, he fell ill on May 2, 1921, and on the 13th of the same month he passed away, leaving behind a scientific legacy and, most importantly, a powerful scientific therapeutic school.

During the years of activity P. Shatilov published 8 works on bacteriology and 31 more works on various fields of medical knowledge – on pathological anatomy, hematology, radiology, anthropology, chemistry and pharmacology, but his researches on clinic and diagnostics of internal diseases are especially significant. The study of cardiac activity today is impossible to imagine without percussion and auscultation, the principles of which were formed by P. Shatilov, who also studied the pulse, heart rhythms, pathological noises in the heart. For his students, P. Shatilov formed the most important thesis – any doctor who can think clinically will be able to make even the most difficult diagnosis.

However, Shatilov's research on the treatment of infectious diseases also seems interesting. It is interesting that even here, in science, P. Shatilov put social needs above his own. When the vaccination of the Turkish doctor Gamdi failed, in 1920 P. Shatilov and S. Kotsevalov were the first to get preventive vaccinations against typhus and set an example for their closest students to do the same [2; 13].

It is interesting that the scientist thoroughly approached the study of the causative agents of epidemics raging in the city. Depending on the obtained data, the doctor built a scheme of treatment of patients and first of all emphasized the importance of prevention. It should be mentioned that at that time the concept of systemic prevention as such was not widespread, so Shatilov can be considered a pioneer among domestic doctors. His ideas about vaccination were bold, but not unfounded.

However, another thing is interesting as well: his approach to the study. In 1919, in the journal "Medical Practice" (Vrachebnoe Delo), P. Shatilov published an article in which he carefully studied the influenza virus, epidemics of which had raged in recent years, and in 1889-1892 influenza was recognized as a pandemic. Petr Shatilov analyzed the opinions of leading European scientists on the causative agent of influenza and analyzed the symptoms of the disease, as well as pointed out the complications that arise against the background of influenza. P.I. Shatilov studied the course of

the disease and covered its influence on the body's systems – respiratory, digestive, nervous, circulatory, and other ones – in detail.

However, the doctor concluded that the virulence of the pathogen may have changed, the human body may have changed, but a significant factor that leads to the disease is a decrease in immunity. He claimed that the reasons for this decrease were namely social problems – malnutrition, nervous tension, difficult living conditions and "appalling conditions of modern existence" [14]. Petr Shatilov delivered a report on the flu epidemic in his speech on October 26, 1918, at a meeting of the Kharkiv Medical Society, which was attended by 175 members of the society and 350 invited guests [15].

The fight against the plagues arose in 1919–1921 at the national level, because doctors were constantly trying to extinguish the "continuous outbreaks of epidemics", but all in vain [16]. Not only typhus but also cholera raged. Kharkiv Provincial Executive Committee appropriated a lot of funds for anti-epidemic measures and streamlining the sanitary condition of the city, but this was not enough to overcome the disease [17]. The Kharkiv medical community did not stay away – in the sections of the Kharkiv Medical Society, P. Shatilov repeatedly made a report on typhus and emphasized the fight against it [15]. At the initiative of the governing bodies of health care in the city under the People's Commissariat of Health of the USSR in 1920 a state commission for the study of typhus was established, headed by Petr Shatilov [18, p. 108; 19, p. 98.].

Petr Shatilov's activity in the medical field is a complete sacrifice to medical science. The scientist even donated his remains to scientific institutions. His activity was fruitful, and the scientific therapeutic school was successful. P. Shatilov's students worked in many cities of Ukraine, spreading and improving the knowledge of their teacher.

Shatilov's position today should become exemplary, because he was first and foremost a socially-oriented person – he did not refuse to help the sick people, he supported students, tested a typhoid serum on himself, worried about the fight against plagues, neglecting his own safety. Such devotion is impressive and should be an example for today's doctors, students, all those who are involved in the medical field. The medical personalia proves that all the doctor's actions were primarily closely related to the social background. He saw the main threat in

the low quality of life, so in his research he emphasized this, and in practice, he involved the public, conducted educational work. His contribution to medical science is invaluable, and the name of Shatilivka, where the doctor's country house was located, was forever engraved as a toponym.

The medical personalia dedicated to P. Shatilov does not claim to be exhaustive. However, factual inaccuracies and significant conceptual errors have been corrected here. Studying with the involvement of specific historical research methods made it possible to depict the life and work of P. Shatilov against the background of the history of Kharkiv, to which he gave his whole life. The actions of P.I. Shatilov is a reaction to the challenges of time, which makes it possible to assert the active public position of the scientist.

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This is another example of the fact that the physician's personality cannot be studied encyclopedically, it is necessary to approach this with a broader methodological toolkit in order to obtain a result from a new angle.

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STUDENTS' EXPERIENCE OF STRESS WITH DIFFERENT FRAMEWORK CONDITIONS AND DIFFERENT ORIGINS

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Abstract

Background: Students are exposed to numerous stress factors. The large number of demands and high strain can lead to a higher drop-out rate. For this reason, the aim of the study is to examine and comparing the experience of stress among German and international students during their studies under adaptation to generally stressful conditions. The international students performed a complete study program in Germany. **Methods:** Data from 194 students (41.8% women, 58.2% men) were evaluated. The average age of the participants was 23.0±3.44 years. Our sample consisted of 80 international students. The questionnaire on strains during the study (and at the workplace) was used. We registered the frequency and the intensity of the stress factors in everyday study life. We factor analyzed the 34 stress items, which gave five stress factors. We then looked at the differences between German and international students on these factors, while adjusting for generally stressful conditions. **Results:** The most important stressors were unfavorable working hours, incompatibility of tasks, climate, excessive demands, high responsibility, lack of information, social isolation, emotional strain and financial problems. The stressors differed in 17 out of 34 stressors in the groups of students of different origin. The international students experienced more physical and psychosocial strain and they experienced resources less often than German students did, but if they felt them, it was more intense. **Conclusions:** Strains during studies and their individual demands vary. German and international students have different perceptions of stress during study programs. There is a need for health promotion and prevention programs, which should be integrated during study.

Keywords: Students, stress factors, international students, strain, demand, factor analysis.

Introduction

Background

The initiation of the Bologna reforms resulted in extensive changes in the demand and resource profiles of students in Europe, which made a systematic health reporting necessary [1]. The number of students has grown significantly in recent years [2]. Current studies showed that one out of every two students was regularly under stress [1]. When asked about stress-related factors, 75 % of the students associated those with time pressure, 64 % with performance pressure and almost 40 % with fear of the future

and work overload. Along with a clear feeling of exhaustion in almost 50 % of cases, exposure to multiple sources of stress is of great importance [3, 4]. In addition to the stressors of environmental conditions, such as noise, seating arrangements in lecture halls and their lack of clarity, numerous psychological stressors were named, such as the increasing time pressure and need to rush [5]. Common sources of stress among students are their financial situation, part-time work, relationships, caring for children and own health [4, 6, 7]. Stressors may have an adverse effect on the chance of students to complete their study program successfully.

Effects of study-related stress on the course of study

It has been shown that the volume of stressful life experiences is exponentially associated with

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the average perceived impairment of academic performance [8]. There are noticeable differences between bachelor and master students [1]. Bachelor students face the added pressure of getting into a good master's program that the master students do not have to worry about. Pressure by forthcoming examinations, performance demands as well as the financial situation seems to be significantly reduced for master students, according to previous studies. Higher numbers and intensity of demands can lead to an elevated drop-out rate [9]. Approximately one quarter of these dropouts is due to failure to achieve performance requirements and one in two is due to excessive study requirements [10]. According to the German Academic Exchange Service in 2012, 28 % of German students dropped out of their study, compared to 46 % of international students in Germany.

The mental health of students

Psychosocial problems, exhaustion, psychosomatic complaints or fears resulting in sleep disorders, nervousness, concentration problems or mood swings are prevalent among German students [11]. Students showed increased alcohol consumption [12]. While male students are more likely to consume alcohol or stimulants [7, 13, 14], female students show other spontaneous reactions to the stressors, for example, crying, eating or being restless [15]. The dysfunctional use of social media is also widespread and results in pronounced concentration problems and mental disorders due to a lack of functional solutions [16]. In addition to the study and the workplace, the predominant areas of life are health, family situation and partnership, including social contacts. Studies show that about 27% of students are suffering from psychological impairments. The rate of depressive disorders in the student population is 18%, which is significantly higher than the German population average of 5% [17]. Another study showed that the risk of burnout prevalence doubled from the third to sixth year of study of medicine [18].

2. Purpose, subjects and methods:

2.1. The purpose of this international study is to measure and compare the common stressors among German and international students and examine these stressors in relation to the student's background and general conditions. We hypothesized a differing perception of stress. The following questions were examined:

- Are there differences in the perception of the frequency and the intensity of study- or work-related stressors among German and international students?

- Do these differences remain unchanged after controlling for other generally stressful conditions?

2.2. Subjects & Methods

The international students that came to Germany to perform a full study program at a university were recruited. The subjective stress-strain concept was applied as a theoretical method [19].

In the survey 194 students (41.8 % women (n=81) and 58.2 % men (n=113)) was participated. The students came from diverse faculties of the two universities. The surveys were conducted in the period 2010–2013 and 2018. The average age of the participants was 23.0 ± 3.44 years (range: 18–34 years). The sample comprises 80 international participants among 36 countries (e. g. Cameroon (n=9), Syria (n=7), Palestine (n=4), Russia (n=4), Bulgaria (n=4), Israel (n=4), Peru (n=3), Argentina (n=3), Georgia (n=3), Iran (n=2), Yemen (n=2), and other countries all over the world with one or two students. They aged between 20 and 30 years (24.7 ± 2.40 years). The average age of German students was slightly lower (21.7 ± 3.53 years) compared to the international students. The gender ratio within the groups of students with and without German origin was relatively similar ($p=0.442$): 45 German women (39.5%) and 69 German men (60.5%) vs. 36 international women (45.0%) and 44 international men (55.0%).

The call for voluntary participation to the study was made through flyers with information and contact details. As well as the questionnaires laid out in paper format, which were available to all present at the first semester event in the lecture hall. The students filled out independently without any time limit. In the case of language barriers of international students (all questions were in German), an interpreter assisted in understanding and answering the respective questions.

Questionnaire on strains during the study (and at the workplace)

This questionnaire collects socio-demographic data of the participants as well as information on the study program, the time in hours per week required for the study, the financing of the study program, possible employment and the individual protective factors of the students [20]. In addition, the strain and the resulting demands during the study and the possible secondary employment were queried. The first step is an evaluation of the existence of the stressor, whether the respective statement (stress) occurs in everyday study life (never, rarely, sometimes, often). In the second step, the strength of the stressor is evaluated on

a four-level scale (as not at all, a little, quite strong or very strong). Thus, this questionnaire reflects typical stressors in the categories of psychological and physical stress, stress in connection with the financing of the study program, time stress during the study program and also family stress.

The students were asked about the frequency and the intensity of the following stress factors: time pressure, noise exposure, dirt pollution, physically heavy work, forced posture, lifting/carrying, unfavorable working hours, incompatibility of tasks, dangerous substances pollution, remain seated for long periods, long daily journey, risk for infection, accident risks exposure, climate, monotony, work overload, work underload, high accountability, little room for maneuver, no organization possibilities, lack of information, sexual harassment, conflicts with the faculty, conflicts with colleagues, conflicts with customers/patients, social isolation, fear of unemployment, emotional stress, problems in dealing with personal computers, bullying, financial difficulties, work-family conflict because of study/work, enjoy studying, collegial and open atmosphere in the environment, support from family/partner in professional matters.

At last, the following four factors were considered generally stressful conditions: working alongside studying, caring for children, nursing relatives and travel distance to place of work or study of more than 120 minutes. Of the total sample, these factors were cited as the main stressors. Therefore, they were included in the factor analysis. Based on the results of the potentially general stressful conditions, the students were divided into subgroups without ($n=108$ (55.7%)) and with ?1 stressful condition; $n=86$ (44.3 %).

Statistical methods

All analyses were performed in Stata v.16. We performed a factor analysis on the items, with principal (axis) factors extraction method (PF), because the items had a high degree of uniqueness. We tested the appropriateness of using factor analysis by running Bartlett's test of sphericity and calculating the Kaiser-Meyer-Olkin Measure of Sampling Adequacy (KMO). We did this procedure separately for the items measuring stress through frequency and the ones measuring stress through intensity. The items that loaded highly and uniquely on each factor were then combined into a composite factor score. These factor scores were then used in Mann-Whitney-U tests to compare the scores of German and international students. We also calculated regression models with the factor scores as the

dependent variable and origin (German vs. international) as the independent variable, while adjusting for the effect of generally stressful conditions. Here we used robust standard errors because most of the regression models showed heteroskedasticity and non-normal residuals.

3. Results & Discussion

Results

For 108 of 194 students (55.7%), there were no potentially stressful general conditions that could affect their study: 57 (50.0 %) German students and 51 (63.75 %) international students ($p=0.058$). For 86 participants (44.3%) potentially stressful general conditions were found (38.7 % with one, 5.2 % with two and 0.5 % with at least three). Of the 57 students of German origin with potentially stressful general conditions, 46 had only one, 10 had two and one German student had more than two potentially stressful general conditions. All 29 international students stated that they had only one potentially stressful general condition. There was no significant difference in the distribution of participants with generally stressful conditions among German and international students ($p=0.058$). The average age of students without stressful conditions was 22.5 ± 3.13 years, similar to the average age of those with stressful conditions 23.5 ± 3.72 years.

The average travel time to the university of 8.2 ± 15.67 km was 21.6 ± 18.19 minutes. The participants reported that they spent on average 19.2 ± 9.39 hours per week on lectures, seminars and traineeships. They spent an average of 15.6 ± 10.89 hours per week on the preparation and follow-up. Only four German students (2.1 % of the total sample) had children. Twenty-seven (23.9 %) German students had their studies financed 100 % by their parents, compared to 39 (48.8 %) of the international students. Only two German (1.8 %) and six (7.5 %) international students financed their studies completely through their own income. Most students received some sort of funding through some combination of parents, own income and/or scholarships or similar arrangements.

The frequency of stressors during the studies and/or possible work during the studies were surveyed. The most frequently reported stressors in the overall sample were time pressure (which 34 % reported feeling often) and long periods of sitting (39.2 %). These were followed by unfavourable working hours, incompatibility of tasks, climate, excessive demands, high responsibility, lack of information, social isolation, emotional strain, and financial problems.

German students more frequently reported enjoying the study and work as well as the collegial and open atmosphere in the environment. 35.7% of German students answered the question "enjoyment of studies and work" with "sometimes" and 58.9% with "often" (vs. 48.8% and 28.7% in the other group). They also felt more support (considering the answers "sometimes" and "often" together) for professional interests from their immediate circle (90.2% vs. 80.0%).

After this analysis of individual stressors, a factor analysis was undertaken. The KMO was 0.758, which was above the acceptable threshold of 0.6, and indicated that the sample was big enough to show patterns that could yield factors. Bartlett's test of sphericity was significant at $p < .001$, which indicated that the correlation matrix of all variables in the factor analysis was significantly different from an identity matrix. Taking together, this indicated that factor analysis could be performed.

A factor analysis with principal (axis) factors extraction method (PF) was performed on the 34 variables measuring the frequency of stressors. Parallel analysis indicated that five factors should be extracted: factor A physical strain, factor B psycho-social strain, factor C conflicts, factor D organizational strain, and factor E resources. Together they explained 83% of the variance in the data. A promax rotation gave 22 variables with factor loadings higher than 0.4, without cross-loadings. The factors and their related items are presented in *Table 1a*. All factors had Cronbach's α above .70, apart from Factor D with $\alpha = .40$. *Table 1b* shows the frequency of stressors in comparison of German and international students that had particular influence on the factor analysis. Significantly more Germans than international students reported sometimes or often stressors such as physically heavy work, lifting/carrying, remain seated for long periods,

Table 1a

Factor analysis of items measuring frequency of stress factors among students

Variable	Factor A	Factor B	Factor C	Factor D	Factor E
Time pressure	0,05	0,52	0,06	0,00	0,16
Noise exposure	0,28	0,01	0,07	0,26	0,03
Dirt pollution	0,82	-0,08	0,00	0,01	-0,09
Physically heavy work	0,85	0,05	-0,02	-0,02	-0,08
Forced posture	0,31	0,25	-0,10	0,27	-0,10
Lifting/carrying	0,88	0,00	0,04	-0,22	0,03
Unfavourable working hours	0,17	0,57	-0,19	0,13	0,06
Incompatibility of tasks	0,02	0,72	-0,07	0,15	0,12
Dangerous substances pollution	0,54	0,01	0,03	0,13	-0,11
Sitting still for long periods	-0,12	-0,06	0,02	0,62	0,22
Long daily journey	0,05	0,19	0,07	0,29	0,11
Risk for infection	0,20	0,15	-0,06	0,33	0,15
Accident risks exposure	0,57	-0,11	0,03	0,20	0,02
Climate (coldness, hotness, draft, etc.)	0,13	0,41	-0,11	0,02	-0,13
Monotony	-0,03	0,17	-0,10	0,52	-0,07
Work overload	-0,16	0,58	0,01	0,13	0,02
Work underload	0,04	-0,25	0,24	0,38	0,13
High accountability	0,27	0,37	0,15	-0,11	0,05
Little room for maneuver, no organization possibilities	-0,23	0,31	0,31	0,20	-0,11
Lack of information	-0,09	0,17	0,17	0,41	-0,24
Sexual harassment	-0,02	-0,15	0,36	0,15	-0,02
Conflicts with faculty	-0,02	0,05	0,57	0,12	0,08
Conflicts with colleagues	0,04	-0,09	0,74	-0,03	0,07
Conflicts with customers/patients	0,27	0,04	0,45	-0,29	0,17
Social isolation	-0,28	0,43	0,00	-0,19	-0,31
Fear of unemployment	-0,04	0,13	0,35	0,00	-0,21
Emotional stress	-0,06	0,59	0,02	-0,09	-0,19
Problems in dealing with personal computers	-0,02	0,07	0,37	0,15	-0,08
Bullying	0,01	0,20	0,37	-0,14	-0,21
Financial difficulties	0,05	0,58	0,13	-0,23	0,14
Work-family conflict because of study/work	0,12	-0,01	0,34	0,25	-0,11
Enjoy studying	0,00	0,03	0,16	-0,10	0,67
Collegial and open atmosphere in the environment	-0,10	0,12	0,01	0,16	0,76
Support from family/partner in professional matters	-0,14	0,04	-0,03	0,03	0,69
Cronbach's α	.84	.75	.70	.40	.72

Note. Extraction method = principal axis factors. Rotation method = oblique promax. Factor loadings $> .40$ are in bold. Five factors explained a total of 83% of the variance. $N=183$. Bold marking means that the stressors elicited the strongest response from the data. Factor A physical strain, Factor B psycho-social strain, Factor C conflicts, Factor D organizational strain, and Factor E resources.

Table 1b

Frequency of stress factors in the total sample and the subgroups of students of German and international students

Presence of stress factor	Total	Germany		Freign Countries	P _{Mann-Whitney-U}
		Frequency [%]			
Time pressure					
never	0,5	0,9	0	0,524	
rare	24,2	27,2	20,0		
sometimes	41,2	40,4	42,5		
often	34,0	31,6	37,5		
Dirt pollution					
never	57,2	50,0	67,5	0,078	
rare	25,8	30,7	18,8		
sometimes	13,9	14,9	12,5		
often	3,1	4,4	1,3		
Physically heavy work					
never	41,2	32,5	53,8	0,007	
rare	31,4	39,5	20,0		
sometimes	22,7	24,6	20,0		
often	4,6	3,5	6,3		
Lifting/carrying					
never	45,4	34,2	61,3	0,001	
rare	30,4	39,5	17,5		
sometimes	18,0	21,1	13,8		
often	6,2	5,3	7,5		
Unfavourable working hours					
never	29,4	30,7	27,5	0,299	
rare	21,1	24,6	16,3		
sometimes	36,1	20,1	16,0		
often	13,4	10,5	17,5		
Incompatibility of tasks					
never	23,7	21,9	26,3	0,001	
rare	30,4	38,6	18,8		
sometimes	34,5	34,2	35,0		
often	11,3	5,3	20,0		
Dangerous substances pollution					
never	72,2	75,4	67,5	0,683	
rare	21,6	19,3	25,0		
sometimes	4,1	3,5	5,0		
often	2,1	1,8	2,5		
Sitting still for long periods					
never	13,4	4,4	26,3	< 0,001	
rare	19,1	15,8	23,8		
sometimes	28,4	23,7	35,0		
often	39,2	56,1	15,0		
Accident risks exposure					
never	53,6	40,4	72,5	< 0,001	
rare	27,8	34,2	18,8		
sometimes	13,9	18,4	7,5		
often	4,6	7,0	1,3		
Climate (coldness, hotness, draft, etc.)					
never	25,8	28,9	21,3	< 0,001	
rare	28,4	39,5	12,5		
sometimes	25,8	22,8	30,0		
often	20,1	8,8	36,3		
Monotony					
never	25,8	28,1	22,5	0,487	
rare	36,6	36,8	36,3		
sometimes	28,4	24,6	33,8		
often	9,3	10,5	7,5		
Workoverload					
never	11,9	10,5	13,8	< 0,001	
rare	34,5	46,5	17,5		
sometimes	43,3	38,6	50,0		
often	10,3	4,4	18,8		
Lack of information					
never	21,1	19,3	23,8	0,383	
rare	30,4	35,1	23,8		
sometimes	37,1	34,2	41,3		
often	11,3	11,4	11,3		

continuation Table 1b

Conflicts with faculty				
never	65,8	62,7	70,0	0,018
rare	27,4	33,6	18,8	
sometimes	6,8	3,6	11,3	
often	0	0	0	
Conflict with colleagues				
never	67,5	60,4	77,5	0,037
rare	25,1	32,4	15,0	
sometimes	6,8	6,3	7,5	
often	0,5	0,9	0	
Conflict with customers/patients				
never	81,1	73,6	91,3	0,021
rare	12,1	17,3	5,0	
sometimes	6,3	8,2	3,8	
often	0,5	0,9	0	
Social isolation				
never	33,7	47,8	13,8	< 0,001
rare	20,7	29,2	8,8	
sometimes	26,9	18,6	38,8	
often	18,7	4,4	38,8	
Emotional stress				
never	14,5	18,6	8,8	< 0,001
rare	32,6	45,1	15,0	
sometimes	30,1	27,4	33,8	
often	22,8	8,8	42,5	
Financial difficulties				
never	27,5	25,7	30,0	0,012
rare	24,4	31,9	13,8	
sometimes	28,5	28,3	28,7	
often	19,7	14,2	27,5	
Enjoy studying				
never	1,6	0,9	2,5	< 0,001
rare	10,9	4,5	20,0	
sometimes	41,1	35,7	48,8	
often	46,4	58,9	28,7	
Collegial and open atmosphere in the environment				
never	2,1	0	5,0	< 0,001
rare	9,4	6,3	13,8	
sometimes	37,0	31,3	45,0	
often	51,6	62,5	36,3	
Support from family/partner in professional matters				
never	4,7	3,5	6,3	< 0,001
rare	9,3	6,2	13,8	
sometimes	28,5	21,2	38,8	
often	57,5	69,0	41,3	

Notes. In this table, only the stressors that included into factors A through E are listed and faced as important stressors.

and accident risk exposure. Resources were also more available for German students than for international students. The international students were more strained (sometimes and often) by social isolation emotional stress and incompatibility of tasks than the Germans.

After recording the stressors, the intensity of the demands resulting from them was asked. The stressors that elicited the strongest responses were social isolation (25.9% "very strong" and 20.7% "quite strong"), emotional stress (26.6% "very strong" and "quite strong") and financial difficulties (24.0% "very strong" and 23.4% "quite strong"). The perceived intensity of the stressors varied greatly in the groups of different origins.

Here too, a factor analysis was performed for the items measuring intensity of stressors. The KMO was 0.793, and Bartlett's test was significant at $p < .001$. A factor analysis with PF method was performed on the 34 variables measuring intensity of strains. Parallel analysis indicated that five factors should be extracted. Together they explained 84% of the variance in the data. A promax rotation gave 25 variables with factor loadings higher than 0.4, without cross-loadings. The factors and their related items are presented in Table 2a. All factor had Cronbach's α above .70, apart from Factor D, with $\alpha = .55$. The Table 2b shows the expression of stress caused by the different stress factors in

Table 2a

Factor analysis of items measuring intensity of stress factors among students

Variable	Factor A	Factor B	Factor C	Factor D	Factor E
Time pressure	0,10	0,74	0,00	-0,20	0,06
Noise exposure	0,43	0,05	0,04	0,03	0,02
Dirt pollution	0,76	-0,02	-0,04	-0,06	-0,05
Physically heavy work	0,82	0,08	-0,04	-0,15	0,03
Forced posture	0,44	0,11	-0,11	0,25	0,07
Lifting/carrying	0,81	0,01	0,03	-0,21	-0,16
Unfavourable working hours	0,27	0,50	-0,16	0,13	-0,06
Incompatibility of tasks	0,16	0,47	0,08	0,11	0,00
Dangerous substances pollution	0,50	-0,04	0,21	0,17	-0,05
Sitting still for long periods	0,04	-0,12	-0,18	0,37	0,21
Long daily journey	0,21	0,00	0,08	0,15	0,14
Risk for infection	0,18	-0,10	0,05	0,20	0,00
Accident risks exposure	0,48	-0,25	0,13	0,18	0,02
Climate (coldness, hotness, draft, etc.)	0,05	0,53	-0,23	0,24	-0,09
Monotony	0,10	0,26	-0,02	0,30	-0,02
Work overload	0,08	0,59	-0,05	0,12	0,07
Work underload	-0,13	-0,13	0,14	0,58	-0,24
High accountability	0,11	0,60	-0,02	-0,14	0,14
Little room for maneuver, no organization possibilities	-0,10	0,34	-0,11	0,44	0,15
Lack of information	-0,14	0,06	-0,11	0,58	0,22
Sexual harassment	-0,11	-0,06	0,20	0,49	-0,16
Conflicts with faculty	0,00	-0,08	0,65	0,08	0,10
Conflicts with colleagues	-0,03	0,04	0,80	0,02	-0,05
Conflicts with customers/patients	0,05	0,05	0,65	-0,27	0,07
Social isolation	-0,22	0,76	0,07	0,00	-0,06
Fear of unemployment	0,04	0,23	0,23	0,24	-0,07
Emotional stress	-0,09	0,78	0,17	-0,03	-0,09
Problems in dealing with personal computers	-0,11	0,14	0,12	0,29	0,04
Bullying	0,01	0,23	0,35	0,13	0,07
Financial difficulties	-0,03	0,36	0,17	0,06	0,13
Work-family conflict because of study/work	0,09	-0,04	0,22	0,14	0,29
Enjoy studying	0,11	-0,05	0,03	-0,11	0,74
Collegial and open atmosphere in the environment	-0,10	-0,03	0,01	0,04	0,82
Support from family/partner in professional matters	-0,14	0,08	0,01	0,01	0,75
Cronbach's α	.78	.85	.76	.55	.82

Note. Extraction method = principal axis factors. Rotation method = oblique promax. Factor loadings $> .40$ are in bold. Five factors explained a total of 84% of the variance. $N=188$. Bold marking means that the stressors elicited the strongest response from the data. Factor A physical strain, Factor B psycho-social strain, Factor C conflicts, Factor D organizational strain, and Factor E resources.

comparison of the German and international students. Highly significant differences were found in the stress factors time pressure, unfavourable working hours, climate, work overload, high accountability, social isolation, and emotional stress. Here, the international students gave higher values than the German students. General conditions had an additional influence in the stress factors physically heavy work, lifting/carrying, conflicts with customer/patients.

There was a large degree of overlap between the contents of the factors from the two analyses. Factor A and B shared most items, though the analyses showed one or two items loaded uniquely high on either frequency or intensity. Factor C and E were identical. Factor D, however, had only one item in common among the two factor analyses. It was also the factor with the worst internal reliability. Since the reliability scores of Factor D: organi-

zational strain were so low ($\alpha=.55$), they were excluded from further analysis.

We made sum scores of the items with loadings greater than .40 on each of the factors. Then we tested regression models where the factor scores were regressed on the students' origins and general conditions. Here too, in order to answer the question of what influence the generally stressful conditions have on the experience of stressors in the study, the variable general condition was included in the GLM analysis as a covariate. The results of the frequency factors are shown in Table 3, and the results of the intensity factors are shown in Table 4.

We ran regression models with origin predicting Factor A-E stressors, with robust standard errors in order to deal with heteroskedasticity and non-normality of residuals that were present in the data. In these models, we

Table 2b

Expression of stress caused by the different stress factors in the total sample and in the group comparison of students from different backgrounds and with different framework conditions for study

Beansprucht durch...	Total	Germany	Foreign countries	p _{Mann-Whitney-U}	GLM with general conditions as covariate		p _{Bonferroni}
	AV±SD Median (min-max)				F	p	
Time pressure	1.57±0.856 1 (1-2)	1.24±0.747 1 (0-3)	2.05±0.794 2 (0-3)	< 0.001	24.237	< 0.001	< 0.001
Noise exposure	0.69±0.863 0 (0-3)	0.60±0.822 0 (0-3)	0.78±0.927 0.5 (0-3)	0.367	0.940	0.393	0.175
Dirt pollution	0.28±0.580 0 (0-3)	0.22±0.488 0 (0-2)	0.35±0.695 0 (0-3)	0.409	3.921	0.022	0.071
Physically heavy work	0.48±0.743 0 (0-3)	0.36±0.542 0 (0-2)	0.69±0.936 0 (0-3)	0.031	14.529	< 0.001	< 0.001
Forced posture	0.79±0.934 0 (0-3)	0.69±0.866 0 (0-3)	0.89±0.968 1 (0-3)	0.220	4.823	0.009	0.062
Lifting/Carrying	0.48±0.707 0 (0-3)	0.45±0.594 0 (0-2)	0.53±0.842 0 (0-3)	0.848	12.063	< 0.001	0.122
Unfavourable working hours	1.04±0.986 1 (0-3)	0.83±0.813 1 (0-3)	1.4±1.121 1.5 (0-3)	< 0.001	12.079	< 0.001	< 0.001
Incompatibility of task	1.19±1.006 1 (0-3)	1.12±0.944 1 (0-3)	1.34±1.102 1.5 (0-3)	0.103	3.541	0.031	0.077
Dangerous substances pollution	0.25±0.539 0 (0-3)	0.18±0.462 0 (0-2)	0.36±0.641 0 (0-3)	0.012	4.253	0.016	0.014
Accident risk exposure	0.34±0.633 0 (0-3)	0.39±0.603 0 (0-2)	0.30±0.701 0 (0-3)	0.117	2.773	0.065	0.597
Climate (coldness, hotness, draft, etc.)	1.09±1.109 1 (0-3)	0.71±0.786 1 (0-3)	1.66±1.252 2 (0-3)	< 0.001	19.442	< 0.001	< 0.001
Work overload	1.42±0.969 1 (0-3)	1.21±0.853 1 (0-3)	1.71±1.058 2 (0-3)	< 0.001	6.339	0.002	0.001
Work underload	0.34±0.657 0 (0-3)	0.40±0.654 0 (0-2)	0.24±0.661 0 (0-3)	0.009	2.832	0.062	0.190
High accountability	0.97±0.921 1 (0-3)	0.60±0.670 1 (0-3)	1.51±0.968 2 (0-3)	< 0.001	27.730	< 0.001	< 0.001
Litte room for maneuver, no organization possibilities	0.98±1.018 1 (0-3)	0.83±0.953 1 (0-3)	1.21±1.076 1 (0-3)	0.010	3.254	0.041	0.016
Lack of informtion	1.42±1.013 2 (0-3)	1.45±0.975 2 (0-3)	1.41±1.064 2 (0-3)	0.929	0.048	0.954	0.790
Sexual harassment	0.10±0.414 0 (0-3)	0.12±0.460 0 (0-3)	0.09±0.396 0 (0-3)	0.822	1.785	0.171	0.820
Conflicts with faculty	0.51±0.888 0 (0-3)	0.50±0.815 0 (0-3)	0.54±0.993 0 (0-3)	0.709	4.610	0.011	0.433
Conflicts with colleagues	0.40±0.760 0 (0-3)	0.43±0.746 0 (0-3)	0.35±0.797 0 (0-3)	0.152	2.061	0.130	0.725
Conflicts with customer/patients	0.23 ± 0.616 0 (0-3)	0.32 ± 0.683 0 (0-3)	0.14 ± 0.522 0 (0-3)	0.021	9.004	< 0.001	0.182
Social isolation	1.33 ± 1.243 1 (0-3)	0.82 ± 1.049 0 (0-3)	2.09 ± 1.127 3 (0-3)	< 0.001	32.006	< 0.001	< 0.001
Emotional stress	1.59 ± 1.094 2 (0-3)	1.27 ± 1.021 1 (0-3)	2.09 ± 0.983 2 (0-3)	< 0.001	14.702	< 0.001	< 0.001
Enjoy studying	0.53±0.876 0 (0-3)	0.41±0.752 0 (0-3)	0.69±1.001 0 (0-3)	0.080	2.654	0.051	0.032
Collegial and open atmosphere in the environment	0.39±0.770 0 (0-3)	0.29±0.644 0 (0-3)	0.51±0.900 0 (0-3)	0.081	0.909	0.438	0.050
Support from family/partner in professional matters	0.38±0.761 0 (0-3)	0.27±0.574 0 (0-3)	0.53±0.941 0 (0-3)	0.128	0.581	0.619	0.022

Notes. GLM = generalized linear model. In this table, only the stressors that included into factors A through E are listed and faced as important stressors.

Table 3

Frequency of different stress factors in the overall sample and the subgroups of students of German and foreign origin

	Total	Foreign countries		Mann-Whitney-U		GLM with general conditions as covariate				
		Germany AV±SD Median (min-max)	Foreign countries AV±SD Median (min-max)	Z	p	F	R ²	p	b _o	b _{GC}
Factor A:	0.69±0.67	0.79±0.65	0.55±0.67	3.14	.002	31.89	.26	<.001	-.15	.64***
Physical strain	0.6(0-2.8)	0.6(0-2.8)	0.2(0-2.8)							
Factor B:	1.50±0.60	1.3±0.45	1.79±0.66	-5.21	<.001	27.71	.23	<.001	.53***	.30***
Psycho-social strain	1.38(0.13-3)	1.31(0.13-2.25)	1.88(0.38-3)							
Factor C:	0.36±0.49	0.42±0.5	0.28±0.47	2.21	.026	11.93	.11	<.001	-.10	.30***
Conflicts	0(0-2)	0.33(0-2)	0(0-2)							
Factor E:	2.36±0.62	2.55±0.46	2.1±0.72	4.49	<.001	12.01	.13	<.001	-.43***	.06
Resources	2.5(0-3)	2.67(1-3)	2(0-3)							

Note. Regression with robust SE. * $p < .05$, ** $p < .01$, *** $p < .001$. b_o = origin, b_{GC} = general conditions. For interpretation of b values: baselines are German students and students without general conditions, respectively. (N=191-194).

Table 4

Intensity of stress factors in the overall sample and the subgroups of students of German and foreign origin

	Total	Foreign countries		Mann-Whitney-U		GLM with general conditions as covariate				
		Germany AV±SD Median (min-max)	Foreign countries AV±SD Median (min-max)	Z	p	F	R ²	p	b _o	b _{GC}
Factor A:	0.47±0.48	0.41±0.36	0.56±0.6	-0.71	.480	10.29	.11	<.001	.18*	.28***
Physical strain	0.29(0-2.57)	0.29(0-1.43)	0.29(0-2.57)							
Factor B:	1.27±0.71	0.95±0.49	1.73±0.73	-7.14	<.001	34.44	.30	<.001	.79***	.11
Psychosocial strain	1.19(0-3)	0.94(0-2.38)	1.88(0.25-3)							
Factor C:	0.38±0.62	0.41±0.63	0.34±0.61	0.98	.327	5.52	.06	<.001	-.03	.30**
Conflicts	0(0-3)	0(0-3)	0(0-2)							
Factor E:	0.43±0.69	0.33±0.58	0.58±0.81	-2.23	.026	2.73	.03	.068	.25*	.01
Resources	0(0-3)	0(0-2.5)	0(0-3)							

Note. Regression with robust SE. * $p < .05$, ** $p < .01$, *** $p < .001$. b_o = origin, b_{GC} = general conditions. For interpretation of b values: baselines are German students and students without general conditions, respectively. (N=188-194).

adjusted for the effect of generally stressful conditions and background (German or international). For frequency of stressors, international students experienced psychosocial strain more often than German students did ($b=0.53$, $p<.001$). German students experienced resources ($b=-0.43$, $p<.001$) more often than international students. These with one or more generally stressful conditions experienced physical strain ($b=0.64$, $p<.001$), psychosocial strain ($b=0.30$, $p<.001$) and conflicts ($b=0.30$, $p<.001$) more often than those without. For intensity of stressors, international students experienced physical strain slightly more than German students ($b=0.18$, $p<.05$), and psychosocial strain much more strongly ($b=0.79$, $p<.001$). However, they also experienced resources more strongly than German students did ($b=0.25$, $p<.05$). These with generally stressful conditions experienced physical strain ($b=0.28$, $p<.001$) and conflicts ($b=0.30$, $p<.01$) significantly more strongly.

Conclusions

The present study examined 194 students of German and international origin with regard to whether there were differences in study-related stress and demands. The study looked at whether additional generally stressful conditions, for

example existing part time job, the presence of children or taking care of relatives and a daily travel time of 120 minutes or more to the university, increased these study-related burdens. Although only German students had children in comparison to the international students, we see only a small influence of this variable because it was only 2.1 % of the total sample. Nearly 45 % of the students reported at least one of the general conditions that were stressful. The results also showed that the main stress factors of the two groups of students differed significantly. In general, the international students experienced stress factors more often and more intensely than the German students did.

When looking at the items making up the factor of physical stress, there were differences in "physically heavy work", "lifting/carrying", "unfavorable working hours" and "incompatibility of tasks". This stress is more pronounced among international students than among their German fellow students. Considering the general conditions, this characteristic remains. We suspect that both German and international students have part-time work, but that the international students tends to have jobs that are physically more difficult or at least that they perceive to be physically more difficult. It is also possible that the working hours

are unfavourable, with increased time pressure and possibly precarious working conditions. We hypothesized it; we found no study that examined this. Perhaps, the time pressure is exacerbated by the language barriers that international students must overcome to participate in class, answer questions, write term papers, essays, reports, dissertations, and theses. International students take longer to use the language of their host country, especially the academic language of their subject in the language of their host country, than do domestic students. Based on data from the German National Educational Panel Study, the language used at home does not affect the students' learning [21]. A study showed that young people are extra sensitive to health problems if they work in precarious conditions [22]. Precarious conditions can be study-related situations or due to a second job. Working on a job more than 20 to 25 hours a week increases the probability of dropping out of study and decreases the probability of timely graduation [23, 24].

They also reported more stress from time pressure, which was similar to values reported by 1 [1] and 25 [25]. The international students also more often reported emotional stress compared to the German students. Data used from seven waves of panel data from the German National Educational Panel Study (NEPS) with 6,386 individuals (included 1,002 international students) found no support for an immigrant-native gap in life satisfaction [26].

First, new role conflicts caused by breaking away from family and friends and the associated independence are suspected to be a crisis-prone biographical phase between adolescence and adulthood [11], which appears to be particularly significant for international students. Overcoming this causes orientation difficulties in the formation of one's own identity [11]. In addition, role conflicts also arise, where students try to perform several social roles at the same time. In this context, the contradictions between the effort of special personal initiatives and self-responsibility and the restrictive requirements of institutional rules and examination regulations have a particularly strong effect [27]. The fact, that many decisions that have a long-term impact on future professional life must be made before this development phase is completed, presents students with further challenges. Thus, fears and coping limits cross each other [11]. The high incidence of social isolation (e.g., due to insufficient integration) among nearly 78% of international students (vs. 23% German students) could also speak for this.

Reasons for problems with integration in their own country and culture at German students are for example: not studying at the university of choice, greater distances between home and place of study, more frequent journeys back to home, knowledge of returning home and thus avoidance of social contacts. There is also probably a high pressure of expectation or pressure not to disappoint, as the family pays for the financial costs of the study to a larger degree and thus enables their child to study in a foreign country. Studies showed that the success of individual students is influenced by school and family characteristics [28], but the immigration background has only a minor effect on study success [29].

There has been an increase in performance problems after the Bologna reform, which is accompanied by a growing dissatisfaction with the decreasing autonomy in the choice for their study content, insufficient study conditions and a general condensation of the material of learning [10].

Almost 69% of international and 43 % of the German students in our sample stated that they were overworked sometimes or often. The autonomy of the students is limited in the long term by the modularization of the study programs, which also leads to a lower expectation of self-efficacy [10]. In our sample, only 28 % of German students, but almost half of the international students reported a lack of room for maneuver and organizational possibilities. Even if the general conditions are taken into account, group differences were found in the stressors of time pressure, climate, high accountability and social isolation. It is also possible that social integration factors play a central role in explaining the different characteristics of stress factors and their stress profile between students of different origins. A study of over 70,000 Swedes found important indicators of poorer mental health in social integration: low social activity, lack of trust in others, lack of social support or financial burden [30]. In a study of international medical students at German universities, the language barrier was their main challenge [31].

The limitations of the study are that it did not take into account the exact time of the semester at which the survey of individual students was undertaken. For example, surveys at the end of the semester can result in higher demands than at the beginning, as the general conditions have already been in place for several weeks and, especially at the end of the semester, examinations and oral exams may also be required. For international students, holiday at home could have

a positive effect on the stress level, which is most likely to be lower at the beginning of the semester than at the end. Four factors were considered as generally stressful conditions, which were cited by the total sample: working alongside studying, caring for children, nursing relatives and travel distance to place of work or study of more than 120 minutes. It should be noted that the international students in this study had no children to care for during their full-time study in Germany. The methodology does not allow to provide explanations for their findings. The results are compared with other studies.

The results showed that international students are more exposed to physical stressors. The type of secondary employment was not queried. It is assumed that international students are more likely to have unfavourable and physically more burdensome secondary jobs (for example waiters, student assistant). The questionnaires were presented in paper format, which offer less options of filling it out anonymously compared to a digital form. The risk of socially desirable answers might thus be elevated. The questions were in German, which may have made them harder for the international students to understand. Furthermore, it was not recorded in which semester the students were, which could also play a role. Medical students in their third or ninth semesters of medical school showed the highest values for perceived stress [32]. Nevertheless, the results illustrate the need for preventive and health promoting programs for students in a university setting- as the promotion of health and social competence [33]. However, we cannot generalize from this small study. Thus, we cannot make recommendations for political decisions. For this, larger studies that also look at students at the beginning, during the study period and at the end

should be conducted. Data were collected before ongoing Covid 19 pandemic. In general, the strains on students are all still valid; are in some cases increased by the pandemic.

List of abbreviations

NEPS National Educational Panel Study

PF principal (axis) factors extraction method

Declarations:

Ethics approval and consent to participate

The Otto von Guericke University in Magdeburg, Germany (register no. 65/08) gave positive ethical opinions. The study complied with the guidelines of Declaration of Helsinki. The consent of the study participants was given in writing.

Consent for publication

All authors give their consent to publication.

Funding Sources

There are no sources of financing.

Competing Interests

The authors declare that there is no conflict of interest.

Availability of data and material (data transparency)

The data can be requested from the authors.

Authors' contributions

IB is the first author of the publication and responsible for data collection. HK performed statistical method and controlled the English version as a native speaker. BT made additions to the first version of publication and translated into English. SD is also co-editor the manuscript. All authors have read and approved the manuscript

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PATHOPHYSIOLOGICAL ASPECTS AS THE OBJECT OF TREATMENT TACTICS IN ACUTE PANCREATITIS (REVIEW)

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Summary

The review presents a modern view on the features of the course and treatment of acute pancreatitis, based on a cascade of pathophysiological mechanisms of this disease. A number of concepts of acute pancreatitis development and course are based on randomized prospective and retrospective studies of this problem are reviewed. Attention is paid to the mechanisms of organ failure development in acute pancreatitis. In accordance with the above, the main positions of treatment measures for acute pancreatitis, which are based on the principles of tactics "step-up approach" were featured. Among them, attention is paid to the features of the conservative treatment program, minimally invasive surgical interventions, as well as the management of the postoperative period of patients. Minimally invasive surgical interventions perform the main tasks of surgical treatment in acute pancreatitis, but significantly reduce surgical trauma compared to "open" methods. Adequate management of the postoperative period of patients is carried out through the implementation of protocols "fast-track surgery".

Keywords: acute pancreatitis, organ failure, tactics "step-up approach".

Acute pancreatitis is a sudden inflammatory process in the pancreas with possible involvement of the adjacent organs or even organs of other systems [1, 2]. Today, the incidence of acute pancreatitis is ahead of all urgent diseases of the abdominal cavity.

Acute pancreatitis causes major morbidity and mortality. According to global estimates, the incidence of acute pancreatitis was shown to be 33–74 cases per 100 000 person a years and a mortality of 1–60 per 100 000 persons a years. In European countries acute pancreatitis occurs from 4.6 to 100 cases per 100 thousand population [3–5]. According to British pancreatologists, the incidence of acute pancreatitis ranges from 15 to 42 cases per 100 thousand population during a year, with an annual increase of 2.7 % [1].

Among the leading causes of acute pancreatitis the authors highlight the presence of gallstones and alcohol abuse. Moreover, in women over 60 years of age the leading role is played by biliary pancreatitis, and in men alcoholic predom-

inates. In about 30% of cases it is an idiopathic acute pancreatitis (when it is not possible to identify the leading etiological factor in the development of the disease) [1, 2, 4, 5].

Pancreas is essentially the first target organ of autoenzyme aggression and the pathophysiology of acute pancreatitis, despite the etiological factor, consists in activation and release of pancreatic enzymes into the interstitial space, autodigestion and multiple dysfunction of organs (MODS) of active systems after release mediators. In the early stage of enzyme release and as a manifestation of distant autoenzyme aggression, a picture of local (in the parenchyma of the gland) and widespread (in adjacent organs) vasculitis develops. Inflammatory mediators in this case acquire destructive functions, organ failure develops, including intestinal endotoxemia and bacterial translocation, which is the main mechanism of septic complications in acute pancreatitis. Regarding the role of the intestine in the pathogenesis of the disease, this is confirmed by the fact that most of the bacteria that cause secondary pancreatic infection are of enteral origin.

Acute pancreatitis is a dynamic process with a variety of pathophysiological mechanisms of local and systemic complications. Adequate

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assessment of the state of the body's defense and awareness of the interaction between the various components of the immune system allows quick identification of emerging disorders and determine the strategy of targeted therapy [1–3].

The tactics, methods and ways of treating acute pancreatitis and its complications have been discussed in the literature for a long time, which leads to the formation of opposing views on this issue. In such a situation, it is important and relevant to timely assess the severity of the patient's condition, so that it is possible to predict the further development of the disease and accordingly choose the right treatment tactics. According to the international recommendations, severity of the patient's condition should be determined within the first 24 hours after hospitalization of the patient to the hospital. Therefore, the use of world-famous scales and prognostic systems, in particular Marshall's multiorgan dysfunction scale, SOFA scale, APACHE II scale, and BISAP scale, plays an important role in adequately assessing the severity of acute pancreatitis in a patient.

Acute pancreatitis is characterized by a wide range of clinical manifestations from mild to severe necrotic inflammation, which occurs with the systemic inflammatory response syndrome (SIRS), MODS and then organ failure. Severe acute pancreatitis is characterized by the presence of persistent MODS, as noted above, which largely determines the outcome and the possibility of death in the patient. Organ failure, as a generic term, can be defined as significant functional impairment of an organ system that is critical to sustenance of life. Severity of organ dysfunction can be quantified based on the parameter best defining the primary function of that particular organ (e.g. partial pressure of arterial oxygen (PaO₂) for pulmonary function or serum creatinine for renal function). In the case of acute pancreatitis, 3 organ systems are considered most important (respiratory, renal and cardiovascular) which are most commonly involved. According to world studies, the frequency of organ failure in acute pancreatitis can be 8–20% [4, 8, 9–11]. Risk factors for the development of organ failure in acute pancreatitis are age, the presence of comorbidities, obesity, triglyceride levels, etiology, the degree of local damage to the pancreas and genetic predisposition [12–14].

Although the development of organ failure and its consequences have long been confirmed in acute pancreatitis, there are separate concepts of primary organ failure, which develops early

due to acute pancreatitis (aseptic inflammation) and may precede necrosis, and secondary organ failure, which develops due to infected pancreatic necrosis induced sepsis. Infection of necrotic tissue of the pancreas is an ominous harbinger of secondary organ failure development, which can cause "late" death in acute pancreatitis. It should be noted that the prognostic development of primary organ failure is much worse than secondary. Because primary organ failure develops so rapidly and leads to "early" death that the doctor has almost no time for treatment. In secondary organ failure, as a rule, the patient's condition allows for a number of therapeutic measures, after which the fight against sepsis comes to the fore [4, 10].

The main type of treatment of acute pancreatitis is complex conservative treatment and surgery in the presence of indications for it.

The main goal of treatment tactics in acute pancreatitis is to reduce the likelihood of developing infected pancreatic necrosis and the possibility of death. Over the recent 10 years, the results of treatment of patients with acute pancreatitis have improved slightly, but the incidence of various infectious complications still remains high (ranging from 40 to 70% of cases), which in turn can lead to development of sepsis with the development of organ failure. The total mortality in severe forms of acute pancreatitis can reach 15% in sterile forms and 30% in infected. Secondary pancreatic infection is a further factor that often leads to adverse effects, and is diagnosed in approximately 40% of patients and is associated with high mortality, which exceeds 40% with the development of systemic complications.

At present, the world-wide accepted indication for surgical intervention in acute pancreatitis is development of a secondary pancreatic infection. According to the authors, indications for surgical treatment of acute pancreatitis are usually deterioration of the general condition of the patient on the background of conservative therapy (persistent hyperthermia, increased pain, the appearance of positive peritoneal symptoms), the development of purulent-septic complications, peritonitis [2, 3].

It is known that the principles of surgical interventions in pancreatic necrosis were laid down by B. Moynihan in 1925, and the main surgical methods for the control of secondary pancreatic infection and sepsis over the past 40 years included: 1) "open method" of treatment in the form of necrosectomy, sanitation and open management

of the focus of infection; 2) necrosectomy with routine relaparotomies and re-sanitation of the source of infection; 3) "closed technique" with necrosectomy, drainage and with or without continuous washing [2, 6]. But even today the principles of treatment of necrotic pancreatitis and the role of surgery remain controversial. In the 1990s, more than 60% of patients with acute pancreatitis were treated with open surgical interventions. In 1991, E.L. Bradley and K. Allen recommended conservative treatment of sterile necrosis of the pancreas in selected cases, and M. Gagner was the first to perform and describe minimally invasive video-laparoscopic surgical treatment of secondary pancreatic infection in 1996, including laparoscopic retrocolic, retroperitoneoscopic interventions [2, 5, 6].

Subsequently, it was hypothesized that percutaneous drainage of infected pancreatic necrosis and fluid collectors may have a positive therapeutic effect. This recommendation was based on clinical observations, which indicated that there was no need for maximum removal of all necrotic tissue for successful treatment of patients with infected pancreatic necrosis. By draining infected fluid collectors, the authors proved that the clinical condition of patients can improve after these interventions, and necrotic tissues can be successfully treated in the subsequent immune system of the patient. That is, the purpose of drainage is to remove the infected fluid, not necrosis [5, 22].

Since 2010, the world community of pancreatologists has abandoned open surgical necrosectomy and initiated introduction of a "step-up approach" tactics to the surgical clinic. Because open necrosectomy led to the appearance of massive SIRS with the further development of organ failure and local purulent-septic complications. The use of minimally invasive techniques in the complex treatment of acute pancreatitis, such as percutaneous drainage, transluminal endoscopic necrosectomy through the stomach or duodenum, laparoscopic necrosectomy and retroperitoneal surgical drainage is becoming more common. Sometimes it is a primary drainage followed by necrosectomy, if necessary, or, in the case of acute biliary pancreatitis, during the first surgical intervention, the abdominal cavity and the omental bag are adequately sanitized, and during the second, a cholecystectomy is performed. This reflects the principles of "step-up approach" tactics in modern pancreatology. In some clinics, due to this tactic in the treatment of necrotic acute pancreatitis it is possible to reduce mortality in its infected forms to 15.4 % [22, 23].

An important component of the "step-up approach" tactics is modern conservative treatment, which allows significant limitation of the indications for the implementation of early surgical intervention in acute pancreatitis, and surgical methods should be used only for absolute indications. The main principles of conservative treatment of acute pancreatitis: correction of disorders of central hemodynamics and peripheral blood circulation, respiratory support, analgesia, decompression of the gastrointestinal tract, adequate protein and energy supply, prevention and treatment of purulent infection, suppression of secretory activity of the pancreas, hepatoprotection, prevention and treatment of intra-abdominal hypertension syndrome. Non-narcotic analgesics are usually preferred to provide adequate analgesia. At the expressed pain syndrome, especially in combination with intestinal paresis, the extended epidural analgesia on ThVII-ThVIII levels by introduction of solutions of local anesthetics is widely used. Hemodynamic support during intensive care in conditions of toxemic and enzymatic shock begins with the correction of hypovolemia and dehydration, as well as microcirculation disorders. Central venous pressure is maintained at 100 mm of water column, diuresis – 40–60 ml/hour. At unstable hemodynamics and disturbance of perfusion of tissue at adequate liquid resuscitation use of vasopressors is shown. Respiratory support (oxygen therapy and artificial lung ventilation) in the conditions of intensive care unit is justified in respiratory failure ($\text{SaO}_2 < 95\%$, $\text{PaO}_2 < 70$ mm Hg). In order to block pancreatic secretion, somatostatin and polyvalent serine protease inhibitor unilastatin are used, which also reduces the synthesis of proinflammatory cytokines by immunocompetent cells and endothelium, reduces the activity of leukocyte elastases and lysosomal hydrolases, and other. Prevention and antibacterial therapy of infectious complications is carried out in accordance with the international recommendations of the IAP/APA for the treatment of acute pancreatitis. Antibiotics with a broad spectrum of action are prescribed, which are active against most probable pathogens of pancreatic infection and are able to penetrate into the tissue of the pancreas, gland secretion, parapancreatic tissue (mostly carbapenems) [1, 5, 6, 23, 24].

The main task of surgical intervention is the timely evacuation of exudate from the abdominal cavity during enzymatic toxemia or necrotic areas of the gland, when they already exist, with minimal risk to the patient's life.

Puncture-drainage methods are the next stage of the diagnostic and treatment algorithm in patients with acute necrotic pancreatitis. In some clinical cases, they can be considered as a direct alternative to surgery and can be successfully performed in 54 % of cases under ultrasonographic or computed tomography control [25–27].

A number of authors position percutaneous drainage interventions as a temporary preoperative measure or a direct alternative to surgery in a limited group of patients. Installation of percutaneous drainage improves the demarcation of foci of pancreatic necrosis and reduces surgical trauma in the future. Drainage sizes 14–32 French are used for drainage. The catheter should be optimally placed in the left or right retroperitoneal space, depending on the location of the fluid collector. Some sources indicate that catheters of large diameters (up to 28Fr) may be more effective, given the morphological specifics of pancreatic and peripancreatic necrosis, which contain a large number of dense necrotic elements. The procedure of gradually increasing the size of drainage catheters, which allows you to evacuate necrotic tissue, is called percutaneous necrosectomy [2, 5, 6, 23, 25, 27].

The transluminal endoscopic techniques occupy an important niche in the treatment of acute necrotic pancreatitis. The endoscopic method of treatment of peripancreatic fluid accumulations began its history in 1975, when the case of transgastric cyst drainage was first described in the literature. The results of research conducted in the early 2000s showed the first successes of the new technique: the success of drainage in 70–100 %. Of course, in recent decades, the endoscopic method has undergone a major evolution – from simple transgastric aspiration to transluminal necrosectomy using ultrasound monitoring and special stent systems. According to a number of authors, transgastric necrosectomy avoids dangerous complications associated with transcutaneous puncture (bleeding, perforation of hollow organs, formation of external pancreatic fistula), and provides a more direct approach to the foci of necrosis. The final stage of the intervention is the placement of stents (double-pigtail) 5–10 Fr, usually two, or a nasogastric catheter inserted into the cavity of the omental bag. Sanitation of the cavity should be carried out within 24 hours by irrigation with saline solution with a volume of 1 liter. Evaluation of endoscopic drainage results should be performed within the next 72 hours. Repeated endoscopic procedure should be performed in cases of no clinical improvement [2, 3, 5, 6, 28].

As for videolaparoscopy, it performs both diagnostic and therapeutic tasks. When performing videolaparoscopy, the diagnosis of acute pancreatitis should be confirmed and other acute abdominal diseases should be ruled out [23, 25, 28]. Significant signs of acute pancreatitis include edema of the mesenteric root of the colon, effusion with high amylase activity (2–3 times the activity of blood amylase), "vitreous edema" (serous infiltration of fatty tissue), the presence of foci of steatonecrosis (arising from the action of lipases and phospholipases). In favor of severe acute pancreatitis indicate hemorrhagic nature of the exudate (cherry, pink, brown), common areas of steatonecrosis, significant hemorrhagic infiltration of retroperitoneal tissue beyond the pancreas. The condition of the biliary system, in particular the gallbladder (whether it is tense, able to empty, or contains concretions) should also be assessed during the intervention. If the gallbladder is tense, unable to empty, the surgery must end with the unloading of the biliary system in the form of cholecystostomy.

The analysis of the literature shows that transabdominal necrosectomy techniques in terms of frequency of use in clinical practice are significantly inferior to retroperitoneoscopic. Laparoscopic access to the pancreas is similar to that of open surgery: through the gastrocolic ligament or mesocolon. The ability to achieve the most complete removal of necrotic tissue makes the method particularly attractive [1, 2, 5, 6, 22, 23, 28, 29].

A number of publications report the success of single-port laparoscopic necrosectomy and laparoscopically-assisted necrosectomy (hand-assisted) [29–36].

Video-Assisted Retroperitoneal Debridement (VARD) is the most common minimally invasive technique in the United States and the Netherlands. The undoubted advantage of the method is the lack of contact with the abdominal cavity, which prevents its infection. The technique was first described by Horvath et al. in 2001. VARD is an integral part of the step-up approach in the treatment of acute necrotic pancreatitis. Transcutaneous drainage is considered a mandatory step prior to VARD. Drainage of the left retroperitoneal space is technically possible in 95 % of cases. The essence of the technique is subcostal access to the retroperitoneal space, the reference point for which is the retroperitoneal drainage. At achievement of necrotic masses the indirect necrosectomy is carried out. In the future, using a laparoscope by insufflation of carbon dioxide, a direct (video-assisted) part of the operation is performed [23, 33, 37–41].

The problem of comprehensive treatment of patients with acute pancreatitis remains relevant, as well as the problem of adequate management of this category of patients in the postoperative period. It is not news for surgeons and resuscitators that only half of the success of treatment of a patient with acute pancreatitis depends on timely intervention, and half still depends on adequate treatment in the postoperative period, because this pathology, as mentioned above, has a rather complex cascading pathophysiological mechanisms of development [42–48].

The application of the step-up approach in clinical practice is closely intertwined with the implementation of the concept of multimodal rehabilitation of surgical patients through the implementation of the protocols Enhanced Recovery After Surgery (ERAS) or "fast-track surgery". This helps to reduce the cost of treatment without compromising its quality. The ERAS concept envisages a set of measures in the peri- and postoperative period aimed at reducing the time of hospitalization and rehabilitation after the intervention. Since patients with acute pancreatitis are the category of patients who most often need long-term (what to hide, and sometimes prolonged) and costly inpatient treatment, attempts to implement the concept of ERAS during their treatment are relevant and cost-effective. The concept of "fast-track surgery" requires coordinated

action of all medical staff, as well as full understanding between the patient and the doctor, who motivates and sets the patient's daily tasks. Studies of the pathophysiological mechanisms of any surgical intervention have shown that the key is the failure of physiological activity of internal organs in response to surgical stress. These changes in the functions of internal organs are mediated by metabolic changes caused by surgical trauma and the activation of a number of cascade systems. Multimodal rehabilitation with an emphasis on preoperative patient information, reduced response to surgery, optimized pain relief, early mobilization and early feeding reduced the number of complications, length of stay in the ward, and therefore the cost of treatment [48–50].

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

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FORENSIC MEDICAL EXAMINATION OF LIVING PERSONS IN CASES OF INJURY OF THE EXTERNAL RESPIRATORY ORGANS

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Abstract

Background. Trauma of external respiratory organs in victims is often a reason for the referral to forensic medical examination by law enforcement. The purpose of this work was to analyze the peculiarities of formation of forensic medical expert conclusion, based on the results of determining the gravity of bodily injuries in victims with closed trauma of the organs external respiration, depending on their morphological and clinical characteristics and gravity, to find the ways to unify expert assessment. **Subjects and Methods.** 183 conclusions of forensic medical examination in Kharkiv Regional Expert Institution, on the cases of a closed blunt trauma of the organs of external respiration, were analyzed. **Results.** According to the mechanism of bodily injuries, in 171,1 (93,4 %) cases there was an impact of blunt solid objects on the neck and chest, in 11 (6 %) cases there was a compression of the neck by hands or other blunt solid objects, in 1 (0,5 %) case – a compression of the neck by hands and a loop. At the given trauma, modern experts' approaches to an assessment of bodily injuries were defined. Severe bodily injuries were defined in 17 (9,3 %) cases of trauma, with the emergence of life-threatening events such as acute respiratory failure, traumatic shock, mechanical asphyxia. Moderate bodily injuries were determined by experts in the 151 (82,5 %) cases, mostly injuries from fractures of ribs and cartilage of the larynx, at absence danger to life. Light bodily injuries were determined by experts in 15 (8,2 %) cases of mostly laryngeal injuries, complicated by its post-traumatic inflammation. The absence of unified scientific and methodological approach for the objective assessment of injuries of the external respiratory system organs has been defined. **Conclusions.** When conducting a forensic medical assessment of such injuries, there are cases of both underestimation and overestimation of the gravity of bodily injuries. According to the results of the performed investigation, further ways to unify morphological and clinical approaches at forensic-medical assessment of these bodily injuries were defined.

Keywords: *forensic medical examination, trauma of external respiratory organs, diagnostic criteria, severity of body injuries.*

Introduction

Forensic medical conclusion is drawn up by experts due to referral of living persons to determine severity of bodily injuries to the relevant expert institutions, namely the bureau of forensic medical examination of the Ministry of Health of Ukraine [1]. According to the legislation of Ukraine, severity of bodily injuries may be defined as severe, moderate, or light, according to the

criteria of "Rules for forensic medical assessment of bodily injuries severity" (1995) [2]. Thus, the main criterion of severe injury is a "danger to life", moderate – "health disorder lasting more than 21 days", light injury – "short-term disorders of health, less than three weeks," or minor transient effects up to 6 days [3]. Determining severity of bodily injuries to the victim is necessary for judicial investigating agencies to determine the extent of criminal liability of the attacker for the injury. Especially important it becomes when causing the victim of closed blunt trauma of the external respiratory organs (ERO) [4–7]. This is due to the fact that such injuries most often affect vital organs, like the airways, chest, lungs, ribs, intercostal muscles, which requires appropriate expert qualifications [8–11].

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Our study of the literature in this field [1, 3, 6, 12–16] showed that experts do not have a single scientific and methodological approach to determining the severity of these injuries ERO. In some cases, according to the opinion of some scientists, it is appropriate to use only morphological approach in which the morphology of the existing injury could already define damage as severe, life-threatening [6, 12, 14]. In other cases, a clinical and morphological approach is used, in which the severity of the injury is clinical, including functional signs of morphologically determined by the expert damage, which indicate a threat to life [1, 3, 13]. In the absence of these clinical signs, the expert must apply other criteria for the severity of injuries.

According to the "Rules ..." , a closed blunt trauma of ERO may be qualified as severe damage only in cases of presence the life-threatening events listed in p. 2.1.3 "o" [2].

2. Purposes, subjects and methods:

2.1. Purpose: to analyze the peculiarities of forensic medical expert conclusion formation based on the results of determining the gravity of bodily injuries in victims with closed trauma of the organs external respiration depending on their morphological and clinical characteristics and gravity to find the ways to unify expert assessment.

2.2. Subjects & Methods

The materials for our work were retrospective analysis of 44000 conclusions of forensic medical examinations for seven years, carried out in the department of examination victims, accused and other persons of Kharkiv Regional Bureau of Forensic Medical Examination (KRBFME). In total, 183 cases of forensic medical examination of closed blunt trauma ERO were processed. The study was retrospective. During our work, we have used the following methods: registration method – the data was written on a specially designed registration card; methods of descriptive statistics; morphological and clinical method – the nature of injuries and clinical signs of dysfunction of injured organs were determined; forensic medical – the bodily injuries severity, evaluated by experts, and used the qualifying features was analyzed. This study was permitted by the ethics and bioethics commission of Kharkiv National Medical University. During examination, oral consent was obtained from all victims. The written consent from victims during forensic medical examinations should not be provided, according to regulatory documents governing their performance.

3. Results & Discussion

The analysis of the carried observations has presented that in the department of examination

of victims, accused and others persons of KRBFME, cases of the ERO blunt trauma examinations were 0,5 % of the total annual quantity of expert examinations. Traumas of ERO were more frequent in males (69 % of cases), more than half of victims (52 % of cases) were of working age – 20–50 years. Mainly, domestic conflicts lead to ERO injuries. It should be noted that a rare occurrence of such injuries was also noted in the literature [5, 7]. This, in turn, requires the collection of observations of such injuries in some cases for a long period of time, to conduct of thorough research [15].

The ERO injuries occurred in the following mechanisms: in 171,1 (93,4 %) cases there was impact of blunt solid objects on the neck and chest, in 11 (6 %) cases there was compression of the neck by hands or other blunt solid objects, in 1 (0,5 %) case – compression of the neck by hands and a loop.

The structures due to forensic medical examinations of ERO injuries were as follows. The damages of the costal skeleton of the chest occupied the first place – 161 (87,9 %) cases. Thus, fractures of several ribs occurred in 101 (55,2 %) observations, fractures of only one rib – in 60 (32,8 %) observations. This followed by the damage to the larynx in closed blunt trauma of the neck (CBTN) – 16 (8,6 %) cases. The third place was occupied by 6 (3,3 %) cases of chest trauma without rib fractures. In 5 (2,7 %) victims this category occurred contusion of lungs, complicated in 2 (1,1 %) cases of post-traumatic pneumonia, in 2 (1,1 %) cases by hemopneumothorax in one (0,5 %) case by hemothorax. In one (0,5 %) case rupture lungs complicated by hemothorax and posttraumatic pneumonia occurred.

At closed blunt trauma of the chest (CBTC) with fractures of the ribs, a contusion of the lungs or contusion of the lungs with rupture, was confirmed, using objective methods of investigation, in 7 (3,8 %) cases. However, in these injuries, hemothorax, pneumothorax or hemopneumothorax was present in 49 (26,8 %) cases. At the same time, hemopneumothorax was present in 31 (16,9%) cases, of which in 25 (13,8%) observations there were fractures of several ribs, in 6 (3,3 %) observations – fracture of one rib. Hemothorax was present in 8 (4,4 %) cases, of which in 6 (3,3 %) cases fractures of several ribs, in 2 (1,1 %) observations fracture of one rib were diagnosed. Pneumothorax occurred in 10 (5,5 %) observations, of which in 3 (1,6 %) cases fractures of several ribs, in 7 (3,8 %) cases fracture of one rib were present.

In addition, in patients with fractures of the ribs and hemopneumothorax in 4 (2,2 %) cases, the experts noted acute respiratory failure (ARF), in 3 (1,6 %) cases – traumatic shock, in 7 (3,8 %) cases a posttraumatic pneumonia developed.

The changes noticed during the investigation of the character of injuries of the larynx at CBTN are presented in *Table*.

In all categories of victims there was an acute post-traumatic laryngitis. During 3 (1,6%) examinations, in victims were diagnosed

expert conclusions. In one (0,5 %) case, the victim had spot signs of posttraumatic pneumonia. In addition, severe injuries were present in 2 (1,1%) cases of CBTC in the absence of rib fractures and hemopneumothorax, and in one (0,5 %) case of laryngeal injury with development of mechanical asphyxia.

It should be noted that in 8 (4,4 %) cases of establishment of severe bodily injuries by the experts, in CBTC, the presence of life-threatening phenomena listed in item 2.2.1 "o" "Rules", in

Characteristics of laryngeal injuries in cases of CBTN

The character of the laryngeal injury		quantity	%		
Post-traumatic laryngitis	Damage to the cartilage of the larynx	Fracture of the plate of the thyroid cartilage	1	0,5	1,0
		Fracture of the plate of the thyroid and arch of the annular cartilage, laryngeal hematoma, grade 2 stenosis	1	0,5	
	Hemorrhage (hematoma) in the larynx	Bleeding into the paralaryngeal tissue, grade 1-2 laryngeal stenosis	2	1,1	1,6
		Hemorrhage in the surrounding soft tissues of the larynx, paresis of its muscles	1	0,5	
	Hemorrhages in the vocal cords, their swelling		4	2,2	
	Absence of any morphological changes in the larynx		6	3,3	
	Fracture of the hyoid bone		1	0,5	
	The total number of observations of laryngeal injuries		16	8,6	

hemorrhages in the vocal cords, their swelling. In 4 (2,2%) cases, the victims had a laryngeal hematoma, hemorrhage in the surrounding soft tissues. In 2 (1,1%) cases in victims were present a fracture of one of the plates thyroid cartilage, while in one (0,6%) victim was present closed fracture of arch cricoid cartilage with displacement fragments. In one (0,5 %) case, the victim had a fracture of the hyoid bone. Grade 1–2 stenosis of larynx was present in 3 (1,6 %) victims, while in one (0,5 %) case in victim with grade 2 laryngeal stenosis had the signs of grad 2 ARF. In one (0,5 %) case, the victim was diagnosed post-traumatic laryngeal muscle paresis. In one (0,5 %) case, laryngeal trauma was complicated by the development of mechanical asphyxia.

Severity of bodily injuries at forensic medical assessment by experts of traumas of ERO estimated the following. Severe injuries by the criterion "danger to life" "Rules ..." estimated by experts in 12 (6,5 %) cases of CBTC with fracture of several ribs and 2 (1,1 %) cases of trauma with fracture one rib. Meanwhile, in 12 (6,5 %) cases there was formation of a hemopneumothorax, in one (0,5 %) a hemothorax, and in one (0,5 %) a pneumothorax and a partial collapse of lungs. However, contusion of lungs or contusion with it rupture was established in 11 (6 %) cases. The presence of a complication of trauma in the form of moderate degree traumatic shock was noted in expert conclusions in one (0,5 %) case, severe degree in 2 (1,1 %) cases. As to the clinical signs, grade 1–3 ARF as noted in 2 (1,1 %)

particular ARF or traumatic shock of severe degree, was not specified in conclusions of experts. In 2 (1,1 %) cases, even when experts referred to the occurrence of life-threatening phenomena in the victims, their presence did not have a convincing scientific justification in expert conclusions, as required by the morphological and clinical approaches to forensic assessment of injuries [1, 3, 14]. Therefore, we believe that the degree of severity of injuries established by experts in these 10 (5,5 %) cases of CBTC is not sufficiently substantiated.

Moderate bodily injuries, by "absence of danger to life" and "health disorder duration" criterion – more than 21 days, according to "Rules ...", were estimated by experts in 89 (48,6 %) cases of CBTC with fracture of several ribs, in 58 (31,7 %) case of fracture of the one rib. Meanwhile, hemopneumothorax was established in 19 (10,4 %) cases, pneumothorax in 9 (4,9 %) cases, hemothorax in 7 (3,8 %) cases. In addition to the damage of moderate degree of bodily injuries of same criterions by experts assigned: 2 (1,1 %) cases of CBTC with contusion of the lungs which in one case was complicated by development of hemothorax (0,5 %), in one (0,5%) case – by posttraumatic pneumonia; one (0,5 %) case – by CBTC with rupture of the lung and development of hemothorax; one (0,5 %) case – by CBTN with the formation of cricoid and thyroid larynx cartilages fractures.

In these forensic medical examinations, experts tried to confirm the duration of the disorder of

health by results of objective research methods, by dynamics of pathological changes. However, in conclusions of 3 (1,6 %) examinations, in one (0,5 %) victim with CBTN and in two (1,1 %) victims with CBTC, ARF was observed. In these cases, it was still possible to qualify the injuries in the victims as severe bodily injuries according to the criterion of "danger to life", in accordance with paragraph 2.1.3 "o" of the "Rules";

Light injuries that caused a short-term health disorder were estimated: in one (0,5%) case the CBTC with lung contusion, absence rib damage and development of post-traumatic pneumonia, in 9 (4,9%) cases CBTN with injury larynx, accompanied by acute posttraumatic laryngitis were observed. At the same time, in patients with CBTC in 3 (1,6%) cases there was laryngeal hematoma, 2 (1,1%) patients has formed grade 1–2 laryngeal stenosis, in one (0,5%) victim paresis muscles of the larynx. 2 (1,1%) victims had hemorrhages in the vocal cords of the larynx. One (1,1%) victim had a fracture of the hyoid bone. However, in 2 (1,1%) cases of CBTN with damage to the larynx in the presence of grade 1–2 stenosis, it would be possible to identify and justify the clinical signs of ARF, which would give grounds for experts to classify these injuries as severe injuries, according to the criterion "danger to life", in accordance with paragraph 2.1.3 "o" of the "Rules...".

Light injuries were estimated by experts in 5 (2,7 %) observations of laryngeal injuries with development of acute posttraumatic laryngitis. In these cases, the experts did not have sufficient data on the final results of laryngeal injuries necessary for the forensic assessment of the examined injury. Additional control diagnostic tests, in particular stroboscopy of the larynx, phoniatic examination by experts during the examinations were not conducted. In these cases, in the absence of information about the final results of the injury and the inability of experts to conduct additional investigations, it was necessary to abandon the determination of the severity of these injuries.

The analysis of the available expert materials allowed establishing that the medical documentation provided to the experts does not always detect and correctly treat laryngeal cartilage damage with the presence of their fractures. In medical institutions and during examinations, computed tomography was not always performed, which allows to detect fractures of the laryngeal cartilage. At the same time, some scientific papers emphasize the importance of this study in such injuries [4, 8, 16]. Experts do not always detect signs of ARF, which makes it impossible to determine the danger to the life of the victim and, accordingly, to correctly determine the

severity of the injuries. A clear definition of the signs of ARF requires the use of morphological and clinical approaches in assessing the severity of injuries [3]. The victims are not always referred by experts to a specialized hospital, to conduct additional diagnostic tests, including those which allow determining the degree of impaired function of the damaged organs and the consequences of their damage.

Conclusions

1) At carrying out forensic medical examinations of ERO traumas, cases of damages of a costal skeleton of the thorax prevailed (87,9% of cases). Damage of cartilaginous skeleton of the larynx were present only in 1,0% of cases. Substantiation of the presence of clinical signs of danger to life due to injury is the most difficult issue in cases of such examinations for forensic medical experts.

2) Annually, 0.5% of forensic medical expert conclusions are examinations of victims with ERO injuries.

3) According to experts' evaluation of ERO blunt trauma, severe bodily injuries were estimated in 9,3% of cases, in the occurrence of life-threatening phenomena, namely ARF, traumatic shock, mechanical asphyxia. Moderate bodily injuries were estimated in 82,5 % of cases, mainly in injuries with fractures of the ribs and cartilage of the larynx, in the absence of danger to life. 8,2 % of cases of CBTC, in the absence of rib fractures and laryngeal injuries, with the occurrence of posttraumatic inflammation, were classified as light injuries.

4) Forensic medical expert assessment of ERO blunt trauma could let both underestimation and overestimation of the severity of injuries, which is connected with lack of a unified scientific and methodological approach of such examinations.

5) The prospect of further research is to unify the morphological and clinical approaches in determining the severity of injuries in ERO trauma, on the basis of continuing scientific work, to establish all possible clinical and morphological manifestations of such trauma.

Declarations:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure.

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Data Transparency

The data can be requested from the authors.

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CONTRIBUTION OF ADIPOQ GENETIC POLYMORPHISM TO THE FORMATION AND COURSE OF COMORBIDITY OF NON-ALCOHOLIC FATTY LIVER DISEASE AND RENOPARENCHYMAL ARTERIAL HYPERTENSION

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Abstract

Background. Nowadays nonalcoholic fatty liver disease (NAFLD) is considered to be a multisystem disease that is primarily associated with components of the metabolic syndrome and is associated with cardiovascular and renal impairment. The comorbidity of NAFLD with renoparenchymal arterial hypertension (RPAH) has not been sufficiently studied. **The purpose** of the study was to investigate the influence of G276T genetic polymorphism of ADIPOQ on the severity of metabolic disorders, inflammation, liver, artery and kidney damage in the comorbidity of NAFLD and RPAH. **Materials and methods.** The study included 87 patients with comorbidity of NAFLD and RPAH, grade 2. The mean age of patients was 50.78 ± 9.35 years. The vast majority of patients were overweight or obese. Moreover, the study involved investigation of 2 groups of comparison with the isolated course of NAFLD (60 patients) and RPAH (30 patients). The control group was composed of 20 healthy volunteers. Parameters of carbohydrate and lipid metabolism, liver and kidney's function, adiponectin, fetuin-A, cytokeratin-18, pro-inflammatory cytokines levels were investigated. For diagnostic of non-alcoholic steatosis and indication parameters of arteries, an ultrasound method was used. T allele was detected in 62 (35.6%) patients of the main group, which was significantly ($p < 0.05$) different from the control group (22.5%). In the presence of patients with comorbidity NAFLD and RPAH G/T and T/T genotypes, carbohydrate metabolism disorders are more pronounced than in the G/G genotype. Thus, index HOMA in this group was 4.52 ± 0.87 , which was significantly higher than patients with G/G genotype – 3.77 ± 0.53 ($p < 0.01$). The G276T polymorphism of the ADIPOQ is not associated with markers of liver and kidney damage in patients with NAFLD + RPAH. The presence of G/T and T/T genotypes in patients with comorbidity of NAFLD and RPAH is associated with an increase in interleukin-6 and fetuin-A compared to the G/G genotype. Patients with comorbidity of NAFLD + RPAH and with the T allele of the polymorphic marker G276T of the ADIPOQ gene are more likely to have impaired endothelium-dependent vasodilation, indicating more significant vascular reactivity disorders – $7.72 \pm 1.25\%$ for the genotype G/G, and $7.00 \pm 1.10\%$ for the genotype G/T ($p < 0.01$). **Conclusions.** The presence of the T allele of the polymorphic marker G276T of the ADIPOQ is associated with the development of comorbidity of NAFLD and RPAH.

Keywords: *nonalcoholic fatty liver disease, renoparenchymal arterial hypertension, adiponectin gene polymorphism, metabolic disorders.*

Introduction

Nowadays nonalcoholic fatty liver disease (NAFLD) is considered to be a multisystem disease that is primarily associated with components of

the metabolic syndrome (MS) and is associated with cardiovascular and renal impairment [2, 18]. Meanwhile, many questions about the mechanisms of chronic kidney disease (CKD) in patients with NAFLD remain unclear, especially in combination with hypertension (AH) [1, 19]. The comorbidity of NAFLD with renoparenchymal arterial hypertension (RPAH) has not been sufficiently studied.

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It is well known that genetic factors play an important role in the development and course of such common diseases as NAFLD and AH [8, 11, 12]. Hypoadiponectinemia is a proven pathogenetic factor in the development of both NAFLD and AH [4, 5]. Adiponectin levels have been shown to have individual genetic differences [21].

The production and activity of adiponectin depends on the structure of the adiponectin gene (ADIPOQ), located on chromosome 3 at locus 3q27. The polymorphic marker G276T of the ADIPOQ gene is considered to be the most clinically significant in the development of insulin resistance (IR), obesity, and type 2 diabetes [9, 20].

2. Purpose, subjects and methods:

2.1. The purpose of the study was to investigate the influence of G276T genetic polymorphism of ADIPOQ on the severity of metabolic disorders, inflammation, liver, artery and kidney damage in the comorbidity of NAFLD and RPAH.

2.2. Subjects & Methods

Patients were examined at the Department of Gastroenterology and Therapy of the Government Institution "L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine". Clinical and biochemical studies were conducted in the clinical diagnostic laboratory of the Government Institution "L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine" and laboratory "Alpha Labservice".

The study included 87 patients with comorbidity of NAFLD and RPAH, grade 2. All patients had CKD no more than stage IIIA as a result of chronic pyelonephritis. The mean age of patients was 50.78 ± 9.35 years. Among them were 51.7 % men and 48.3 % women. The distribution of patients by sex was uniform. The vast majority of patients were overweight or obese.

The study did not include patients with type 1 and 2 diabetes, other diffuse and focal liver diseases (viral hepatitis, alcoholic liver disease, liver cirrhosis, etc.), the presence of other comorbidities in patients with NAFLD: coronary artery disease (CAD), rheumatic heart defects, oncological diseases, systemic connective tissue diseases, CHF II B – III stages, AH I and III stages, echo-negativity, patients' refusal to study, pregnancy and lactation.

Moreover, the study involved investigation of 2 groups of comparison with the isolated course of NAFLD (60 patients) and RPAH (30 patients). The control group consisted of 20 healthy individuals of the same age category, male and female.

The research was performed in compliance with the basic provisions of the "Rules of ethical principles of scientific medical research with human participation", approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EEC Directive No. 609 (dated 24.11.1986), orders of the Ministry of Health of Ukraine No. 690 dated 23.09.2009, No. 944 dated 14.12.2009, No. 616 dated 03.08.2012. Each patient signed an informed consent to participate in the study.

Clinical examination of patients included assessment of the parameters of objective examination: in particular, anthropometric data and blood pressure (BP) according to standard methods.

Non-alcoholic steatosis and indication parameters of arteries were evaluated by an ultrasound method (ultrasound diagnostic system "GE", USA). The degree of endothelium-dependent vasodilation (EDVD) was determined in a sample with reactive hyperemia [3].

Concentration of total cholesterol (TC) and its fractions: high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides (TG), aminotransferases (AST, ALT), gamma-glutamyltranspeptidase (GGT) were determined by standard generally accepted methods. The HOMA index was also determined. The glomerular filtration rate (GFR) was calculated by the formula CKD-EPI.

The AviBion Human Adiponectin (Acrp30) Elisa Kit test system (Ani Biotech Oy Orgenium Laboratories Busines Unit, Finland) was used to determine adiponectin levels. Fetuin-A values (fet-A) were determined in serum by ELISA (Biovendor, Czech Republic). The levels of cytokeratin-18 (CK-18), which is a marker of inflammation and apoptosis of the liver [7], in the blood plasma were determined by ELISA using a set of CK-18 (M65) Human ELISA Kit manufactured by Biotech (China). The concentrations of pro-inflammatory cytokines (tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6)) in the blood serum were evaluated using Vector-Best kits.

Based on the data of the polymer chain reaction with direct (5'-GGCCTCTTTCATCACAGACC-3') and reverse (5'-AGATGCAGCAAAGCCAAAGT-3') primers, the genetic polymorphism of ADIPOQ was determined. The amplification products were incubated with BsmI restriction enzyme in buffer. The hydrolysis products were isolated in a polyacrylamide gel and visualized under ultraviolet light. Three ADIPOQ genotypes (G/G, G/T and T/T) were identified by G276T polymorphism.

Statistical processing of the results was performed using computer programs Microsoft Excel and STATISTICA using standard methods of variation statistics. To assess the significance of the difference in pairwise changes, we used the t – Student test ($M \pm \sigma$). The difference was considered statistically significant at $p < 0.05$.

3. Results & Discussion

A corresponding comparative analysis of the distribution of ADIPOQ alleles and genotypes in the NAFLD + RPAH comorbidity and control groups was performed.

In patients with NAFLD + RPAH, the homozygous G/G genotype was found in 35 (40.2 %) patients, the heterozygous G/T genotype in 42 (48.3 %), and the homozygous T/T genotype in 10 (11.5 %) patients. In the comparison groups, the distribution of genotypes did not significantly differ from the comorbidity group and significantly differed from the control group (*Table 1*).

It was found that the T allele was detected in 62 (35.6%) patients of the main group, which was significantly ($p < 0.05$) different from the control group (22.5%) (*Table 1*).

Then we proceeded to the analysis of anamnestic, clinical-laboratory, anthropometric and instrumental-functional features in the NAFLD + RPAH group.

A difference between groups of patients with G/G and T/T genotypes in terms of body mass index (BMI) was found. Patients with G/G and G/T genotypes of the ADIPOQ had significantly lower BMI ($p < 0.01$), respectively, than patients with T/T genotype ($p < 0.01$).

The influence of the polymorphism of the studied gene on blood pressure was not detected ($p > 0,05$) (*Table 2*). In the analysis of Doppler parameters there were significant differences of EDVD – $7.72 \pm 1.25\%$ for the genotype G/G, and $7.00 \pm 1.10\%$ for the genotype G/T ($p < 0,01$). The thickness of the intima-media complex of the common carotid artery (TIM CCA) was greater with G/T genotype compared with T/T genotype ($p < 0.05$).

Significant differences in the analysis of carbohydrate metabolism between patients were found. Carbohydrate metabolism was worst in patients with the T/T genotype compared to patients with the G/G genotype. Thus, HOMA-IR in this group was significantly higher than patients with G/G genotype ($p < 0.01$).

When evaluating the lipid profile, we did not find the dependence of lipid parameters on ADIPOQ genotypes. There was also no association between ADIPOQ genotypes and renal function ($p > 0.05$). GFR in the group G/G genotype was 71.46 ± 12.19 ml/min/1.73 m² and did not differ from patients with G/T and T/T genotypes – 68.76 ± 12.29 and $65.67 \pm 13,68$ ml/min/1.73 m², respectively ($p > 0.05$).

At the same time, the G276T polymorphism of the ADIPOQ significantly affected the levels of fet-A and adiponectin. Thus, in patients with G/G genotype adiponectin was more than in the G/T genotype ($p < 0.01$), and at T/T genotype – ($p < 0.01$).

Also, the pro-inflammatory cytokine IL-6 was significantly higher in the group G/T genotype compared with the group G/G genotype ($p < 0.05$).

Given the known negative effect of the T allele, the groups of G/T and T/T genotypes were combined and all indicators were evaluated in comparison with the G/G genotype group (*Table 3*).

Significant differences were found in BMI, insulin, HOMA, IL-6, adiponectin, EDVD and fet-A. Thus, fet-A in the group of genotype G/G was 301.47 ± 25.14 ng/ml against 315.22 ± 17.29 ng/ml in the group of genotype G/T + T/T ($p < 0,01$). Worse indicators were in carriers of the T allele, which indicates the influence of this parameter on anthropometric, proinflammatory, vascular and metabolic factors in patients with comorbidity of NAFLD and RPAH.

There were no significant differences in other indicators ($p > 0.05$).

Importantly, there is an association between an increase in the T allele and an increase in fetuin

Table 1

Distribution of ADIPOQ alleles and genotypes in groups of NAFLD + RPAH comorbidity, comparison and control

Parameters	NAFLD + RPAH group	NAFLD group	RPAH group	Control group
	n=87	n=60	n=30	n=20
G/G	35 (40.2%)*	18 (30%)*	12 (40%)*	13 (65%)
G/T	42 (48.3%)*	34 (56.7%)*	14 (46.7%)*	5 (25%)
T/T	10 (11.5%)	8 (13.3%)	4 (13.3%)	2 (10%)
G allele	112 (64.4%)*	70 (58.3%)*	38 (63.3%)*	31 (77.5%)
T allele	62 (35.6%)*	50 (41.7%)*	22 (36.7%)*	9 (22.5%)

Note: * – statistically significant differences when compared with the control group ($p < 0.05$).

Table 2*Parameters in patients with comorbidity NAFLD + RPAH depending on ADIPOQ genotypes*

Parameters	Genotype G/G, n=35	Genotype G/T, n=42	Genotype T/T, n=10
BMI, kg / m ²	31.74±3.92	31.59±3.53	34.37±2.50**^
SBP, mm Hg	171.74±5.07	172.57±4.41	172.90±5.38
DBP, mm Hg	101.83±3.61	102.81±3.60	101.80±3.94
Average BP, mm Hg	131.19±3.64	132.11±3.44	131.66±4.32
TIM CCA, sm	0.88±0.12	0.93±0.13	0.84±0.11^
EDVD,%	7.72±1.25	7.00±1.10*	7.30±1.39
AST, U / l	45.97±28.63	57.00±36.70	48.40±14.84
ALT, U / l	51.91±32.00	69.81±54.83*	56.20±12.84
GGT, U / l	64.53±26.59	73.30±39.63	58.40±24.77
TC, mmol / l	5.93±0.80	5.97±0.94	6.14±0.64
TG, mmol / l	2.24±0.89	2.18±0.97	2.48±1.14
HDL, mmol / l	1.25±0.47	1.25±0.34	1.16±0.25
LDL, mmol / l	3.88±0.84	4.04±0.96	4.13±0.56
Blood glucose, mmol / l	5.63±0.54	5.64±0.52	5.78±0.57
HOMA-IR	3.77±0.53	4.20±0.76	4.52±0.87**
Creatinine, μmol / l	97.37±9.60	100.74±12.28	93.00±15.30
GFR, ml / min / 1.73 m ²	71.46±12.19	68.76±12.29	65.67±13.68
IL-6, pg / ml	20.32±3.59	21.75±2.30*	21.58±2.93
TNF-α, pg / ml	11.16±2.28	11.86±1.74	10.46±1.93
Adiponectin, ng / ml	6.36±0.52	6.10±0.45*	6.13±0.52**
Fet-A, ng / ml	301.47±25.14	314.16±17.90*	319.64±14.38**
CK-18, U / l	309.59±51.82	321.31±52.25	312.80±62.31

Note: * – statistically significant differences between G/G and G/T genotypes; ** – statistically significant differences between G/G and T/T genotypes; ^ – statistically significant differences between G/T and T/T

Table 3

Comparative evaluation of metabolic parameters of patients with comorbidity of NAFLD and RPAH in G/G and G/T + T/T genotypes ADIPOQ

Parameters	Genotype G/G, n=35	Genotype G/T+T/T, n=52
BMI, kg / m ²	31.74±3.92	33.86±3.52*
SBP, mm Hg	171.74±5.07	172.6±34.56
DBP, mm Hg	101.83±3.61	102.62±3.65
Average BP, mm Hg	131.19±3.64	132.02±3.59
TIM CCA, sm	0.88±0.12	0.91±0.13
EDVD,%	7.72±1.25	7.06±1.15*
AST, U / l	45.97±28.63	55.35±33.66
ALT, U / l	51.91±32.00	67.19±49.75
GGTP, U / l	64.53±26.59	70.43±37.50
TC, mmol / l	5.93±0.80	6.00±0.88
TG, mmol / l	2.24±0.89	2.24±1.00
HDL, mmol / l	1.25±0.47	1.23±0.32
LDL, mmol / l	3.88±0.84	4.06±0.90
Blood glucose, mmol / l	5.63±0.54	5.67±0.53
HOMA-IR	3.77±0.53	4.26±0.79*
Creatinine, μmol / l	97.37±9.60	99.25±13.11
GFR, ml / min / 1.73 m ²	71.46±12.19	68.17±12.49
IL-6, pg / ml	20.32±3.59	21.72±2.40*
TNF-α, pg / ml	11.16±2.28	11.59±1.84
Adiponectin, ng / ml	6.36±0.52	6.12±0.46*
Fet-A, ng / ml	301.47±25.14	315.22±17.29*
CK-18, U / l	309.59±51.82	319.67±53.77

Note: * – statistically significant differences between G/G and G/T + T/T genotypes.

levels, which, according to researchers, may affect the course of NAFLD, hypertension and CKD. Interesting are the data concerning the correlations of levels of fet-A and adiponectin, which also has an important influence on the pathogenesis of NAFLD. It is a key regulator of end-organ damage in obesity, CKD, and NAFLD [6, 13]. The genes for fet-A and adiponectin are located in 3q27 in the human genome. They can work in concert to regulate IR. Indicators of both of these proteins are closely related to the components of MS, but in opposite directions. Higher fet-A and low adiponectin may contribute to IR and the development of type 2 diabetes [16, 23].

Analyzing the obtained results, we can state the presence of the influence of the G276T polymorphism of the ADIPOQ on metabolic and inflammatory parameters, as well as the condition of the arteries in patients with comorbidity of NAFLD and RPAH. The meta-analysis of Liu J et al., 2019 [10] also testifies to the influence of the G276T polymorphism of the ADIPOQ on the origin and course of NAFLD. Regarding carbohydrate metabolism disorders in NAFLD, our data are the same as those obtained in recent studies [17]. The data of our study confirm the influence of the G276T polymorphism of the ADIPOQ gene on biochemical parameters in patients with NAFLD and AH [10, 14, 15].

Conclusions

It can be stated that the presence of the T allele of the polymorphic marker G276T of the ADIPOQ is associated with the development of more pronounced metabolic and pro-inflammatory changes in patients with comorbidity of NAFLD + RPAH.

In the presence of patients with comorbidity NAFLD and RPAH G/T and T/T genotypes, carbohydrate metabolism disorders are more pronounced than in the G/G genotype.

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The G276T polymorphism of the ADIPOQ is not associated with markers of liver damage in patients with NAFLD + RPAH.

The presence of G/T and T/T genotypes in patients with comorbidity of NAFLD and RPAH is associated with an increase in IL-6 and fet-A compared to the G/G genotype.

Patients with comorbidity of NAFLD + RPAH and with the T allele of the polymorphic marker G276T of the ADIPOQ gene are more likely to have impaired EDVD, indicating more significant vascular reactivity disorders.

Thus, the role and place of G276T polymorphism of the ADIPOQ gene in patients with comorbidity of NAFLD and RPAH have been established.

Limitations of the study

The control and comparison groups included a small number of patients, while sufficient to determine statistically significant differences. For a more accurate distribution of genotypes and the effect of this on the course of diseases, it is desirable to conduct larger studies with the involvement of a larger number of patients.

Declarations:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure.

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Data Transparency

The data can be requested from the authors.

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CALCIUM-PHOSPHORUS RELATIONSHIPS IN THE COMBINED COURSE OF STABLE CORONARY HEART DISEASE IN PATIENTS WITH OBESITY

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Abstract

The purpose of the study was to optimize the diagnosis and prediction of the development of structural and functional disorders of bone tissue in patients with SCHD and obesity. Thus, lipid profile analysis showed a clinically significant increase in total cholesterol and triglycerides in patients with SCHD. Serum bone mineral status did not exceed normal values, but serum total calcium levels were significantly higher in patients with SCHD and obesity compared to other groups. The indicators of calcium-phosphorus metabolism in the daily urine of patients with SCHD were significantly higher. When conducting densitometric studies in patients with SCHD with normal weight, osteopenic conditions were diagnosed more often than in patients with overweight and obesity. That is, the comorbid course of SCHD and obesity is a high risk of osteodeficiency, which is confirmed by early changes in calcium-phosphorus metabolism.

Keywords: *stable coronary heart disease, obesity, mineral metabolism, osteoporosis.*

Introduction

According to the European Association of Cardiologists, coronary heart disease (CHD) accounts for about 7.5 million deaths per year and in almost 75 %, lethal cases of stable coronary heart disease (SCHD) are registered in low- and middle-income countries [1, 2]. Although successful methods of diagnosis and treatment of various forms of SCHD have been developed so far, the lack of confirmation of a single theory of atherosclerosis, immature system of preventive measures and comorbid disease, does not significantly reduce the number of patients with SCHD. Besides, no less significant problem of modern society is obesity, which is rightly called the non-infectious epidemic of the 21st century [2]. According to the WHO statistics, the number of obese people has more than tripled since 1975 [3, 5, 6]. It has been established that among the adult population of Europe, obesity is the cause of SCHD in 35 % of cases [2, 4].

Comorbid pathology, namely, atherosclerosis as an etiological factor in development of coro-

nary heart disease and obesity, leads to negative consequences, characterized by development of complications, among which there is the frequency and medical and social significance of structural and functional disorders of bone architecture [2–4]. But one of the positive aspects of obesity is considered to be its protective effect on development of osteoporosis (OP) [2]. This fact is denied in some scientific papers, but a number of clinical studies have shown a link between the degree of obesity, the manifestations of atherosclerosis and bone mineral density (BMD) [6].

There is an assumption that a certain similarity between the mechanisms of OP development and atherosclerosis is due to the processes that take place with the participation of mononuclear cells [2]. This structural unit in atherosclerosis is differentiated in the vascular wall into macrophage-like "foamy" cells, and in OP – in osteoclasts [5, 8, 9]. Hyperproduction of propulsive growth factors, which, in turn, induce bone resorption, also plays an important role in the development of atherosclerotic vascular lesions [2, 7, 10]. Histological similarity was also found between atherosclerotic plaque and bone tissue [11, 12]. In this case, it can be assumed that the protective effect of adipose tissue in osteopenic conditions is a predictor of accelerated formation of athero-

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sclerotic plaques [2, 5]. This assumption became the scientific hypothesis of this study.

2. Purpose, subjects and methods:

2.1. The purpose was to optimize the diagnosis and prediction of development of structural and functional disorders of bone tissue in patients with SCHD and obesity.

2.2. Subjects & Methods

98 persons with SCHD (of them 79 with concomitant obesity -main group, 19 with normal weight -comparison group) were involved in the study. The mean age of patients in the main group was 52.4 ± 1.44 years, in the comparison group – 51.8 ± 1.94 years. The duration of SCHD history was 2.9 ± 1.2 and 2.4 ± 1.6 years, respectively. Gender ratios corresponded to the following: women predominated in both groups – 54.8 % and 52.9 %, respectively. Body mass index was calculated by Quetelet's index. The mean BMI was 31.87 ± 0.26 % in the main group and 23.8 ± 0.24 % in the comparison group. The control group included 20 healthy individuals of the same gender and age. At an earlier stage of the study, the data were published in scientific articles Pasiyeshvili L., Ivanova K. [2, 5].

This research was conducted in compliance with all relevant diagnostic and treatment standards of the requirements for the ethical component of clinical trials (GCP, 1997). Before the study, the patients were informed about the essence of the study, its purpose and possible results. All study participants provided written informed consent. This study was approved by the local ethics committee according to the recommendations of the ethical committees for biomedical research, Ukrainian legislation on health protection, the 2000 Helsinki Declaration and the directives of the European Partnership 86/609 on the participation of people in biomedical research [6].

The diagnoses of obesity and SCHD were verified the basis of unified clinical protocols of medical care "Obesity" and "Stable coronary heart disease" (WHO, 1997; Order of the Ministry of Health of Ukraine No. 152 dated 02.03.2016).

The state of bone mineral metabolism was assessed by the content of total and ionized calcium and serum phosphorus.

The indicators of lipid metabolism were determined by the content of total cholesterol (TC), low lipoprotein cholesterol (LLC), very low lipoprotein cholesterol (VLLC) and high density lipoprotein (HDL), triglycerides (TG) using standard test systems. The atherogenic index (AI) was calculated using the formula: $AI = (TC - HDL) / HDL$.

Bone mineral density was determined by X-ray dual-energy bone densitometry of the lumbar spine (DEXA-Dual-energy X-ray Absorbtiometry). Deviation of BMD from the normal values was determined by the value of the T-criterion (T-score), an indicator adopted by the WHO to verify osteopenic syndrome. T-test is the number of standard deviations from the mean peak of bone mass of a healthy population [2, 5].

T-test was calculated automatically using DEXA software and a database of BMD values of healthy age- and sex-matched individuals, downloaded into the memory of the device. The values of the T-test + 2.5 ... -1 standard deviation (SD) from the peak bone mass were considered normal indicators of BMD. Osteopenia included T-criteria -1 -2.5 standard deviations, osteoporosis – T-criteria -2.5 standard deviations and below [8, 13].

Prior to the examination, the patients did not receive therapy for osteoporotic conditions correction.

Exclusion criteria were acute coronary syndrome, chronic heart failure of functional class IV (NYHA) and other diseases accompanied by osteodeficiency (intestinal disease, diabetes, thyroid disease, etc.).

Statistical analysis was performed using the software package "Statistica 10.0". For quantitative characteristics, the results were presented as the median (Me) with an interquartile range [Q25 %; Q75 %] taking into account the lack of normal distribution [2, 5]. Quantitative and ordinal variables were compared using the Mann-Whitney criteria. In all procedures of statistical analysis, the significance level p was assumed to be equal to or less than 0.05.

3. Results & Discussion

The study of patients with SCHD allowed positioning of this category as a group of high cardiovascular risk. In addition to the traditional characteristics of this risk (age, high functional class of angina, the presence of chronic heart failure, various comorbid conditions), most patients in the main group were characterized by the absence of clinical manifestations of osteopenic syndrome.

Comparative analysis of lipid metabolism revealed a significant difference between the groups (*Table 1*).

Thus, the level of TC in patients with SCHD with obesity was 1.04 times higher than in patients with isolated SCHD ($p < 0.005$) and 1.27 times higher than in healthy people ($p < 0.001$). Analysis of LLC also revealed a significant difference between the groups: it was 1.6 times higher in the main group compared to the control and 1.7 times higher in

Table 1*The level of lipid metabolism in patients with SCHD and its combination with obesity*

Indexes	Main group n=79	Comparison group n=19	Control group n=20
TC, mmol/l	5.89 (5.65;6.24)*	5.64(4.97;6.0)*	4.63 (4.25;4.79)
LLC, mmol/l	4.33 (4.09;4.62)*	4.24 (3.69;4.61)*	4.24 (3.69;4.61)
VLLC, mmol/l	0.73 (0.64;0.86)*	0.6 (0.55;0.64)*	0.38 (0.36;0.41)
HDL, mmol/l	0.82 (0.76;0.88)*	0.81(0.77;0.92)*	1.4 (1.23;1.55)
RG, mmol/l	1.61 (1.41;1.9)*	1.32 (1.22;1.41)*	0.82 (0.78;0.9)
AI	6.27 (5.70;6.8)*	5.63 (5.13;6.6)*	1.91 (2.96;2.65)

Notes: $p < 0.05$ *, – in relation to the control group.

the comparison group compared to the control ($p < 0.001$). LLC values in patients with SCHD did not differ statistically. The level of VLLC was 1.2 times higher in the main group than in the comparison group and 1.9 times higher than in the control group ($p < 0.001$). The difference in VLLC values of the comparison and control groups also had a significant difference ($p < 0.001$). The results of HDL were significantly lower in the main and comparison groups mmol/l relative to the control group, ($p < 0.001$), and did not differ statistically in patients with SCHD, ($p = 0.36$). TG values were 1.2 times higher in the main group compared with the comparison group and 2 times higher than in the control group ($p < 0.001$). The TG level of the comparison group was also significantly higher than in the control group ($p < 0.001$). The AI of the main group was 1.1 times higher than in the comparison group 3.3 times higher than the control group. These data coincide with previously obtained results, which show that the characteristic potentially atherogenic indicators of the blood lipid profile are not so much an increase in TC levels, but an elevated TG level and a decreased level of LLC [12]. Some indicators of lipid metabolism in SCHD significantly differed from the control group, but were within the normative values, which may be the result of receiving lipid-lowering therapy.

Analysis of mineral metabolism revealed some patterns (Table 2). Although the level of phosphorus-calcium metabolism did not exceed the reference values, there was a tendency to increase total calcium in patients with SCHD and obesity compared with isolated SCHD and the control

group ($p < 0.001$). The difference in blood phosphorus parameters was not significant, but there was a tendency to increase phosphorus levels in patients with SCHD and obesity mmol/l compared with the control group ($p = 0.36$).

Experimental studies show that elevated calcium levels may play an important role in the pathogenesis of cardiovascular disease. Thus, there are studies in which a positive relationship has been established between normal serum calcium levels and atherosclerosis of the carotid arteries [2, 14, 15], as well as between blood calcium levels and obesity [16, 17].

Comparative analysis of indicators of phosphorus-calcium metabolism in urine (Table 3) revealed a significant difference between the level of urinary calcium in patients of the main group, comparison group and control one with a tendency to increase urinary calcium excretion in patients with SCHD and obesity. Thus, the level of calcium in the daily urine of the main group was 2 times higher than in the comparison group ($p < 0.001$). Urinary phosphorus levels were statistically lower in patients with SCHD with normal weight compared to other groups, but was within the reference values ($p < 0.001$).

That is, in the presence of atherosclerosis there is an increased excretion of calcium in the urine and concomitant obesity exaggerate this process [2]. These data deny the assumption that adipose tissue plays a protective role in the development of osteoporosis. At the same time, the results of the densitometric study showed the opposite result. Thus, when conducting a densitometric study in the comparison group,

Table 2*The content of phosphorus-calcium metabolism in the serum of patients with SCHD and comorbidity with obesity (mmol/l)*

Indexes	Main group n=79	Comparison group n=19	Control group n=20
Phosphorus	1.5 (1.4;1.7)	1.5 (1.35; 1.6)	1.44 (1.22; 1.58)
Total calcium	2.5(2.4;2.56)*	2.4(2.35; 2.46)*	2.21 (2.13; 2.27)

Notes: $p < 0,05$ *, – in relation to the main group.

Table 3

The content of indicators of phosphorus-calcium metabolism in the urine of patients with SCHD and its combination with obesity

Indexes	Main group n=79	Comparison group n=19	Control group n=20
Phosphorus, g/day	1.34 (0.99;1.72)	0.98(0.77;1.12)**	1.07 (0.86.1.45)
Calcium, mg/day	377(230;450)*	320(220;400)*	195 (158.5;289)

Notes: p < 0.05 * – in relation to the comparison group; p < 0.05 ** – in relation to the control group.

osteopenic conditions were diagnosed in 54 % of patients (35.6 % – osteopenia, 18.4% – osteoporosis) against 28.5% of osteopenia in patients of the main group (p < 0.05). There were no signs of osteoporosis in patients with SCHD and obesity.

Thus, the changes in calcium-phosphorus metabolism in patients with SCHD and obesity can be considered as a predictor of osteopenic conditions. Whereas, according to the results of densitometric research, the percentage of patients with osteopenic conditions is lower in the presence of excess weight or obesity. Probably, the level of protective mechanisms is influenced by the degree of obesity and the peculiarities of adipose tissue distribution, so the data obtained require further study.

Conclusions

The course of stable coronary heart disease occurs against the background of changes in blood lipid spectrum and calcium-phosphorus metabolism. In patients with SCHD in combination with obesity there is an increase in total calcium and serum phosphorus, which can be considered as a factor that enhances the development of atherosclerotic vascular lesions.

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The comorbid course of SCHD and obesity is an unfavorable factor of high risk of developing osteodeficiency states, which is confirmed by early changes in calcium-phosphorus metabolism.

For the purpose of early diagnosis of osteoporotic conditions in patients with SCHD and obesity, it is advisable to determine the bone mineral density according to the indicators of phosphorus-calcium metabolism and/or conduct a densitometric study.

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Statement of Ethics

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The data can be requested from the authors.

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PRO-ATHEROGENIC LIPID PROFILE IN PULMONARY TUBERCULOSIS PATIENTS WITH CONCURRENT INSULIN RESISTANCE

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Abstract

Background. The problem of studying lipid metabolism in patients with tuberculosis is of interest to scientists around the world. The purpose of the study was to investigate lipid profile in pulmonary tuberculosis patients with concurrent insulin resistance. **Materials and methods.** Forty-one patients with pulmonary tuberculosis were examined. Insulin resistance index (HOMA-IR), total cholesterol level (TC), triglycerides (TG) level, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol and atherogenic index (AI) were measured. The patients were divided into two groups: group 1 – 26 patients with tuberculosis and insulin resistance (HOMA-IR > 2.7); group 2 – 15 patients with tuberculosis without insulin resistance (HOMA-IR < 2.7). **Results.** Group 1 patients had severe course of TB with fever, severe fatigue and weakness, profuse sweating, weight loss, cough and shortness of breath. Median TC indices differed at significant level ($p = 0.012$): group 1 – 4.82 mmol / L, group 2 – 4.25 mmol / L. TG level was higher in group 1 patients – 1.32 mmol / L than in group 2 patients – 1.28 mmol / L. LDL cholesterol values were higher in group 1 patients – 3.2 mmol / L, vs. group 2: 2.5 mmol / L. The AI was higher in group 1 ($p = 0.005$): 3.9 units against 2.8 units in group 2 patients. **Conclusions.** Insulin resistance in pulmonary tuberculosis patients was associated with severe course of the disease, severe clinical manifestations and impaired external respiration. Pro-atherogenic disorders of lipid metabolism in pulmonary tuberculosis patients with concurrent insulin resistance can be considered as the degree of endogenous intoxication.

Keywords: *pulmonary tuberculosis, insulin resistance, lipid disorders.*

Introduction

Lipids play an essential role in life processes. As one of the main components of biological membranes, lipids affect their permeability, participate in the transmission of nerve impulses, and the creation of intercellular contacts. Fat serves as a very efficient source of energy in the body, either directly or potentially in the form of stored adipose tissue [1, 2].

The scientific data on the effect of lipid metabolism on the immune reactivity of the body are extremely contradictory and contain information about both the development of metabolic immunosuppression and the activation of the immune system function [3, 4].

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The state of lipid metabolism in tuberculosis patients has long been considered an important component of the immunobiological state of the organism, although the assessment of the nature of these connections has undergone dramatic changes over time. Today the overwhelming majority of researchers consider total cholesterol in the biological environment of the host organism as a contributing factor to persistence and replication of *M. tuberculosis*. The problem of studying the indices of lipid metabolism in patients with tuberculosis (TB) for many years is of interest to scientists around the world [5, 6]. It is known that TB is accompanied by severe disorders of lipid metabolism of the macroorganism, which subsequently acquire the quality of independent factors, and can independently affect the further course of the disease and the outcome of treatment. Even more severe manifestations of dyslipidemia are observed in patients with

combined pathology of tuberculosis / diabetes mellitus [7]. Elevated insulin levels stimulate lipogenesis de novo in hepatocytes, but are unable to inhibit lipolysis in insulin-resistant adipose tissue cells – adipocytes, which leads to increased free fatty acids in the liver and the formation of excessive amounts of low and very low density lipoproteins. The state of lipid metabolism in patients with TB against a background of concomitant insulin resistance (IR) is not well understood. Therefore, this issue has attracted our attention.

1. Purpose, subjects and methods

1.1. The purpose of the study was to investigate lipid profile in pulmonary tuberculosis patients with concurrent insulin resistance.

2.2. Subjects and methods

Forty-one patients with firstly-diagnosed pulmonary tuberculosis were included in the study. The patients with co-morbid pathology (diabetes mellitus, chronic nonspecific lung disease, chronic hepatitis, HIV / AIDS) were excluded from the study. Data from patients who were overweight (BMI >25) were not taken into account when calculating the body mass index. The study did not include children and adolescents, the elderly, pregnant women, people from vulnerable groups, and patients who did not consent to the processing of personal information. The study was approved by the ethics commission of the Kharkiv National Medical University. Examination and diagnosis were made according to the current order of the Ministry of Health of Ukraine. All participants of the study underwent an oral glucose tolerance test, determined fasting insulin levels, and insulin resistance index (HOMA-IR) and body mass index (BMI) were calculated. Total cholesterol level (TC), triglycerides (TG) level, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol and atherogenic index (AI) were also measured.

For statistical data processing, a package of general-purpose data processing programs Statistica for Windows version 13.2 was used. At the first stage of calculation, descriptive statistics were obtained for indicators measured on a quantitative scale. Such characteristics included median and mean as a measure of position; standard deviation and quartiles as measures of scattering; minimum and maximum value as indicators of sample size. Kolmogorov-Smirnov criterion was used to verify the coincidence of the distribution of quantitative indicators with the normal one in the groups. Because the law of

distribution of the studied numerical indicators differed from the normal one, the statistical significance was checked using the Mann-Whitney U-test. Qualitative traits were compared using the Pearson test χ^2 . The differences were considered statistically significant at $p < 0.05$.

3. Results & Discussion

According to the calculation of the HOMA-IR, patients were divided into two groups. Group 1 consisted of 26 patients with pulmonary tuberculosis and insulin resistance (TB/IR) (HOMA-IR > 2.7); Group 2 – consisted of 15 patients with pulmonary tuberculosis without insulin resistance (TB) (HOMA-IR < 2.7). The age of patients ranged from 20 to 55 years. The age groups were identical. By sex, patients in Group 1 (TB / IR) were almost halved: 58.85 % of the group were men (14 people) and 46.15 % (12 patients) were women. Among the surveyed Group 2 (TB), the vast majority (93.33 %, 14 patients) were men. This distribution was statistically significant, $p < 0.01$.

The vast majority of patients in Group 1 (TB / IR) (17 patients (65.4 %)) were identified at the time of treatment and indicated the presence of intoxication and "chest" complaints, which bothered them from 2 weeks to 2 months, while patients of Group 2 (TB) were detected mostly actively, during a screening chest x-ray examination (8 patients (53.3 %)) and did not notice any deviations in general well-being and health status (*Table 1*).

Radiologically, patients of both groups were characterized by bilateral lung lesions: group 1 (TB / IR) – 15 patients (57.7 %), group 2 (TB) – 12 patients (80 %). The predominant clinical form was infiltrative TB (group 1 (TB / IR) – 88 %, group 2 (TB) – 100 %), although among the patients of group 1 there were other, more severe forms of the disease: fibro-cavernous – 8 % and disseminated – 4 %. Almost the same proportion of patients in both groups had destructive changes in the lungs: 16 patients (61.5 %) of group 1 (TB / IR) and 9 patients (60 %) of group 2 (TB). However, when determining the function of external respiration, half of patients with insulin resistance (13 people – 50 %) were found to have respiratory disorders of a mixed type of extremely severe severity, while patients without insulin resistance only 6 patients had such changes (15.38 %) ($p = 0.005$).

As a result of the comparison of lipid metabolism indices between examined groups, we found significant difference in the levels of total cholesterol, low-density lipoprotein cholesterol and the atherogenic index ($p < 0.05$) (*Table. 2*).

Table 1

Patient's complaints

Complaints	Group 1 (TB/IR)	Group 2 (TB)
Weakness	18 (69.2 %)	7 (46.6 %)
Fatigue	15 (57.7 %)	5 (33.3 %)
Loss of appetite	8 (30.8 %)	4 (26.7 %)
Low grade fever	16 (61.5 %)	7 (46.7 %)
Fever	8(30.8 %)	2 (13.3 %)
Increased sweating	17 (65.4 %)	6 (40 %)
Wet cough	18 (69.2 %)	6 (40 %)
Dry cough	6 (23.1 %)	1 (6.7 %)
Pain in the chest	4 (15.4 %)	1 (6.7 %)
Weight loss	13(50 %)	4 (26.7%)
Dyspnea	8(30.8 %)	0

Table 2

Lipid metabolism indices of examined patients

Indices	Mean	Median	Min	Max	Std.Dev.
Group 1					
Total cholesterol, mmol/L	4.53	4.82*	3.33	7.95	0.43
Triglycerides, mmol/L	1.28	1.32	1.17	1.48	0.09
HDL cholesterol, mmol/L	1.16	1.13	0.98	1.45	0.17
LDL cholesterol, mmol/L	3.14	3.2**	1.6	6.5	0.44
VLDL cholesterol, mmol/L	0.59	0.56	0.51	0.66	0.04
Atherogenic index, units	2.78	3.9***	1.89	3.52	0.54
Group 2					
Total cholesterol, mmol/L	4.30	4.25*	2.94	6.08	0.66
Triglycerides, mmol/L	1.24	1.28	1.12	1.36	0.09
HDL cholesterol, mmol/L	1.14	1.17	0.97	1.26	0.11
LDL cholesterol, mmol/L	2.63	2.5**	1.0	4.3	0.62
VLDL cholesterol, mmol/L	0.56	0.58	0.51	0.62	0.04
Atherogenic index, units	2.31	2.8***	2.10	3.15	0.45

* p <0.05.

Among the group of patients with pulmonary tuberculosis and concurrent insulin resistance on admission to the hospital, the indices of TC were generally higher than those obtained in the group of patients without insulin resistance. The minimum level of TC in group 1 (TB / IR) was 3.3 mmol / L, and the maximum was 7.95 mmol / L. For group 2 (TB), these values were 2.94 mmol / L and 6.08 mmol / L, respectively. Medial values of TC indices differed at a statistically significant level between groups (p = 0.012): group 1 (TB / IR) – 4.82 mmol / L, group 2 (TB) – 4.25 mmol / L.

Plasma TG level was also higher in group 1 (TB / IR) patients – 1.32 mmol / L than in group 2 (TB) patients – 1.28 mmol / L (medial values are given). However, no statistical significance was obtained in this difference.

As well as when comparing the Medial values of HDL cholesterol were lower in patients with TB and insulin resistance than in those who didn't have insulin resistance (0.98 mmol / L and 1.09 mmol / L). The median VLDL cholesterol values were almost indistinguishable between group 1 (TB / IR)

and group 2 (TB) (0.6 mmol / L and 0.58 mmol / L, respectively).

LDL cholesterol values were higher in patients of group 1 (TB / IR) and ranged from 1.6 mmol / L to 6.5 mmol / L with a median value of 3.2 mmol / L, compared with patients in group 2 (TB): the minimum level is 1.0 mmol / L, the maximum is 4.3 mmol / L, the medial value is 2.5 mmol / L. The obtained difference was statistically significant (p = 0.004).

The atherogenic index was higher in the group of patients with tuberculosis who had insulin resistance (p = 0.005). Its medial value was 3.9 units against 2.8 units in patients with tuberculosis without insulin resistance.

Our study revealed that those pulmonary tuberculosis patients, who was diagnosed with concurrent insulin resistance had severe course of tuberculosis. The majority of these patients complained of fever, severe fatigue and weakness, profuse sweating, weight loss, cough and shortness of breath. Decreased insulin sensitivity may occur due to disruption of various molecular

pathways. The exact underlying cause of insulin resistance remains unclear, with a number of key mechanisms proposed, including oxidative stress, inflammation, insulin receptor mutations, endoplasmic reticulum stress, and mitochondrial dysfunction [8, 9]. Therefore, we make the assumption that the development of insulin resistance in patients with tuberculosis was associated with the severe course of the disease.

Our study also revealed significant disorders of lipid metabolism (increase in the levels of total cholesterol, low-density lipoprotein cholesterol and atherogenic index) in pulmonary tuberculosis patients with concurrent insulin resistance. The same changes were found by other scientists [10, 11] and can be explained as the systemic alteration of lipid metabolism by insulin resistance, which then leads to the development of dyslipidemia and the well-known lipid triad: high levels of plasma triglycerides, low levels of high-density lipoprotein, and the appearance of small dense low-density lipoproteins

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Conclusions

Insulin resistance in pulmonary tuberculosis patients was associated with severe course of the disease, severe clinical manifestations and impaired external respiration.

Pro-atherogenic disorders of lipid metabolism in pulmonary tuberculosis patients with concurrent insulin resistance can be considered as the degree of endogenous intoxication.

Declarations:

Statement of Ethics

The authors have no ethical conflicts to disclose.

Consent for publication

All authors give their consent to publication.

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RESULTS OF TREATMENT OF PATIENTS WITH MIDFACIAL FRACTURES

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Abstract

Background. Fractures of the bones of the facial skeleton, in particular the midface area, are one of the most frequent reasons for patients to apply to maxillofacial inpatient care, not only in Ukraine but also abroad. Along with more modern treatment technologies (osteosynthesis using titanium miniplates and minigrad for fixation bone fragments), methods of repositioning of fragments with subsequent tamponade of the maxillary sinus with iodoform tampon and without tamponade and fixation of fragments are used. A certain group of patients is treated conservatively, which is associated with their reluctance to undergo surgery, minimal displacement of fragments or minimal cosmetic and functional impairments. **The purpose of the study.** Comparative evaluation of the results of treatment of patients with fractures of the midface area by repositioning the fragments of the zygomatic-orbital complex without fixating the fragments and their subsequent fixation by tamponade of the maxillary sinus with iodoform tampon. **Object and methods of research.** The comparison was made of the results of treatment of 70 patients with fractures of the midface area, among which 13 patients were treated by the method of repositioning fragments of the zygomatic-orbital complex (ZOC) without fixation and without maxillary sinus tamponade, 29 patients underwent repositioning of ZOC fragments with subsequent fixation of fragments with iodoform tampon – the tamponade of the maxillary sinus was performed on the affected side. For comparison, the results of conservative treatment of 28 patients with fractures of the midface area were used. **Results.** It was found that the reliable ($\chi^2=11.43$; $p<0.05$) majority of patients (64 %) sought treatment within 0–3 days after injury. 83–89 % of patients who underwent repositioning of the fragments had fresh small-fragment fractures. The reliable ($\chi^2=11.43$; $p<0.05$) majority of them simultaneously had 3–4 sites of bone fractures of the midface area, hemisinus of varying degrees and paresthesia in the infraorbital area. In the majority of patients who underwent repositioning of bone fragments with and without tamponade (85 % and 93 %, respectively), the final displacements ranged from 3.1 to 6 mm. In patients treated conservatively, in most cases (93 %) the displacements were greater than 3.1 mm, which remained after treatment. **Conclusion.** In the majority of patients treated with the studied methods, in the long term, the displacement of bone fragments remained, which had functional and cosmetic consequences. In all studied groups, a certain cosmetic effect was achieved over time, as evidenced by a reliable ($\chi^2=160.9$; $p=0.00000$) decrease in the indicator by the VAS.

Keywords: *fractures of the midface area, reposition of fragments without fixation, reposition of fragments with fixation, tamponade of the maxillary sinus, computed tomography, visual analogue scale.*

Introduction

Traumatic fractures of the maxillofacial area account for 14 to 17 % of all facial injuries [1]. The frequency of severe or complex maxillofacial

injuries, according to a number of authors, has been declining over the past 10 years [2].

Traumatic fractures of the bones of the facial skeleton, in particular the midface area, are one of the most frequent reasons for patients to apply to maxillofacial inpatient care, not only in Ukraine but also in foreign countries [3–9].

It is known that fractures of the midface area cause severe deformities, which affects the appearance of patients' faces [10].

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Quite often these fractures cause various other concomitant pathological conditions that can cause impaired nasal breathing, occlusion, vision, etc. [11].

The most common injuries of the skull and maxillofacial area occur as a result of road traffic accidents, street and household injuries, injuries in the area of military conflicts [12, 13].

In order to achieve the maximum cosmetic and functional result in patients with midface fractures, treatment should be started as soon as possible [14].

Surgical methods of treatment are most often used in Ukraine and in near and not-so-near abroad for the treatment of midface fractures with displacement of fragments [15–17]: reposition of fragments without fixation and reposition of fragments with fixation, which is performed by tamponade of the maxillary sinus with iodoform

of 28 patients with fractures of the mid face area (third group), who were treated conservatively or refused surgery were used for comparison.

All patients in the first group were male. The average age of patients was (29.6 ± 10.8) years old with a range of 20 to 57 years, i.e. all patients were of working age. The second group consisted of 28 (97 ± 3.2) % of men and one woman. The mean age of patients was (29.4 ± 9.6) years old with a range of 18 to 62 years. Of all patients in this group, only one patient was of retirement age. The group of patients receiving conservative treatment of fractures of the midface area consisted of 28 people, among whom there were 25 (89 ± 5.9)% of men and 3 (11 ± 5.9)% of women. Of all patients in this group, only one patient was of retirement age.

Table 1 shows the distribution of patients in the study groups by the mechanism of injury.

Table 1

Distribution of patients with fractures of the midface area by the mechanism of injury, (%)

Mechanism of injury	Group			Total (n=70)
	1 (n=13)	2 (n=29)	3 (n=28)	
Falling	4 (31 ± 12.8)	14 (48 ± 9.3)	10 (36 ± 9.1)	28 (40 ± 5.9)
Household	0	0	3 (10 ± 5.7)	3 (4.0 ± 2.3)
Criminal	8 (62 ± 13.5)	15 (52 ± 9.3)	11 (37.7 ± 5.7)	34 (49 ± 6.0)
Due to road traffic accident	1 (7.0 ± 5.9)	0	3 (10 ± 5.7)	4 (6.0 ± 2.3)
Industrial	0	0	1 (3.6 ± 2.8)	1 (1.0 ± 0.9)

tampon, external fixation, using a Kirschner wire, balloon tamponade of the maxillary sinus, Foley catheter, etc. [18–23].

Thus, it is of practical interest to compare common methods of treating midface fractures of different etiology and localization in order to further improve them.

2. Purposes, subjects and methods:

2.1. Purpose of the study was the comparative evaluation of the results of treatment of patients with fractures of the midface area by repositioning the fragments of the zygomatic-orbital complex without tamponade of the maxillary sinus and repositioning the fragments of the zygomatic-orbital complex with subsequent tamponade of the maxillary sinus.

2.2. Subjects & Methods

We compared the results of treatment of 70 patients with fractures of the midface area, among whom 13 patients were treated by the method of repositioning the maxillary sinus fragments without fixation and without maxillary sinus tamponade (first group), 29 – by the method of repositioning fragments with maxillary sinus tamponade (second group). The results of treatment

According to the data of *Table 1* it can be noted that the largest number of injuries was criminal (49 %) and as a result of falling (40 %), other types of injuries were rare.

The examination of patients at hospitalization included: general clinical blood and urine tests, biochemical blood tests, electrocardiography, X-ray or fluorography of thoracic organs, cone-beam computed tomography (CBCT) of the skull/midface area.

Evaluation of the severity of clinical manifestations of traumatic injuries before treatment, as well as the course and outcomes of treatment, was performed using a visual analogue scale (VAS) [24]. The VAS, used in our study, was modified by us and allowed to objectively evaluate the initial condition and outcomes of treatment of patients with fractures of the midface area. According to the VAS, the following symptoms were evaluated in points: intensity of pain, presence of nasal breathing and nosebleeds on the side of the injury, sensitivity impairments, presence of edema, subcutaneous emphysema, soft tissue hematoma, hemosinus of the maxillary sinus, restriction of mouth opening, "stairs"

symptom (including malocclusion), visual impairment on the side of the injury, and the magnitude of the displacement of the fragments was also taken into account (according to the data of CBCT).

An objective evaluation of the effectiveness of treatment was performed by comparing the magnitude of displacement of bone fragments before and after treatment. For the convenience of presenting information, a scoring scale was introduced, according to which: 0 points – no displacement, 1 point – displacement from 1 to 3 mm; 2 points – 3.1–6 mm; 3 points – 6.1–9 mm; 4 points – 9.1–12 mm; 5 points – 12.1–15 mm; 6 points – more than 15 mm.

The results of the study were processed using the STATISTICA – 13.3 software package (license AXA9051924220FAACD-N). Descriptive statistics methods and nonparametric χ^2 Pearson and Mann-Whitney criteria were used. In cases of significant variance of indicators, the medians (Me) and quartiles (25 %; 75 %) were calculated.

3. Results & Discussion

The results of the study of the health encounter terms after injury are shown in *Table 2*. It can be noted that reliable differences in the frequency of encounters within a certain period of time from the moment of injury were detected only between the second and third groups.

matic-orbital complex). The patients of this group were divided by the fracture side in the following way: 12 (41 ± 9.1) % of patients had fractures on the right side, 17 (59 ± 9.1) % – on the left side. In the third group 3 (11.0 ± 5.9) % of patients had linear fractures of the midface area – zygomatic-orbital complex, 23 (82 ± 7.3) % – small-fragment fractures of zygomatic-orbital complex, 2 (7.0 ± 4.8) % – large-fragment fractures of zygomatic-orbital complex.

The patients of the third group were divided by the fracture side in the following way: 7 (25 ± 8.2) % of patients had fractures on the right side, 17 (61 ± 9.2) % of patients – on the left side, 4 (14 ± 6.6) % of patients had Le-Fort fractures (on both sides).

The distribution of patients in the study groups by the localization of fractures is shown in *Table 3*. According to the data of *Table 3* it can be noted that in the reliable majority of patients of all groups, fractures are localized in zygomatic-orbital complex (40 %), and are accompanied by fractures of the zygomatic arch and bone (50 %).

Usually with injuries of the midface area there are bone fractures in several places (*Table 4*).

According to the data of *Table 4* it can be noted that in the reliable ($\chi^2 = 11.43$; $p < 0.05$) majority of cases (64 %) 3–4 sites of fractures of the midface area, known in the literature as

Table 2

Distribution of patients by the terms of health encounter, (%)

Group	Term of health encounter, day			
	0	1–3	4–7	More than 7
1 (n=13)	2 (15±9.9)	6 (46±13.8)	4 (31±12.8)	1 (8.0±7.5)
2 (n=29)	4 (14±6.4)	10 (34±8.8)	7 (24±7.9)	8 (28.0±8.3)
3 (n=28)	12 (43±9.4)*	11 (39±9.2)	2 (7.0±4.8)	3 (11.0±5.9)
	$\chi^2 = 5.52$			
Total	18	27	13	12

Note: * – differences in the frequency of encounter of patients within a certain period after injury between the second and third groups are reliable ($p < 0.05$).

According to the data of *Table 2* it can be noted that the reliable ($\chi^2 = 11.43$; $p < 0.05$) majority of patients (64 %) sought treatment within 0–3 days after injury.

All patients of the first group, 24 (83 ± 7.0) % of patients of the second and 25 (89 ± 5.9) % of patients of the third group had fresh fractures, which constituted the reliable majority in each group.

All patients of the first group had closed small-fragment fractures of the midface area, in 92 % of cases – with localization on the left side. The patients of the second group had closed small-fragment fractures of the midface area (zygo-

"tripod fracture" and "tetrapod fracture", were observed simultaneously.

Some patients of the first group, in addition to fractures of the midface area had: fractures of the mandible – 2 (15 ± 9.9) % and fractures of the nasal bones – 6 (46 ± 13.8) %. In the second group the following were observed: fractures of the mandible – 1 (3.6 ± 2.8) % and fractures of the nasal bones – 10 (34 ± 8.8) %. 18 (62.4 ± 9.0) % of patients in this group had no concomitant fractures. In the third group there were fractures of the mandible in 3 (11.0 ± 5.9) % of cases, fractures of the nasal bones – in 11 (46 ± 13.8) %, mandible and nose – 12 (43 ± 9.4) % of cases.

Table 3

Distribution of patients of the studied groups by the fracture localization

Groups	Localization of the fracture				
	ZOC	ZOC and ZAC	ZA or ZB	ZOC, ZA and ZB	Le-Fort
1 (n=13)	4 (31±12.8)	0	0	9 (69±12.8)	0
2 (n=29)	12 (41±9.1)	1 (3.0±2.8) $\chi^2=12.42$	0	16 (55±9.2)	0
3 (n=28)	12 (43±9.4)	1 (3.6±2.8)	1(3.6±2.8)	10 (36±9.1)	4(14±6.6)
Total	28 (40±5.9)	2 (3.0±2.0) ^{1,2} $\chi^2=28.68$ $\chi^2=40.01$	1 (1.4±1.0) ^{1,2} $\chi^2=31.71$ $\chi^2=43.23$	35 (50±6.0)	4 (5.6±2.8) ^{1,2} $\chi^2=23.33$ $\chi^2=34.16$

Notes: ZOC – zygomatic-orbital complex; ZAK – zygomatic-alveolar complex; ZA – zygomatic arch; ZB – zygomatic bone; ¹ – differences in the incidence of ZOC fractures and other fractures are reliable ($p<0.05$); ² – differences in the incidence of ZOC fractures in combination with ZA and ZB and other fractures are reliable ($p<0.05$).

Table 4

Distribution of patients by the number and localization of fracture sites, (%)

Group	SFZA	Walls of MS	Number of fracture sites			
			1	2	3	4
1 (n=13)	0	3 (23±11.7)	1 (8.0±7.5)	0	3 (23±11.7)	6 (46±13.8)
2 (n=29)	0	4 (14±6.4)	3 (10.0±5.6)	2 (7.0±4.7)	7 (24±7.9)	13 (45±9.2)
3 (n=28)	1 (3.6±2.8)	3 (11.0±5.9)	1 (3.6±2.8)	7 (25±8.2)	4 (14±6.6)	12 (43±9.4)
Total	1 (1.4±1.0)	10 (14±4.1)	5 (7.0±3.0) ¹ $\chi^2=25.28$	9 (13±4.0) ¹ $\chi^2=16.64$	14 (20±4.8) ¹ $\chi^2=9.46$	31 (44±5.9)

Notes: SFZA – solitary fracture of zygomatic arch; MS – maxillary sinus; ¹ – differences in the incidence of four and other number of fractures are reliable ($p<0.05$).

Paresthesia in the infraorbital area was observed in all patients of the first and second groups, in the third group it was in 27 (96 ± 3.7) % of patients. One of the indications for surgical treatment is the presence of hemosinus. Table 5 shows the distribution of patients according to the degree of hemosinus.

According to the data of Table 5 it can be noted that the reliable majority of patients (90 %) of all groups have hemosinus of varying degrees, which occurred against the background of damage to the walls of the maxillary sinus.

An important indicator that determines the further tactics of treatment of patients is the magnitude of displacement of bone fragments (Table 6).

The analysis of the distribution of patients according to the magnitude of displacement (Table 6) showed that in the first group before the treatment 54 % of patients had a displacement of 9 mm or more, in the second group there were 37 % of such patients, and after the treatment there were no such patients in the groups. Most patients of these groups (85 % and 93 %, respectively).

Table 5

Distribution of patients with fractures of the midface area by the degree of hemothorax, (%)

Group	Degree of hemothorax			Total
	1/3 of sinus	2/3 of sinus	Total	
1 (n=13)	2 (15±9.9)	6 (46±13.8)	3 (23±11.7)	11 (85±9.9)* $\chi^2=12.46$
2 (n=29)	4 (14±6.4)	14 (48±9.3)	9 (31±8.6)	27 (93±4.7)* $\chi^2=43.1$
3 (n=28)	4 (14±6.6)	10 (36±9.1)	11 (46±13.8)	25 (89±5.9)* $\chi^2=34.57$

Note: * – differences in the incidence of hemosinus in the corresponding group and its absence are reliable ($p<0.05$).

Table 6

Distribution of patients of the studied groups by the magnitude of displacement of bone fragments before and after treatment, (%)

Conditions of registering	Group	Displacement, points				
		1	2	3	4	5
Before	1 (n=13)	0	3 (23±11.7)	3 (23±11.7)	6 (46±13.8)	1 (8.0±7.5)
	2 (n=29)	0	4 (14±6.4)* $\chi^2=25.02$	14 (48±9.3)	10 (34±8.8)	1 (3.6±2.8)
	3 (n=28)	2 (7.0±4.8)	15 (54±9.4)	6 (21±7.7)	4 (14±6.6)	4 (14±6.6)
After	1 (n=13)	2 (15±9.9)	7 (54±13.8)	4 (31±12.8)	0* $\chi^2=7.8$	0
	2 (n=29)	2 (7.0±4.7)	23 (79±7.6)	4 (14±6.4)	0* $\chi^2=12.08$	0
	3 (n=28)	2 (7.0±4.8)	15 (54±9.4)	6(21±7.7)	4(14±6.6)	4(14±6.6)

Notes: * – differences in the frequency of the corresponding points in the group before and after treatment are reliable ($p < 0.05$).

respectively) had the final displacements in the range of 3.1–6 mm. In the third group of patients treated conservatively, in most cases (93 %) the displacements were greater than 3.1 mm, which remained after conservative treatment.

Thus, in all studied groups, the displacement of bone fragments, which had not only cosmetic but also functional consequences, remained in the majority of patients.

In order to evaluate the cosmetic effect before and at different periods of treatment, the points according to the VAS were calculated.

For clarity of the presentation, scale diagrams were constructed (Figure). Friedman criterion, which is used to analyze repeated measurements associated with the same object, was used to evaluate the results obtained by the VAS.

In all studied groups, a certain cosmetic effect was achieved over time, as evidenced by a reliable ($\chi^2=160.9$; $p=0.00000$) decrease of the indicator. In the first and second groups according to Figure there is an increase in the indicator after surgery, due to postoperative edema.

Further, the indicator by the VAS decreases. In the third group, where the patients were not operated, the indicator was decreasing throughout

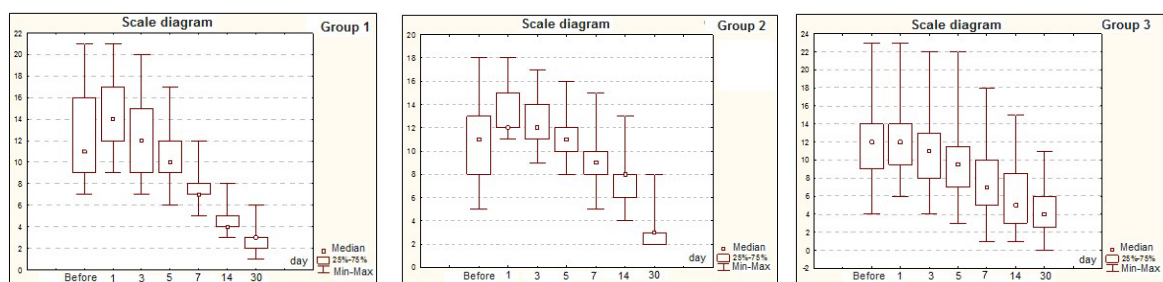
the observation period. No reliable differences were found between the groups by the VAS before surgery and 30 days after it.

In modern clinical practice, visualization and clinical methods are used to evaluate the results of treatment of facial area fractures [25, 26].

There are data in the literature on the use of the VAS points as clinical indicators. The authors use the VAS to evaluate the condition of patients by fractures of the nasal bones [27], fractures of the mandible [28], but in the available literature we have not found information on the use of the VAS to evaluate the quality of treatment of fractures of the midface area.

Therefore, in this study we used the VAS developed by us, which made it possible to objectively evaluate the results of treatment of patients with fractures of the midface area. To evaluate the anatomical features of fractures and the quality of their correction in different ways, CBCT was used.

We have found that both methods of repositioning the fragments allow, to a certain extent, to obtain a positive result in the treatment of fractures of the midface area, but in most cases the displacement of bone fragments remains. If



Scale diagrams of the indicator by the VAS in the studied groups

patients are treated conservatively, the displacement of bone fragments remains forever. This indicates the imperfection of the analyzed methods.

Thus, a comparative analysis of the results of treatment of patients with fractures of the midface area showed that in most of them there were final cosmetic and functional deficiencies, which remained in the long-term observation. Displacement of bone fragments can remain when using any of the analyzed treatment methods.

Conclusions

1. Evaluation of the period of seeking medical care showed that the reliable ($\chi^2=11.43$; $p<0.05$) majority of patients (64%) sought treatment within 0–3 days after injury.

2. 83–89 % of patients, who underwent repositioning of fragments, had fresh small-fragment fractures. The reliable ($\chi^2=11.43$; $p<0.05$) majority of them simultaneously had 3–4 sites of bone fractures of the midface area, hemosinus of varying degrees and paresthesia in the infra-orbital area.

3. In the majority of patients, who underwent repositioning of bone fragments with and without tamponade (85 % and 93 %, respectively), the final displacements were in the range of 3.1–6 mm. In patients treated conservatively, in most cases (93 %) the displacements were greater than 3.1 mm,

which remained after treatment. In the majority of patients treated with the studied methods, in the long term, the displacements of bone fragments remained, which had functional consequences.

4. In all studied groups, a certain cosmetic effect was achieved over time, as evidenced by a reliable ($\chi^2=160.9$; $p=0.00000$) decrease in the indicator by the VAS.

The prospect for further research is a comparative evaluation of the results of treatment of fractures of the midface area using the methods of bone osteosynthesis methods to fixate the fragments using standard titanium mini-plates and individual 3-D simulated titanium mini-grids.

Declarations:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure.

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Data Transparency

The data can be requested from the authors.

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COGNITIVE IMPAIRMENTS IN PATIENTS WITH TREATMENT RESISTANT EPILEPSY UNDERGOING COMPLEX REHABILITATION

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Abstract

Background. The study of features of comorbid pathology in patients with epilepsy is of particular interest due to the high prevalence of this pathology and a significant impact on the quality of life of patients and their social adaptation. **Aim.** The aim of the research was to detect versatile cognitive impairments and affective disorders in epilepsy, and to study the results of cognitive training and psychoeducation. **Materials and methods.** The theoretical analysis of modern scientific researches in the field of cognitive and affective impairments during epilepsy was carried out. We studied the features of clinical and psychopathological manifestations in patients, suffering from epilepsy. The study covered 146 patients (85 men and 61 women) who were in inpatient care. The following psychodiagnostic techniques were used: the MOCA test, the Toronto Cognitive Assessment (TorCA), the MiniMult test, the Munsterberg test, the quality of life scale, the Hamilton scale of depression and anxiety. **Results.** This publication offers the results of a study of cognitive and affective disorders the quality of life in patients who suffer from epilepsy and the results of online cognitive training and psychoeducation. We found cognitive decline in 88 % of patients with epilepsy and improvement of cognitive functions by methods of non-pharmacological correction. **Conclusions.** Affective and cognitive disorders significantly affects the quality of life of patients, their ability to work and socialization. The conducted research showed that compared to the control group of healthy persons, patients with epilepsy showed improvement in their cognitive decline, anxiety and depressive disorders. Cognitive online training appeared to be effective for the patients with epilepsy.

Keywords: *Epilepsy, Cognitive disorders, Affective disorders, Cognitive online training.*

Introduction

Epilepsy is a chronic, neuropsychiatric disorder with diverse etiology characterized by persistent predisposition to epileptic seizures, as well as the neurobiological, cognitive, psychological, and social consequences of this condition.

Epilepsy is one of the most common neuropsychiatric disorders, affecting about 65 million people worldwide. As epilepsy prevalence increases with age, 25 % of the first detected cases are diagnosed at the age of 65 or over. Various neuropsychiatric and somatic conditions, such as traumatic brain injury, cerebrovascular

disorders, Alzheimer disease, increase the incidence of epilepsy exponentially [1].

The disease is characterized by heterogeneity of clinical manifestations. In all the variety of mental pathology, there are cognitive disorders, epileptic psychoses, depressive, anxiety and obsessive-compulsive disorders, behavioural disorders, and epileptic encephalopathy. Mental disorders in epilepsy occur more often than in the general population. According to some researchers, about a third of people with epilepsy suffer from comorbid mental disorders: depression, anxiety, dysphoria, which greatly complicate the course of the underlying disease and impair quality of life.

Some researchers believe that mental and behavioural disorders are consequences of epilepsy [2], while others admit the two-way causal relationship between them [3, 4]. Patients with comorbid disorders are more prone to seek

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medical assistance, including a higher suicide rate, lower adherence to treatment recommendations, lower quality of life, and lower control of epileptic seizures [5].

Cognitive dysfunction in epilepsy significantly deteriorates the quality of patients' life, their social functioning and adherence to treatment. The main cognitive functions include perception, attention, memory, praxis, language, executive functions, and social intelligence.

In our opinion, a cure for patients with epilepsy should include not only medication and surgical treatment but also psychotherapeutic methods, namely: psychoeducation and cognitive training. Psychoeducational activities include the dissemination of knowledge about epileptic seizures, treatments, comorbid conditions and life problems. Most psychoeducational interventions involve education and training.

2. Purposes, subjects and methods:

2.1. Purpose of the research was to detect versatile cognitive impairments and affective disorders in epilepsy, and to study the results of cognitive training and psychoeducation.

2.2. Subjects & Methods

The features of clinical and psychopathological manifestations were investigated in patients with epilepsy, monitored in 2017–2020 at the Municipal Medical Institutional of Chernivtsi Regional Psychiatric Hospital. The cognitive decline study covered 146 patients (85 men and 61 women) with epilepsy.

Further, following the eligibility criteria, 96 patients were selected. The study complied with the principles of medical ethics and deontology. The research included the patients aged 18–65 who were diagnosed with epilepsy (F06.63, F06.73, F06.83, and F07.83). Their distribution by age and gender is given in *Table 1*.

Table 1

Age and gender distribution of patients with epilepsy monitored in the study (%)

Patients' age (n=146)	
18-20	8,22
21-30	15,75
31-40	24,66
41-50	21,92
51-60	21,23
61-65	8,22
Patients' gender	
Men	58,2
Women	41,8

The research included three stages. At the first stage, 146 patients, diagnosed with epilepsy, were examined. At the second stage, eligibility criteria were applied to set up three groups of patients PG1, PG2 and PG3. The first group comprised 30 patients, who completed a cognitive training. Psycho-correctional sessions and psychoeducation were also applied to the first group of patients. The second group included 33 patients, who completed a cognitive training. 33 patients of the third group were given standard therapy. In addition, a control group of healthy persons (PG4) was set up for comparative purposes. They completed a cognitive training. At the third stage, patients' and healthy persons' control tests were performed three months after the application of corrective methods.

The methods applied included clinical-psychopathological, psycho-diagnostic, social-demographic and statistical. The psycho-diagnostic method was based on the use of Montreal Cognitive Assessment (MoCA) (Nasreddine Z.S. et al., 2005 p.) [22, 23, 24], Toronto Cognitive Assessment (TorCA), selective attention diagnostics involved Munsterberg's test, the examination of individual personalities and mental conditions involved a shortened version of the Minnesota Multiphasic Personality Inventory, or MMPI (1937), developed by J. C. Kincannon, (MiniMult, 1968) [25], the examination of the range of psychoemotional states was carried out using the Hamilton Rating Scale for Depression (HRDS), Hamilton Anxiety Rating Scale (HARS) (1960) [26, 27], the quality of life was assessed using the method suggested by Mezzich J., Cohen N., Liu J., Ruiperez M., Yoon G. (1999).

The collected data were statistically processed using Excel and Statistica 7.0 for Windows software package. Processing also included the use of Student's t-test, Mann-Whitney U-test, Kruskal-Wallis H test, Wilcoxon signed-rank test, and Spearman's rank correlation coefficient.

3. Results & Discussion

According to MoCA findings, the patients with epilepsy showed cognitive decline, the average score was 20.72, where as healthy persons' average score was 27.36. Test data are given in *Table 2*.

According to the findings of Toronto Cognitive Assessment (TorCA), conducted on 27 patients: 88.9 % had cognitive impairments, 7.4 % had borderline results, and only 3.7 % of patients didn't show any cognitive impairments. Overall, the advantages of applying Toronto Cognitive

Table 2

Patients' cognitive functions assessment data (MoCA Test)

Criteria	PG _{total} (p) (n=146)	PG 4(p) (n=33)	Mann-Whitney U-test
Management	3.09	4.81	<0.001
Name	2.74	3	0.012
Attention	1.28	1.87	<0.001
A series of letters	0.67	0.81	0.104
A series of subtractions	2.03	4.81	<0.001
Speech	1.53	2	<0.001
Speed	0.74	-	
Abstract thinking	1.08	1	0.468
Deferred reproduction	1.97	3.09	0.001
Orientation	5.68	6	0.011
Total score	20.72	27.36	<0.001

The difference between the groups is significant at $p < 0.05$.

Assessment (TorCA) include high sensitivity of the scale and the possibility to study particular cognitive functions, while its disadvantage is a complicated procedure.

Cognitive dysfunction as found in 88 % of patients, mild dementia in 48 %, moderate dementia in 24 % and severe dementia in 16 %. MoCA test results are presented in the diagram (Fig. 1).

Hamilton Depression Rating Scale (HDRS) revealed that 38 % had symptoms of depression, 28 % had mild situational or neurotic depression, 8 % had moderate depression, and 2 % had severe depression.

The distribution of affective disorders in patients with epilepsy are presented in the diagram (Fig. 2).

Hamilton Anxiety Rating Scale (HARS) showed that 20 % of patients had severe anxiety, and 16 % had the symptoms of anxiety.

This study was conducted using the Quality of Life Scale to determine the patients' quality of life. Unexpectedly, a part of the patients evaluated it very high, with the signs of cognitive decline and an objectively reduced level of functioning. A direct correlation between the degree of cognitive decline and subjective assessment of the

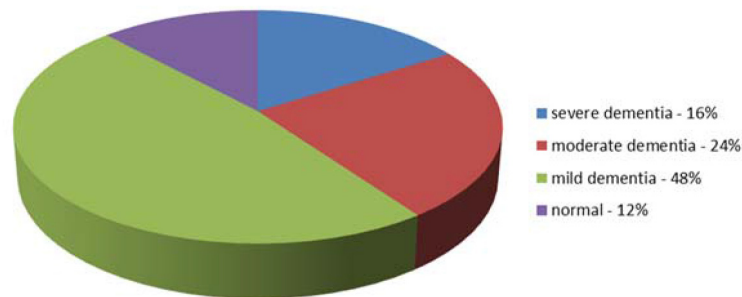


Fig. 1. Cognitive impairments in patients with epilepsy

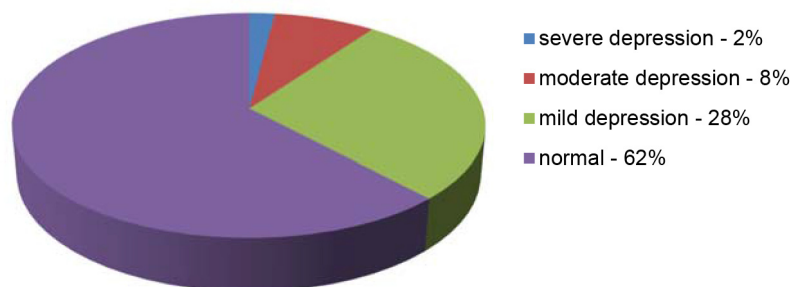


Fig. 2. Affective disorders in patients with epilepsy

quality of life was found: the highest estimation of the quality of life was observed in the patients with more severe cognitive dysfunction. The average rate among all examined persons was 69.45 out of 100, 78.60 were the results of healthy persons (*Table 3*).

The group of patients who completed the cognitive training course only (PG2) also showed certain improvement – by 0.73 points, unlike the group of patients who underwent standard therapy only (PG3) – their indicators fell by 0.22 points. Selective attention improvement was observed:

Table 3

Initial cognitive functions, selective attention, anxiety level and depression test results

Criteria	PG _{total} (p) (n=146)	PG 4 (p) (n=33)	Student's t-test	Mann-Whitney U-test
Quality of Life Scale	69.45	78.60	0.001	0.002
Münsterberg's test	7.72	21	-	<0.001
Hamilton Anxiety Rating Scale	14.17	10.33	-	0.052
Hamilton Depression Rating Scale	7.14	3.81	<0.001	<0.001

The difference between the groups is significant at $p < 0.05$.

The above data showed that the values of Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale indicators are higher in patients with epilepsy than in healthy persons: 14.17 – 10.33 and 7.14 – 3.81, respectively. Munsterberg's test also showed significant decline in selective attention – 7.72 in patients with epilepsy and 21 – in healthy persons.

During the pandemic of COVID-19, the patients were provided with the access to the online version of cognitive training, which is extremely important for improving their cognitive functions. Preparing patients for online training, we faced some technical difficulties. It took about two weeks to adapt to the resource. Some patients were unable to use the resource due to technical issues, lack of computer skills, or the level of their education. In general, the resource is easy to use. Short-term results may fluctuate, however, with long-term use of the resource there is a positive trend, in the group as a whole and in particular participants. Compared with the control group, patients with epilepsy had a greater interest in training and lower number of absences.

The data of *Table 4* point to a more significant improvement of cognitive functions in the group of patients who completed a cognitive training course and psychoeducation (PG1) – by 1.4 points.

PG1 – by 0.63, PG2 – by 0.27, PG3 – by 0.15. Anxiety declined in PG1 – by 11.45, PG2 – by 4.21, while in PG3 it increased by 2.61. Positive dynamics was found according to the Hamilton Depression Rating Scale: PG1 - by 1.7, PG2 - by 2.32, and in PG3 – 2.49. The subjective assessment by patients of the quality of their life rose in all three groups PG1 – by 2.77, PG2 – by 1.21, PG3 – by 1.0, which may indicate the improvement of the general state in all three groups. The above data may be used to confirm the efficiency and effectiveness of the cognitive training for the patients with epilepsy and the benefits of its combination with psychoeducation techniques.

Pathogenetically, epileptic system forms with the presence of several functionally different zones and determinant foci, the formation of secondary and tertiary foci, including mirror foci, which leads to a pronounced rearrangement of cytoarchitectonics of the brain with the establishment of new pathological interneuronal relationships. Cognitive impairment depends on the lesion of the hippocampus. Thus, lesions of the left hippocampus cause a much more pronounced decrease in the level of verbal learning, while atrophy of the right hippocampus is characterized by a lack of nonverbal learning and memory. The cognitive functions of patients with epilepsy are

Table 4

The results of testing cognitive functions, selective attention, anxiety and depression level before and after the cognitive training course and psychoeducation

Criteria	PG 1 (n=30)		PG 2 (n=33)		PG (n=33)	
	before	after	before	after	before	after
MoCA	18.93	20.33	20.30	21.03	20.58	20.36
Quality of Life Scale	67.2	69.97	66.94	68.15	78.06	79.06
Münsterberg's test	9.4	10.03	9.18	9.45	10.06	10.21
Hamilton Anxiety Rating Scale	23.09	11.64	15.34	11.07	6.39	9
Hamilton Depression Rating Scale	6.83	5.13	7.43	5.11	7.91	5.42

affected by heredity, organic damage to the brain, the presence of the epileptic process, treatment with antiepileptic drugs, the particular patient condition and personality traits. The active interaction of the above factors leads to the cognitive function impairment of each patient [6].

Differences in the cognitive status of the patient directly depend on the form of epilepsy and the type of seizures. Generalized tonic-clonic seizures provoke more significant cognitive impairment [7]. Thus, a generalized tonic-clonic attack can lead to decreased attention lasting up to 24 hours [8]. In patients with complex partial seizures, such changes are likely to last less time than in generalized tonic-clonic seizures, but it is clear that in patients with frequent seizures, this phenomenon significantly affects cognitive functioning [6].

The presence of psychiatric comorbidity is another important factor that influences patients' cognitive functioning. Firstly, some mental disorders, such as those associated with neuropsychological deficits [9]. Several studies have found dysfunction in the contour of the orbitofrontal loop in patients with mood disorders, which leads to a specific picture of impaired executive function and attention [10]. Secondly, in some cases, patients with mental disorders may have a poor understanding of their cognitive abilities, especially in mood disorders and anxiety disorders, for which cognitive complaints are an integral part [11].

There is no doubt about the effect on the cognitive functions of patients with epilepsy of some anticonvulsants, whose effectiveness is directly dose-dependent. According to the findings of a cohort study of a large group of patients, cognitive disorders observed in adults with epilepsy reflect the cumulative effect of epileptic processes and low premorbid cognitive ability [12]. Researchers single out four clinical variants of moderate cognitive impairment [13, 14]:

- amnesic monofunctional type – with selective memory impairment with relative preservation of other cognitive functions;
- amnesic multifunctional type, which is characterized by a combination of memory impairment and other cognitive impairments;
- multifunctional type without memory impairment, characterized by multiple cognitive impairments with relatively preserved memory;
- monofunctional non-amnesic type, characterized by the presence of a deficiency of one of the cognitive functions without memory impairment.

Cognitive impairments may manifest themselves to varying degrees, depending on which they can be classified as mild, moderate, severe

and subjective cognitive impairments that are precursors to the further development of cognitive decline. Simultaneously, they may not be objectively confirmed during testing of patients. Most often, drugs are used to treat epilepsy, and if they are ineffective – other therapies, including surgery, which reduce the activity of epileptic foci. However, they are not always effective. According to the statistics, the number of people who do not receive the proper effect of therapy has not changed over the past two decades, and this share is about 30 % of all patients.

Nowadays, we have the following non-pharmacological methods of correction: diet, physical exercises, cognitive training including cognitive stimulation, psychological and behavioural correction methods, psychotherapy (cognitive behavioural therapy, art therapy, music therapy etc.), meditation, and yoga.

When using those methods, cognitive functions may improve owing to neuroplasticity – the brain's ability to reorganize itself physically by forming new neural connections in response to the surrounding [15, 16].

Everyday cognitive activities, in particular, learning new things, promote the establishment of new neuronal connection alongside preserving the old ones, which is in itself protection against the development of cognitive impairments [17].

Cognitive training, conducted through the implementation of specific programs and methods, aim to train memory, attention and other cognitive functions so as to maintain intelligence, develop particular cognitive abilities and to teach compensation and recovery strategies. There are two types of cognitive training: compensatory and recovery [18].

Compensatory cognitive training is aimed at teaching patients to learn new strategies of task solving, enhancing thereby their cognitive abilities. The following strategies are applied: data visualization, distribution by categories, and the use of external hints.

In recovery cognitive training, we implement the measures that aim to improve impaired cognitive functions. During the training that is aimed at particular task resolving, the development of relevant abilities arises. Classical training, cognitive stimulation and online training have been conducted both ways, individually and in groups.

According to the studies, cognitive tasks such as: written and oral calculations, reading, writing, spatial construction may brake epileptiform EEG-discharges in 64 % of cases and provoke them in 7.9 % [1]. Those results enable to theoretically

assume the possibility to create specific cognitive tasks for inhibition of epileptiform activity, and also the possibility to change those cognitive activities, which cause epileptiform discharges, thus reducing the frequency of epileptic seizures. Such cognitive and behavioural measures could also evoke long-lasting changes in excitability [19].

According to the findings of a large randomized controlled study [20], the application of a motivational interview, combined with additional behavioural correcting methods, effectively improves patients' observance of a mode of reception of medication, as compared with controls over 3 and 6 months of observation. In the group with motivational interviews, researchers could also notice a decrease in seizures' severity, improvement in patients' quality of life and an increase of effectiveness of medication within therapeutic and sub-therapeutic range, after improvements of psychological indicators [20].

When applying modified (group-dependent) methods of cognitive behavioural therapy in the group aged 60 and over, the frequency of epileptic fell reduced significantly, as compared with another group where the control of relaxation was used. The result remained unchanged even over three months after treatment. Moreover, both groups witnessed an improvement of psychological indicators such as depression, dysthymia, psychosocial functions and psychological adaptation [21].

Conclusions

Our findings demonstrate that compared to the control group of healthy persons, patients with

epilepsy show improvement in their cognitive decline, anxiety and depressive disorders. Cognitive online training appears to be effective for the patients with epilepsy. The findings of the study point to a more significant improvement of patients' cognitive functioning provided the use of psychoeducation and cognitive training methods along with anticonvulsant therapy compared to the application of cognitive training only.

The results of this research show the need for further study of the factors that influence the occurrence and progression of cognitive disorders, the development and implementation of training aimed to improve cognitive functions and prevent the progression of cognitive disorders. In modern conditions, online training of cognitive functions deserves to be introduced as part of the system of social rehabilitation of patients with epilepsy and cognitive disorders.

Declarations:

Statement of Ethics

The authors have no ethical conflicts to disclosure.

Consent for publication

All authors give their consent to publication.

Disclosure Statement

The authors have no potential conflicts of interest to disclosure.

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Data Transparency

The data can be requested from the authors.

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