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# EXOCRINE AND ENDOCRINE PANCREATIC INSUFFICIENCY IN DEVELOPMENT OF ATHEROSCLEROSIS

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**Abstract**

Objective: To evaluate the effect of chronic pancreatitis (CP) and exocrine insufficiency of the pancreas on the carotid intima media thickness (cIMT) in patients with type 2 diabetes mellitus (DM-2). Materials and methods: 91 patients were examined, they were divided into groups: group 1 – patients with DM-2 (n=31), group 2 – DM-2 combined with CP (n=60). Fasting plasma glucose (FPG), HbA1c, immunoreactive insulin (IRI), HOMA-IR index, C-reactive protein (CRP), serum α-amylase and fecal-1 elastase (FE-1) were assessed. In order to assess the thickness of the cIMT, ultrasonography of the common carotid artery was performed. The control group of healthy volunteers was representative by age and sex. Results. In groups 1 and 2, the average value of cIMT was (1.02±0.1 vs. 1.21±0.15) mm. The parameters of DM-2 management in groups 1 and 2 were (FPG 8.18±0.92 vs. 8.57± 1.2) mmol/l; HbA1c (7.23±0.21 vs. 7.49±0.36)%; IRI (20.31±0.9 vs. 22.53±1.2) μIU/ml; HOMA-IR (6.55±1.5 vs. 8.38±2.2); PSA (1.3±0.12 vs. 6.77±0.31). HOMA-IR correlated with: CRP (r=0.43, p <0.05 in group 1; r=0.61, p <0.05 in group 2); FE-1 (r = -0.55, p <0.05 of group 2); and cIMT (r=0.42, p <0.05 in group 1; r=0.53, p <0.05 in group 2). IRI have relationship with FE-1 (r=0.41, p <0.05 in group 1; r = -0.3, p <0.05 in group 2); CRP (r=0.42, p <0.05 in group 1; r = -0.28, p <0.05 in group 2); HbA1c had close relationships with cIMT (r=0.38, p <0.05 in group 1; r=0.51, p <0.05 in group 2); the relationship between cIMT and CRP was related in group 2 (r=0.39, p <0.05); with α-amylase (r=0.2, p <0.01 group 2). There was no significant relationship between cIMT and FE-1 in the study. Conclusions: the obtained data allow concluding that hyperinsulinemia and insulin resistance have a direct atherogenic effect on the walls of the blood vessels. It is established that the accession of the inflammatory process leads to increasing development of atherosclerotic lesions of the vessel, at the same time, the presence of exocrine dysfunction of the pancreas does not have a significant direct effect on the cIMT.

***Keywords:*** *chronic pancreatitis type 2 diabetes mellitus, atherosclerosis, carotid intima media thickness.*

## Introduction

Modern medicine data show that the pancreas due to a combination of incretory and excretory functions is involved in all physiological processes [1]. Therefore, any disturbance in pancreas function, like chronic pancreatitis (CP) or type 2 diabetes mellitus (DM-2), leads to disturbance of stability of the internal environment of the organism. [2]. The problem of combined pathology DM-2 and CP, which, according to statistic data, is diagnosed in 28–36 % of patients with DM-2, has attracted attention of scientists [3]. In the study [4], main markers of presence DM-2 were highlighted, as well as factors of formation CP in DM-2 patients, the influence of excess body weight, obesity, hyperglycemia and hyperlipidemia, development of hyperinsulinemia and insulin resistance (IR) was recognized as crucial. CP is the result of long-term chronic inflammation and fibrosis of the pancreas [5]. Parallel with CP inflammatory processes the processes of atherogenesis take place in patients with DM-2. The pancreas is an organ that undergoes structural and functional changes due to atherosclerotic damage. Due to vascular lesions of atherosclerotic origin in the islets of the pancreas, blood flow is reduced and hypoxia is observed with a consistent

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functional decrease in beta-cells. The islets undergo structural changes, accompanied by the appearance of hyalinosis and loss of beta-cells. According to D. Rosso et al. [6], 87.5% of patients with DM-2 have thickening and stenosis of the arterioles of the pancreas, and in 50 % – lesions of the islets of Langerhans. Therefore, development of CP in patients with DM-2 is just a question of time. The aged-related pancreatic changes are considered to be related to atherosclerosis (of small vessels) by few studies [7]. Researchers drew attention to the more frequent lesions of the cardiovascular system in patients with combine DM-2 and CP rather than isolated disease and suggested the possibility of promoting development of such lesions by CP [8]. Against a background of various disorders of the metabolic process, atherogenesis occurs not only locally in the vessels of the pancreas, but also in other vessels. That is why some authors have linked cardiovascular events (CVE) to exocrine pancreatic insufficiency [9]. Standard risk factors associated with the development of CVE include age, high blood pressure, higher body mass index (BMI), and smoking which stimulate development of atherogenesis as well [10]. Atherosclerosis is a multifactorial disease involving the interplay of many factors such as hyperlipidemic and hyperglycemic states, inflammation, however, any one of these alone is insufficient to produce an atherosclerotic lesion that is why people with combined diseases more likely to develop atherosclerosis.

Carotid intima-media thickness (cIMT) is a diagnostic marker of subclinical atherosclerosis in the population [11]. According to numerous studies, cIMT associated with prediction of cardiovascular risk in population [12–14]. cIMT has been correlated with CVE [15] and mortality among people with chronic disease and DM [16]. In individuals with DM-2, CIMT has been reported as a predictor of adverse cardiovascular outcomes in previous longitudinal studies [17– 19].

According to statistic data, 75 % of patients with DM-2 die from the causes associated with atherosclerosis, namely, coronary heart disease, ischemic stroke, heart failure [20, 21]. Researchers note that the atherosclerotic vascular lesions in people with DM-2 develop 7–10 years earlier than in people without DM [22]. Thus, the frequency of CVE in patients with DM-2 is associated with atherosclerosis development and the inability to compensate the changes caused by it [23, 24].

The risk of CVE in patients with combined DM-2 and CP is many times higher, because relationship between insulin resistance, hyperglycemia, inflammation and development of atherosclerosis is very complex and covers many factors. A meta-analysis showed that an increase of cIMT by 0.13 mm is associated with increasing risk of CVE by almost 40% in patients with DM-2 [25].

In the available literature, we have not found the data about relationship between exocrine function of the pancreas and the development of atherosclerosis in patients with DM-2 and CP, which was the reason for this study.

**2. Purpose, subjects and methods:**

**2.1. The purpose** To evaluate the effect of exocrine insufficiency of the pancreas and parameters of carbohydrate metabolism on the carotid intima media thickness in patients with diabetes mellitus type 2 and chronic pancreatitis.

**2.2. Subjects & Methods**

The study involved 91 patients with DM-2 who were divided into groups: group 1included the patients with DM-2 (n=31); group 2 – patients with DM-2 and chronic pancreatitis (n=60). The diagnosis of DM-2 was established based on the local guidelines (based on the recommendations of the European Association for Diabetes 2017). The diagnosis of CP was established based on local guidelines and recommendations of the Association of European Gastroenterology (UEG) for the diagnosis and management of CP 2017. The control group included 20 age-matched healthy individuals (10 men). All patients were informed about the study procedure and signed a written consent for participation.

In the study, the parameters of carbohydrate metabolism compensation were determined: fasting plasma glucose level (FPGL) – glucose oxidant method, glycosylated hemoglobin (HbA1c) by immunoturbidimetric method, immunoreactive insulin (IRI) which was determined by the enzyme-linked immunosorbent assay. The HOMA-IR index was calculated using the formula – (FPGL*IRI)/22. The functional state of the pancreas was determined by the content of α-amylase in the blood plasma and fecal elastase-1 (FE-1). The level of quantitative C-reactive protein (CRP) was assessed. The body mass index was calculated according to the formula Kettle – body weight (kg) / height ($m^2$).

cIMT was assessed using ultrasonography (SIEMENS ACUSON S3000) in the proximal and distal parts of the carotid artery. cIMT was measured in B-mode, in the longitudinal section of the artery 1–1.5 cm proximal to the bifurcation along the posterior wall of the artery. The value of the CIMT of the carotid artery was measured three times on each side, and then the average

value for the right and left carotid artery was calculated on the basis of the obtained data from the three-time measurement. The atherosclerotic plague was considered to be a focal structure that protrudes into the lumen of the vessel by 0.5 mm or 50% more than the value of the cIMT of the adjacent areas of the artery, or an increase of cIMT more than 1.3 mm. The thickness norm of cIMT corresponded to the recommendations of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) in 2013 and was 0.9 mm.

The obtained data were processed using the package Statistica Basic Academic 13 for Windows En. Quantitative indicators are given in the form of median (Me) and interquartile range (LQ – lower quartile, UQ – upper quartile), as well as in the form of M ± m, where M is the sample mean, m is the standard deviation. Kolmogorov-Smirnov criterion was used to verify the compliance of the distribution of quantitative indicators with the normal law. Because the law of distribution of numerical indicators differed from normal, non-parametric statistical methods were used: Kruskal-Wallis test (KWT) and Mann–Whitney U-test (MWT). To determine the existence of functional relationships between the parameters, the nonparametric rank correlation coefficients of Spearman (r) was calculated, which was considered statistically significant at $p < 0.05$.

**Conflict of interests**

The authors of the article declare no conflict of interest.

**3. Results & discussion**

The main results of the study are presented in the *Table*. The studied indicators significantly depended on the group (CCU, $p < 0,05$).

The obtained data of carbohydrate metabolism suggest that accession of chronic pancreatitis leads to more poor management of DM-2. FPGL in group 1 is higher than in group 2 (8.18±0.92 vs. 8.57±1.2) mmol / l; management of DM not only in short period of time is poor, but also during a longer period of time according to HbA1c level (7.23±0.21 vs. 7.49±0.36) %; IRI (20.31±0.9 vs. 22.53±1.2) μIU/ml; HOMA-IR (6.55±1.5 vs. 8.38 ±2.2) μIU/ml*mmol/l. Poor management of DM-2 in group 2 can be explained by the fact of loss of glucagon response to hypoglycemia and disturbance of carbohydrate absorption. The signs of inflammation were obtained in group 2. In comparison to group1, group 2 in our study had higher level of CRP (1.3±0.12 vs. 6.77±0.31). The signs of pancreas exocrine disturbance were present only in group 2: α-amylase 29.1 (26.39– 32) vs. 32.64 (29.15–35.40) g/g*L; and FE – 1 – 292.4 (271.1–302.27) vs. 137.51 (131.55–142.2) μg/g. These results confirmed the presence of exocrine pancreatic dysfunction in patients of group 2. In groups 1 and 2 the average value of cIMT was

*Indicators of carbohydrate metabolism, inflammation, functional state of the pancreas and the level of adipocytokines and CMI ICA in the examined patients (Me (LQ–UQ))*

| Parameter | Group 1: DM (n=31) | Group 2: CP + DM-2 (n=60) | Control group (n=20) |
|---|---|---|---|
| Duration of DM-2 (years) | 9.02±1.85 | 9.61±2.13 | – |
| BMI (kg/m$^2$) | 28.18 [24–33] | 30.66 [28–34] | 25.68 [21–23] |
| IRI (μIU/mL) | 20.31 (10.96–25.3)*) | 22.53 (13.95–30.45)*) | 11.07 (8.61–13.46) |
| FPGL (mmol/L) | 8.18 (6.40–9.70)*) | 8.57 (6.5–10.1)*) | 4.75 (4.5–5.0) |
| HbA1c (%) | 7.23 (6.58–7.89) *) **) | 7.49 (6.12–8.72)*) | 5.39 (5.32–5.46) |
| HOMA-IR index (μIU/mL)* (mmol/L) | 6.55 (3.90– 8.99) * )***) | 8.38 (4.69–10.71 ) *) | 2.39 (1.83–2.96) |
| CRP (mg/L) | 1.33 (0.0–2.0)*) ***) | 6.77 (1.19–11.92)*) | 0.12 (0.0–0.23) |
| α-amylase (g/g*L) | 29.1 (26.39–32)*) ***) | 32.64 (29.15–35.40)*) | 24.71 (19.7–28.6) |
| Elastase-1 (μg/g) | 292.4 (271.1–302.27)*) ***) | 137.51 (131.55–142.2)*) | 348.96 (289–381) |
| cIMT (mm) | 1.02 (0.75–1.24) | 1.21 (0.84–1.33) | 0.71 (0.64–0.81) |

*Note.* The difference is statistically significant ($p < 0.05$) when comparing indicators:
*) – probable when comparing identical parameters in control patients;
***) – probable when comparing identical parameters between the groups 1 and 2.

(1.02±0.1 vs. 1.21±0.15) mm with relatively equal duration of DM-2 (9.02±1.85 vs. 9.61±2.13) in the studied groups.

The correlation relationship between the studied parameters was as follows: HOMA-IR correlated with CRP (r=0.43, p <0.05 in group 1; r=0.61, p <0.05 in group 2; FE-1 in group 2 r = -0.55, p <0.05; cIMT in group 1 r=0.42, p <0.05; and in group 2 r=0.53, p <0.05. IRI relationship was associated with: FE-1 r = 0.41, p <0.05 in group 1; and r = -0.3, p <0.05 in group 2; CRP (r=0.42, p <0.05 in group 1; r = -0.28, p <0.05 in group 2; HbA1c had close relationships with cIMT r = 0.38, p <0.05 in group 1; r=0.51, p <0.05 in group 2, this finding can be explained by the fact that HbA1c is a marker reflecting the compensation of DM over a long period of time in comparison to FPGL. However, the study conducted by Gomez-Marcos MA et al. [25] showed that HbA1c level did not correspond to carotid atherosclerotic parameters in the overall population without carbohydrate metabolism disturbance. The relationship between cIMT and CRP in our study was reliable in group 2 (r=0.39, p <0.05), practically the same results were obtained in the study conducted by Magdalena Boncler et al. [26], where CRP correlated with CVE. In our case this relationship in group where patients have chronic inflammation can be explain in the following way: CRP plays a key role in all phases of chronic inflammation and atherosclerosis as well, CRP have directly influences the progression of atherogenesis: such as complement activation, apoptosis and thrombosis according to Elaine et al. study [27]. In the same time, research by Steyers CM et al. [28] maintain that chronic inflammation has been found to be associated with accelerated atherosclerosis and increased risk of CVDs.

There was no significant relationship between cIMT and FE-1 such as a sign of exocrine dysfunction of the pancreas in any of the studied groups.

**Conclusions**

Many patients with DM-2 as the underlying disease also suffer from CP, which remains underestimated. It can be concluded that parameters of carbohydrate metabolism (HOMA-IR, IRI, HBA1c) are directly involved in progression of atherosclerosis in DM-2 patients. These parameters increase their influence in addition to the inflammatory disease against a background of CP, the main ones are IRI and FPG level. It was found that the accession of chronic inflammatory process to the existing DM-2 could lead to significant activation of processes that stimulate the growth of cIMT and enhance the development of atherosclerotic lesions. At the same time, parameters of pancreatic dysfunction (alpha-amylase, fecal elastase-1) do not directly affect the state of cIMT, but they influent on the success of DM-2 management.

Therefore, it can be argued that the deterioration of the metabolic process, namely the existing endocrine dysfunction, the disturbance in glucose metabolism, represented by hyperglycemia, hyperinsulinemia and insulin resistance, has a direct atherogenic effect. The activity of the atherogenic effect can be enhanced in the presence of exocrine dysfunction of the pancreas, since there is an acceleration of atherosclerotic changes in the state of cIMT in patients with DM-2 and CP, which doubles the risk of developing cardiovascular diseases in such patients [29]. Thus, the relationship between CP and CVD in patients with DM-2 appears to exist, but its strength, mechanism of development and importance of existence exocrine insufficiency of the pancreas are not well understood yet in process of atherogenesis, which requires further study.

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# ACTIVITY OF MITOCHONDRIAL ANTIOXIDANT DEFENSE SYSTEM IN YOUNG PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE

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**Abstract**

**Background.** Despite numerous studies, the pathogenesis of gastroesophageal reflux disease remains unclear. **Aim of research:** assessment the activity of antioxidant defense system in young patients with GERD based on expression of biomarker associated with mitochondrial function. **Material and methods.** The study included 45 patients with gastroesophageal reflux disease. The examined contingent was presented by students age from 18 to 25 years. 20 healthy persons were included as control group. Levels of manganese superoxide dismutase were determined in blood serum of study persons with enzyme immunoassays (ELISA, Elabscience, USA). Statistical data processing by the Statistica Basic Academic 13 for Windows En local was made. **Results.** Gastroesophageal reflux disease in young patients is characterized by significantly increasing of manganese superoxide dismutase as compare to control group (7.1700 ng/ml vs 4.4720 ng/ml respectively, $p<0.01$). Presence of erosion in esophagus mucous doesn't accompanied by significant changes of evaluated parameter as compare with non-erosion form of disease in patients. **Conclusion.** The elevation in young patients with GERD the biomarker of mitohondrial antioxidant defense system we may speculate as adaptive response contributing to non-specific citoprotection. Taking to account the publishing facts about dual role of manganese superoxide dismutase it is necessary to monitoring antioxidant enzyme in patients with gastroesophageal reflux disease for prediction of possible complications and outcome.

***Keywords:*** *gastroesophageal reflux disease, young age, manganese superoxide dismutase.*

## 1. Introduction

Gastroesophageal reflux disease (GERD) is classified as chronic acid reflux [1]. According to prospective population-based cohort study, the prevalence of GERD is 2% to 25 % [2]. Symptoms of GERD are experienced in a range from mild to severity in a form of Barrett's esophagus [3]. Pathogenesis of GERD includes multifactorial mechanism firstly acid and acid-pepsin which considered as injury factors for esophageal squamous epithelium [4]. According to the findings based on animal models of chronic acid exposure and histological examination of biopsy material obtained in patients by esophagoscopy, esophageal squamous cells the inflammatory mediators have been revealed. The new theory of pathogenesis esophageal inflammation related to relationship between cytokine profile and esophageal inflammation was proposed [5].

Inflammation induced by cytokines results in overproduction of reactive oxygen species (ROS). The main source of superoxide radicals in the cell are mitochondria, the place for oxygen metabolism. It is known that a lot of diseases of internal organs are accompanied by formation of oxidative stress with damage to biological macromolecules and cell membranes [6]. Oxidative stress is the considered as imbalance between components of pro- and antioxidants systems which have been formed in evolutionary process. In order to block the harmful effect of oxidative stress in case of ROS increase, activation of the antioxidant defense system occurs.

Nonenzymatic scavenger of antioxidant defense are enzymes superoxide dismutases which are the major ROS detoxifying enzymes of the cell and catalyze dismutation of superoxide radicals to hydrogen peroxide and molecular oxygen. Superoxide dismutases are metalloenzymes and hence, require a metal cofactor for their

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activity. The mitochondrial matrix stores manganese superoxide dismutase (MnSOD/SOD2), also called super dismutase manganese or mitochondrial SOD2, the products of the electron transport chain. MnSOD is an integral mitochondrial protein known as a first line antioxidant defense against superoxide radical anions [7, 8]. In the analyzed literature we did not find the data relevant to state of mitochondrial antioxidant defense system in patients with GERD.

**2. Purposes, subjects and methods:**

**2.1 Purpose.** Assessment the activity of antioxidant defense system in young patients with GERD based on expression of biomarker associated with mitochondrial function.

**2.2. Subjects & Methods.** This study involved 45 patients with GERD. The examined group consisted of university students aged from 18 to 25 years, median age was 21.2±2.4 years. 34 patients (75.6%) with GERD were women, and 11 (24.4%) men. The history of GERD did not exceed 3 years. 20 healthy age-matched persons were chosen as a control group.

The study was conducted within the period of 2017–2019 in the inpatient hospital of Department of General Practice-Family Medicine and Internal Diseases of Kharkiv National Medical University (Ukraine) and in the inpatient hospital of Department of Therapy, Rheumatology and Clinical Pharmacology of Kharkiv Medical Academy of Postgraduate Education (Ukraine). GERD diagnosis was verified according to the recommendation of the Montreal Consensus (2006), protocols for the management of patients with GERD. The morphological form of the disease was revealed during esophagogastro-duodenoscopy ("Fuginon" system) according to the recommendations of the Los Angeles classification. A histomorphological study of the obtained biopsy material from the mucous membrane of the esophagus was carried out.

Levels of MnSOD were determined in blood serum with enzyme immunoassays (ELISA, Elabscience, USA). Statistical data processing by the Statistica Basic Academic 13 for Windows En local was made for comparison of categorical variables.

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.

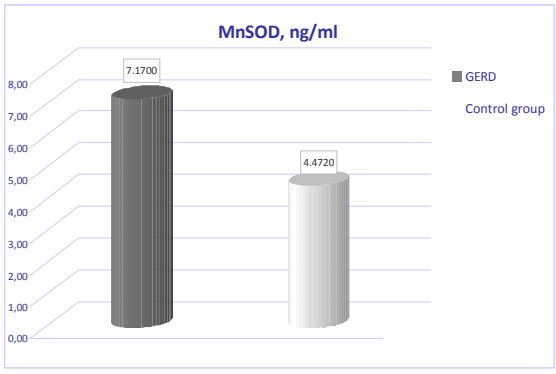
**Conflict of interests**

There is no conflict of interests.

**3. Results and discussion**

The morphological form of GERD was revealed during EFGDS. Erosive GERD was diagnosed in 11 patients (24.4 %), in other cases, study participants had a non-erosive form of GERD – 34 (75.6 %) patients. According to the Los Angeles classification (1994) 7 patients had grade A of erosive esophagitis, 3 examined – B and grade C was registered at 1 patient.

The levels of MnSOD in blood serum of the study patients and controls are presented in *Figure*.




Levels of MnSOD in individuals of study and control groups

The patients had significantly higher serum levels of MnSOD compared to the control persons. Median and interpercentil deviation of MnSOD was 7.1700 (6.1056; 8.1948) ng/ml in patients with GERB and significantly higher compared to control persons – 4.4720 (3.7010; 5.2325) ng/ml ($U = 513$, $p<0.01$).

We evaluated MnSOD plasma levels in patients with GERD depending to morphological forms of the damage to the esophagus mucous assessed by a histomorphological study of the obtained biopsy material. The results are shown in *Table*.

Presence of erosion in esophagus mucous was not accompanied by significant change of evaluated parameter as compared with non-erosion form of disease in patients. Nevertheless the tendency to decreasing MnSOD plasma levels in patients with erosion form GERD was found. The explanation of this facts related to the data

*Levels of MnSOD in patients depending on damage of the esophageal mucous*

| Parameter | Erosive morphological form of GERD | Non-erosive morphological form of GERD | Statistical significance between groups |
|---|---|---|---|
| MnSOD, ng/ml | 6.7666 (5.1572; 8.1946) | 7.2828 (6.1068; 8.1946) | U=347, p>0.05 |

*Note:* [1]p<0.05 – the difference is statistically significant.

that underline that differ stressors (chloric acid, nonsteroid antiinfammatory drugs and others) generate free radicals which not only injure epithelial cells, but also cause free radical accumulation in the mitochondria leading to organ damage, and functiona changes accompanied by cell apoptosis and death [9].

In order to prevent oxidative stress, the cell must respond to ROS by mounting an antioxidant defense system. MnSOD has long been recognized to be important against mitochondria-generated oxidants because of its well-known superoxide dismutase activity. Indeed, several studies have established that many of the cellular effects of MnSOD can be attributed to the superoxide scavenging ability of the enzyme. MnSOD in the mitochondria converts highly toxic superoxide $O_2$ into less toxic hydrogen peroxides $H_2O_2$ [10]. We found elevation of activity of antioxidant enzyme associated with mitochondria in patients with GERD. We may speculate that young patients with GERD according to their age have preserved beneficial capacities of MnSOD to act as a superoxide dismutase, impact on behavioral harmful xenobiotics and protect mitochondria against oxidative damage. This effect is less pronounced in patients with erosion form of GERD.

Taking to account the results of some studies it can be suggested that increased expression of MnSOD may be useful by regulating the mitochondrial redox status, prevent the cells apoptosis and protect of some organs [11]. The opposite situation occurs when a decreased expression of MnSOD resulted in deleterious effects.

Nevertheless, further studies have shown that MnSOD plays multiple roles in cells beyond its proposed antioxidant functions. Ansenberger-Fricano K., da Silva Ganini D., Mao Mao. et al. (2013) in experimental procedure on recombinant MnSOD from human mitochondria cells treated with glucose oxidase or exogenous H2O2 using electron paramagnetic resonance, visible spectrometry studies, gel electrophoresis and Western Blot Analysis, fluorescent Immunocytochemistry, gene-specific quantitative PCR to assay mitochondrial DNA (mtDNA) found that in the presence of H2O2 level of overexpression MnSOD can possesses peroxidase activity, leads to mitochondrial protein oxidation, predisposes mitochondria to oxidative stress, sensitizes mtDNA to oxidative damage [12]. The authors summarized that overexpressed MnSOD may gain the function as a peroxidase contributes to mitochondrial dysfunction. Moreover epidemiologic and clinical studies indicated a conflicting role of $SOD_2$ gene in the production and elimination of $H_2O_2$ that can be considered a protective antioxidant, as well as a pro-oxidant driving cancer [13].

It was identified that a higher expression of $SOD_2$ in human esophageal squamous cell carcinoma samples was associated with TNF ? expression and poor overall survival in patients with cancer, suggesting that $SOD_2$ may act as an oncogene [14]. The expression of $SOD_2$ in breast cancer is significantly correlated with TNM stage and axillary lymph node metastasis. $SOD_2$ may affect the proliferation, invasion and metastasis of breast cancer cells [15].

The recent facts gave comprehensive explanation of activity of MnSOD to hypothesize that mild (2–3 fold) MnSOD expression effectively reduces mitochondrial ROS generally correlating with improved mitochondrial function whereas diminishment or overexpression of MnSOD in mitochondria result in oxidative stress and damage [12]. According to this new interpretation of MnSOD role we should provide the control of levels of antioxidant enzymes in patients with GERD relevant to symptoms and signs, results of esophagoscopy in order to monitor the clinical features and treatment efficacy.

**4. Conclusion**

The present study demonstrates that patients with gastroesophageal reflux disease have a significant increase in manganese superoxide dismutase levels as compared to the persons from the control group that reflects in case of mucosa esophageal inflammation the compensatory reaction of intracellular enzyme directed to tissue protection. Taking to account the published facts about the dual role of manganese superoxide dismutase, it is necessary to monitor antioxidant enzyme in patients with gastroesophageal reflux disease for prediction of possible complications and outcome.

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# THE CHANGES OF MARKERS OF ENERGY HOMEOSTASIS, ADIPOKINES, CARBOHYDRATE METABOLISM IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION ACCOMPANIED BY OBESITY

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**Abstract**

**Background.** Obesity is associated with the changes in energy homeostasis (irisin and adipokine) and the adipokine system (FABP 4 and CTRP 3) and the impact on the development and course of cardiovascular diseases. **The purpose of the study** was to investigate the time course of markers of energy homeostasis, adipokines and carbohydrate metabolism and their relationship in patients with acute myocardial infarction with the presence and absence of comorbid pathology. **Materials and methods.** The study involved 189 patients with acute myocardial infarction with and without obesity. The control group included 20 healthy subjects. Adropin, irisin, FABP 4, CTRP 3, insulin were determined by enzyme-linked immunosorbent assay. **Results of the study.** All groups of patients during the observation were found to have a decrease in the levels of glucose, insulin, HOMA index ($p<0.05$). An increase in adropin, irisin and CTRP 3 and a decrease in FABP 4 in all groups of patients compared with patients by 1–2 days ($p<0.05$) were determined on day 10. The relationship between carbohydrate metabolism and adropin, irisin, FABP 4, CTRP 3 in all groups of patients on days 1–2 was revealed. **Conclusions.** Our findings indicate that the markers of energy homeostasis and adipokine system influence the state of carbohydrate metabolism in patients with acute myocardial infarction with concomitant obesity was determined.

***Key words:*** *adipokines, carbohydrate metabolism, acute myocardial infarction, energy homeostasis, obesity.*

## Introduction

Coronary artery disease is known to be one of the most common cardiovascular diseases in Western Europe and Ukraine [2]. Obesity is a significant factor that causes the adverse course of acute myocardial infarction (AMI) [19]. It is believed that pathological obesity is a chronic systemic inflammatory process [11; 17]. Many adipokines and peptides, which are involved in glucose and lipid metabolism, formation of insulin resistance (IR), and inflammatory reactions, are synthesized in the adipose tissue. The role of adropin, irisin, fatty acid binding protein 4 (FABP 4) and C1q/TNF-Related Protein (CTRP 3) in development of acute myocardial infarction in patients with or without obesity has not been studies in detail [5–9]. Adropine and irisin affect homeostasis of glucose and lipids, play an important role in prevention of insulin resistance, dyslipidemia associated with obesity [1; 3; 4; 10]. Recent studies have found a close relationship between the markers of energy homeostasis and the adipokine system and many major chronic diseases, including obesity, type 2 diabetes, and cardiovascular disease [12–16; 18]. Thus, further study of energy homeostasis and adipokines may reveal new diagnostic aspects of the treatment of CVD-associated obesity.

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## 2. Purpose, subjects and methods

**2.1. The purpose** of the work was to study the time course of energy homeostasis (adropin and irisin), adipokine system (FABP 4 and CTRP 3), carbohydrate metabolism in development of acute myocardial infarction, as well as to investigate the relationship between the components of energy homeostasis, adipokines and carbohydrate metabolism in patients with and without obesity.

**2.2. Subjects and Methods**

The study was performed within the period of 01 September 2018 and 31 December 2019. The study involved 189 patients, including 30 women (15.9 %) and 159 men (84.1 %), who were undergoing in-patient treatment in the infarction department of Kharkiv City Clinical Hospital No. 27 (clinical center of the academe member L.T. Malaya Department of Internal Medicine No. 2, Clinical Immunology and Allergology of Kharkiv National Medical University of Ministry of Health of Ukraine), at the Department of Resuscitation and Intensive Care of the State Institution L.T. Malaya National Institute of Therapy of the National Academy of Medical Sciences of Ukraine and in cardiology department No. 1 of Kharkiv Clinical Railway Hospital of the Health Care Center of the Public Joint Stock Company Ukrainian Railways. All patients were divided into the following groups: group 1 included 69 overweight patients (OW) (including 58 men, 11 women from 40 to 70 years), group 2 consisted of 60 patients with AMI with concomitant obesity (among them 46 men, 14 women from 42 to 70 years). The comparison group consisted of 60 patients with AMI without obesity (55 men, 5 women from 40 to 70 years). The control group included 20 healthy subjects (7 men and 14 women, aged 47 to 60 years).

The diagnosis of AMI was defined made in accordance with the Order of the Ministry of Health No.455 of 02.07.2014 "Unified clinical protocol of emergency, primary, secondary (specialized) and tertiary (highly specialized) medical care and medical rehabilitation of patients with acute coronary syndrome with ST wave elevation based on clinical, electrocardiographic and biochemical criteria". Obesity was identified according to the classification based on the body mass index (BMI), developed by the US National Institutes of Health and approved by the WHO. The treatment of obesity was carried out under the European recommendations of 2018 [19].

Exclusion criteria were type 2 diabetes, autoimmune diseases, diffuse connective tissue diseases, pituitary and hypothalamic diseases, thyroid disease, symptomatic hypertension, heart valve disorders, CHF IV FC to myocardial infarction, chronic obstructive pulmonary disease, marked renal impairment, severe anemia, cancer.

Adropin, irisin, FABP 4, CTRP 3 contents were evaluated by enzyme-linked immunosorbent assay using a set of reagents Human adropin (AD) (Elabscience, Houston, USA), Human Fibronectin type III domain- containing protein 5 (FNDC5) (Elabscience, USA), Human Fatty acid Binding Protein 4 (FABP 4) (Elabscience, USA), Human CTRP 3 (Aviscera Bioscience Inc, Santa Clara, USA) according to the specified instructions for analysis. Insulin content was determined by enzyme-linked immunosorbent assay using the Human Insulin Reagent Kit (Monobind Inc, Lake Forest, USA). Glucose levels were examined by the glucoxidant method in capillary blood on an empty stomach. Assessment of insulin resistance (IR) was performed by calculating the HOMA index.

Mathematical computer processing of research results was performed using "IBM SPPS Statistics 27.0" (IBM Inc., USA, license No. L-CZAA-BKKMKE) and Microsoft Office Excel software. The mean value (M), standard deviation, probability and significance level (p) were calculated. For all groups of patients, the indicators did not have a normal distribution according to the Shapiro-Wilk test. Independent comparisons were performed using the nonparametric Mann–Whitney U-test. Differences were considered significant at a level of statistical significance $p < 0.05$. To assess the relationships between the parameters, we used the method of correlation analysis with calculations of Spearman's correlation coefficients (with a distribution that differs from normal) [20].

The design of the study was approved by the Ethics Commission of Kharkiv National Medical University (Minutes No.2 of 2 April 2018). All patients who participated in the study signed a voluntary informed consent to participate.

**Conflict of interests**

This study was supported by Kharkiv National Medical University (No. 0120U102025; valid term 2020–2022). The funder had no role in the study design, data collection and analysis, decision to publish and preparation of the paper.

**3. Results and discussion**

The results of the study of carbohydrate metabolism on days 1–2 in patients with acute myocardial infarction with and without obesity are presented in *Fig. 1*. The levels of glucose, insulin, IR HOMA index in patients with overweight (OW) and obesity on day 10 did not have a significant difference when compared with the patients with AMI without OW and obesity ($p<0.05$). The patients with AMI, depending on the presence and absence of OW and obesity, were shown to have a decrease in glucose, insulin, IR HOMA index in the time course of observation ($p<0.05$) (*Table 1*).

The results of the study of markers of energy homeostasis and adipokines in patients with AMI

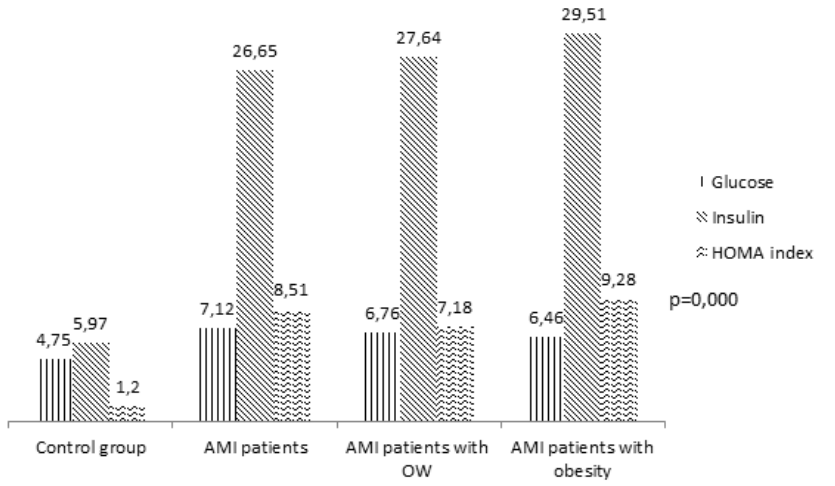


Fig. 1. Carbohydrate metabolism in patients with acute myocardial infarction depending with or without obesity on days 1–2 of observation

***Table 1***

*Determining the time course of carbohydrate metabolism in patients with AMI depending on the presence and absence of obesity*

| Indicators | Control group n=20 | AMI patients n=60 | AMI patients with OW n=69 | AMI patients with obesity n=60 | Probability (p) |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | |
| Glucose 10th day, mmol/l | 4.75±0.08 | 5.57±0.08 | 5.67±0.08 | 5.60±0.11 | $p_{1-2}$=0.307<br>$p_{1-3}$=0.726<br>$p_{1-1}$=0.000<br>$p_{2-2}$= 0.000<br>$p_{3-3}$=0.012 |
| Insulin 10th day, mcU/ml | 5.97±0.43 | 17.17±0.74 | 17.43±0.80 | 18.07±0.70 | $p_{1-2}$=0.869<br>$p_{1-3}$=0.416<br>$p_{1-1}$=0.000<br>$p_{2-2}$= 0.000<br>$p_{3-3}$=0.000 |
| HOMA index 10th day | 1.20±0.08 | 4.24±0.19 | 4.40±0.21 | 4.50±0.19 | $p_{1-2}$=0.996<br>$p_{1-3}$=0.312<br>$p_{1-1}$=0.000<br>$P_{2-2}$=0.000<br>$P_{3-3}$=0.000 |

*Note.* n – the number of examined subjects, M±m – arithmetic mean ± standard deviation, AMI – acute myocardial infarction, OW – overweight.

depending on the presence and absence of obesity within 1–2 days of observation are presented in the *Fig. 2*. The content of adropin on day 10 was lower in patients with AMI with OW compared with the patients with AMI on day 10, but no significant difference was found (p=0.085). The level of adropin on day 10 was lower by 11.13 % in obese AMI patients compared with AMI patients without the signs of OW and obesity on day 10 (p=0.000). An increase in adropin on day 10 was found in patients with AMI with obesity by 29.56 %, AMI with OW by 21.88 % and AMI without signs of OW and obesity by 24.76 % compared with patients on days 1–2 (p = 0.000). The level of irisin on day 10 was significantly lower in patients with AMI with OW by 9.94 % (p=0.026), by 27.56% with obesity (p=0.000) when compared with the patients with AMI. There was a significant increase in the level of irisin for 10 days in patients with AMI with OW by 47.12 %, by 33.73 % of AMI with obesity, by 40.54 % with AMI when compared with patients with AMI with or without OW and obesity on days 1–2 (p=0.000) (*Table 2*).

The studies [1; 12] show that adropin has a significant effect on glucose and lipid homeostasis and may play an important role in prevention of insulin resistance, impaired glucose tolerance, and

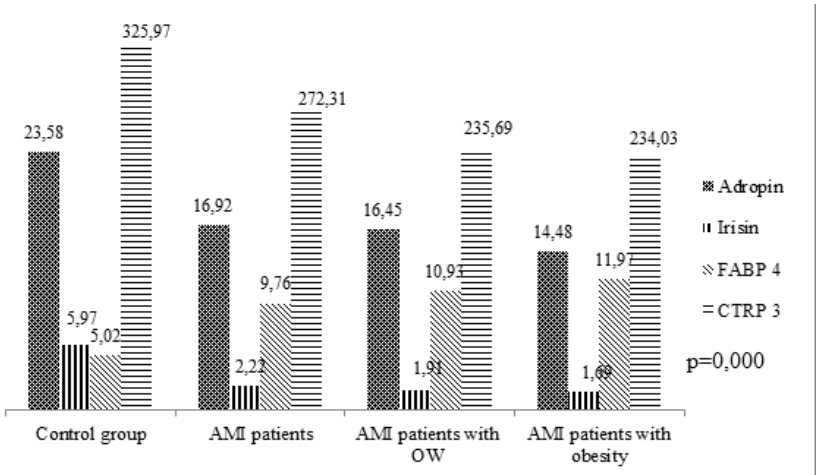


Fig. 2. The markers of energy homeostasis and adipokines in patients with AMI with or without obesity on days 1–2 of observation

***Table 2***

*The changes in the markers of energy homeostasis and adipokines in patients with AMI with or without obesity*

| Indices | Control group n=20 | AMI patients n=60 | AMI patients with OW n=69 | AMI patients with obesity n=60 | Probability (p) |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | |
| Adropin 10th day, pg/ml | 23.58±0.57 | 21.11±0.31 | 20.05±0.35 | 18.76±0.50 | $p_{12}$=0.085<br>$p_{13}$=0.000<br>$p_{11}$=0.000<br>$p_{22}$= 0.000<br>$p_{33}$=0.000 |
| Irisin 10th day, ng/ml | 5.97±0.47 | 3.12±0.11 | 2.81±0.11 | 2.26±0.06 | $p_{12}$=0.026<br>$p_{13}$=0.000<br>$p_{11}$=0.000<br>$p_{22}$=0.000<br>$p_{33}$=0.000 |
| FABP 4 10th day, ng/ml | 5.02±0.43 | 7.72±0.21 | 8.40±0.28 | 9.52±0.49 | $p_{12}$=0.326<br>$p_{13}$=0.009<br>$p_{11}$=0.000<br>$p_{22}$=0.000<br>$p_{33}$=0.000 |
| CTRP 3 10th day, ng/ml | 325.97±9.44 | 292.57±2.88 | 270.68±4.48 | 265.31±5.78 | $p_{12}$=0.001<br>$p_{13}$=0.002<br>$p_{11}$=0.000<br>$p_{22}$= 0.000<br>$p_{33}$=0.000 |

*Note.* n – the number of examined subjects, M±m – arithmetic mean ± standard deviation, AMI – acute myocardial infarction, OW – overweight.

dyslipidemia associated with type 2 diabetes or obesity. The researchers found a significant inverse correlation between adropin and glucose levels, body mass index (BMI) and triglycerides in patients with AMI. The study found that high concentrations of irisin were associated with greater reductions in blood glucose and insulinemia after weight loss in obese subjects. Studies showed a positive correlation between irisin and BMI, glucose, triglycerides [3; 4; 13].

The content of FABP 4 on day 10 significantly decreased in patients with AMI with obesity by 23.31 % compared with patients with AMI on the 10th day ($p<0.05$). However, no significant difference was found when comparing AMI patients with OW and AMI patients on day 10 ($p=0.326$). There was a significant decrease in the level of FABP 4 on day 10 in patients with AMI by 20.90 %, with OW by 23.14 %, by 20.43 % with obesity compared with the patients with AMI

with or without OW and obesity on days 1–2 (p=0.000). The researchers [5; 6; 8] found that FABP4 levels were significantly elevated in obese patients compared to non-obese patients, and serum FABP4 levels were positively correlated with the waist circumference, blood pressure and insulin resistance. According to the results of the studies elevated FABP4 levels were associated with obesity, insulin resistance, type 2 diabetes, hypertension, cardiac dysfunction, and atherosclerosis.

The concentration of CTRP 3 on the 10th day significantly increased in patients with AMI with OW by 7.48 % (p=0.001), by 9.32 % with obesity (p=0.002) compared with the patients with AMI on the 10th day. There was a significant increase in the content of CTRP 3 on the 10th day in patients with AMI by 7.44 %, with OW by 14.85 %, with obesity by 13.37 % when compared with AMI patients with the presence and absence of OW and obesity on days 1–2 (p=0.000) (*Table 2*). The relationship between CTRP 3 and coronary artery disease can be explained by the effect of CTRP 3 on various aspects of atherosclerosis, such as inflammation and metabolic disorders. CTRP3 levels negatively correlated with metabolic risk factors, including waist circumference, triglycerides and glucose levels, and the HOMA index. For CTRP3, the biological function of the metabolic regulator of glucose homeostasis was determined. The study found a significant reduction in CTRP 3 levels in acute coronary syndrome with control subjects [7]. Adjusting cardiovascular risk factors further enhances the relationship between CTRP 3 and coronary artery disease levels. In an experimental study, it was found that the expression of CTRP3 in adipocytes decreased significantly 1 day after AMI and gradually recovered. Plasma CTRP3 levels decreased significantly after AMI, reaching its lowest level 3 days after AMI. The expression or production of CTRP3 changes during cardiac reconstruction after AMI [7].

Thus, there are statistically significant disturbances in the regulation of the adipokine response and energy homeostasis in patients with AMI with concomitant obesity.

**Conclusions**

1. Decreased concentrations of adropin, irisin, CTRP 3 and increased levels of FABP 4 on days 1-2 in patients with acute myocardial infarction and obesity indicate a probable relationship with carbohydrate metabolism and impaired energy homeostasis and adipokine imbalance.

2. The changes of the indicators revealed the changes in the system of energy homeostasis and adipokine response and demonstrated the effect of irisin, FABP 4, CTRP 3 on development of AMI in obese subjects.

3. The results of the study indicate that the presence of obesity in patients with AMI did not affect the changes in the level of adropin during observation.

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# COVID-19 INTERSTITIAL PNEUMONIA (CASE REPORT)

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**Abstract**

A clinical case of treatment of a 54-year-old man with several risk factors, including diabetes, obesity, hypertension, with moderate COVID-19 bilateral pneumonia is presented. His clinical symptoms and signs at presentation included combinations of fever, nonproductive cough, and shortness of breath. Initial chest radiograms faid to show any changes, but chest CT revealed ground glass opacities (GGOs) with fuzzy contours, parenchyma damage (27 %). He was treated according to the Guidelines for diagnosis and treatment of COVID-19 cases (the Order of Ministry of Health of Ukraine No. 762). After a 12-day treatment, the damaged area reduced to 5 % with fibrosis.

***Keywords:*** *SARS-CoV-2, ground glass opacities, cytokine storm, bilateral pneumonia, fibrosis, interstitial pneumonitis.*

## Introducton

COronaVIrus Disease 2019 (COVID-19) is an acute respiratory pathology caused by Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) which has turned into a pandemic affecting many countries of the world and rapidly spreading throughout Ukraine.

By the early 21st century, epidemic coronaviruses were not considered to be virtually dangerous. SARS was first reported in Asia in February 2003 and get around to more than two dozen countries in North America, South America, Europe, and Asia. According to the World Health Organization (WHO), about 8,098 people worldwide became sick and 774 died because of SARS-CoV-1 [1].

Despite the fact that SARS-CoV-1 is pretty similar to SARS-CoV-2, both of them are beta-coronaviruses and are known to enter human cells through the angiotensin-converting-enzyme 2 receptor with human-to-human transmission by close contacts [2]. Older persons with related diseases such as hypertension, heart or lung disease, diabetes or cancer, are more likely to be affected [3]. Comparing with statistical data, SARS-CoV-2 is more contagious and cause greater morbidity. Thus, up to 27.10.2020, there were + 6 677 new cases per day, 355 601 laboratory confirmed cases of the disease, 6 590 fatalities, 145 336 recovered in Ukraine [4].

The onset of COVID-19 has been found since late December 2019 in Wuhan City, China. The patients with fever, malaise, dry cough, and dyspnea were diagnosed with viral pneumonia that was called later Wuhan pneumonia because of the area symptoms. The causative agent is a novel the seventh member of the coronavirus family according to the genome sequencing. On 12 February 2020 the WHO officially named this infection COVID-19. Later, the International Committee on Taxonomy of Viruses on 12 January 2020 officially termed the virus SARS-CoV-2 based on phylogeny, taxonomy and established practice. Beginning in China, COVID-19 rapidly spread to other countries worldwide. On 11 March 2020, the WHO characterized COVID-19 as a pandemic, similar to 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2), and 2009 Pandemic flu (H1N1), which caused an estimated 50 million, 1.5 million, 1 million, and 300,000 human deaths, respectively [5].

Despite the fact, that about 80 % COVID-19 patients recover spontaneously without the need for hospitalization, in about one in five cases, it occurs in severe form with respiratory failure. Risk factors for complications of COVID-19

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include older age (>65 years), cardiovascular disease, chronic lung disease, hypertension, diabetes, and obesity [2].

The new COVID-19 pneumonia has longer latent period (14–21 days vs. 7–8), during which the patient does not experience symptoms, but can spread virus. Such general symptoms as elevated body temperature up to 38°C, dry cough and fatigue are not red flags for the majority of infected people leading to late diagnosis. Inappropriate treatment measures increase the frequency of more advanced forms of disease. Moreover, after full recovering, the person can have PCR positive test during 2–3 weeks.

Typical bacterial pneumonia is known to cause lung inflammation in which alveoli walls are damaged and alveoli are filled with exudate, thus causing pulmonary tissue consolidation. Such picture can be seen easily in the X-ray examination of the thoracic organs. At the same time, the coronavirus activated only septal interstitial tissue. The infiltrate accumulates in the interstitial deposition. Lung damage caused by COVID-19 is not just viral-bacterial pneumonia. It is more appropriate to speak about diffuse parenchyma disease as an expression of interstitial pneumonitis. Everything described compose the nonspecific picture of a "clear" X-ray film. Such type of inflammation can be seen only using a CT scan. That is why Computed Tomography (CT) is used as an important complement for the diagnosis of COVID-19 pneumonia [6].

Despite the fact that a number of guidelines have already been approved, there is no general rule for the treatment of the COVID-19 pneumonia, moreover the treatment methods are constantly being reviewed. Internists and family physicians are still asking questions about an effective treatment. Therefore, we presented a clinical case of successful treatment of a patient with moderate COVID-19 pneumonia that can help doctors of many specialties to understand the issues of diagnosis and treatment as well as control of the COVID-19 infection.

**Clinical case**

A 54-year-old man with bilateral pneumonia was admitted to pulmonology department of Kharkiv City Clinical Hospital No. 13 with bilateral chest pain that intensified with inspiration, nonproductive cough, fever of 39°C, weakness, and malaise.

The patient felt acutely ill 9 days before the admission when the body temperature elevated up to 37.5°C and weakness occurred, followed by a nonproductive cough, bilateral chest pain aggravated by cough. About this time, he began to experience dyspnea, which progressively worsened; his body temperature elevated to 39.3°C. Despite paracetamol treatment, the chest pain, the cough and fever persisted. Few days later, his condition was aggravated by shortness of breath. Thus, he was admitted to the pulmonology department for evaluation of his condition.

Medical history

The patient denied neurological, psychiatric, oncology diseases, myocardial infarction, stroke, hepatitis, HIV, infectious diseases in himself and other relatives. There was no history of previous lung diseases. He had a 15-year history of hypertension and 5-year history of type 2 diabetes mellitus. There were no injuries and surgeries. The patient did not smoke, used alcohol and drugs. There was no history of hereditary diseases. The patient denied allergic disease and response to blood transfusion, introduction of serums, medicines, a variety of nutrients, cosmetics.

Physical examination

On examination, his condition was moderately sever. His consciousness was clear, the patient was oriented. His posture was active with restriction, there was orthopnea. His habitus was characterized by incorrect body built with height of 175 cm and weight of 110 kg, hypersthenic constitution. His skin was warm and moist, there was acrocyanosis, with intact turgor. There was lower extremity edema. The lymph nodes were impalpable. His musculoskeletal system was developed in accordance with the sex and age. The chest was hypersthenic, the supra- and subclavicular fossae were moderately pronounced, the direction of the ribs was moderately slanting, there was no deformation of the sternum. The chest was symmetrical, his respiratory rate was 27 per minute, rhythmic, of moderate depth, and the both parts of the chest equally took part in the breathing act. Comparative percussion of the lungs in supra- and subclavicular regions, over the anterior surface of the chest wall, in the axillary regions, in supra-, inter- and subscapular regions demonstrated dull sound. Auscultation of the lungs showed harsh breathing, bilateral crackles in the supraclavicular and suprascapular regions. The heart rhythm was regular, the cardiac murmurs were not heard. His heart rate was 117 beats per minute, pulse rate was 117 per minute, there was no pulse deficiency. His blood pressure was 110/90 mm Hg, body temperature 38.2° degrees Celsius, with 93 % oxygen saturation. His tongue was white and wet. The abdomen was spherical,

enlarged in size, symmetrical. It was soft and painless to superficial tentative palpation. Pasternatsky's sign was negative on the both sides. The bladder and bowel habits were norm

Laboratoty Investigations

The blood test demonstrated leukopenia, increased ERS and monocytosis. Other laboratory findings are presented in *table 1*.

*Table 1*

| Parameter | Result | Reference Ranges |
|---|---|---|
| Hemoglobin | 118 | 120–160 g/l |
| RBC | 4.3*10¹² | 3.9-5.0* 10¹² / l |
| WBC | 3.2*10 ⁹ | 4.0–9.0 *10⁹/ l |
| ERS | 38 | 1–15 mm/h |
| Band | 4 | 1.0-6.0% |
| Segmented | 56 | 47.0–72% |
| Eosinophils | 1 | 0.5–5.0% |
| Lymphocytes | 30 | 19.0–37.0% |
| Monocytes | 9 | 3.0 |

The blood levels of C-reactive protein, procalcitonin, ferritin, IL-6 were increased; other laboratory findings are shown in *table 2*.

***Table 2***

*Blood biochemistry*

| | Result | Reference Ranges |
|---|---|---|
| CRP | 144 mg / ml | > 3.0 mg / ml |
| Procalcitonin | 134 ng/ml | > 2 ng/ml |
| Ferritin | 468 ng/ml | 346 ng/ml |
| D-dimer | 115.28 ng / ml | 0–250 ng / ml |
| IL-6 | 189 pg/ml | 7 pg/ml |
| AST | 16 U/ l | < 38 U/l |
| ALT | 63 U/ l | < 40 U/l |
| Bilirubin total | 11.2 µmol/l | 5–21 µmol/l |
| Bilirubin direct | 4.1 µmol/l | 2.2–5.13 µmol/l l |
| Bilirubin indirect | 7.1 µmol/l | 6.3–15.4 µmol/l |
| BUN | 6.88 µmol/l | 2,0–6,7 µmol/l |
| Creatinine | 95.5 µmol/l | 53,0–97,2 µmol/l |
| Glycosylated hemoglobin | 9.06 % | 5–7 % |
| Blood glucose | 7.1 mmol/l | 3.3–5.5 mmol/l |

It can be seen that the typical of laboratory findings in the hospitalized COVID-19 patient showed leukopenia and elevated levels of such inflammatory indices as C-reactive protein, IL-6, procalcitonin and ferritin, which are related to "cytokine storm". Cytokine storm is a systemic inflammatory response to infections and leads to excessive activation of immune cells and the generation of pro-inflammatory cytokines like IL-6, IL-1, TNF-α, and interferon [7]. Cytokines are an essential part of the inflammatory process produced by innate macrophages, dendritic cells, natural killer cells and the adaptive T- and B-lymphocytes. However, atypical uncontrolled anti-viral immune response results in continuous activation of immune cells, lymphocytes, and macrophages, which produce immense amounts of cytokines, resulting in a cytokine storm with destructive effects on endothelial cell, vascular barrier, capillary damage, diffuse alveolar damage, multiorgan failure. The consequence of the cytokine storm is lung injury that can progress into ARDS [8].

SARS-CoV-2 infection was confirmed by means of polymerase-chain-reaction (PCR). The PCR test for the qualitative detection of nucleic acid from SARS-CoV-2 in upper and lower respiratory regions is most frequently used and reliable comparing with serological tests in identifying IgM and IgG. Either IgG or total antibodies (IgM + IgG) must be calculated because IgM to SARS-CoV-2 are weak indicators, which can lead to false negative results. Moreover, the serological test to SARS-CoV-2 is best performed at least 2 weeks from the onset of the first symptoms, better 3–4 weeks from the beginning. This is due to the fact that many people with COVID-19 have no antibodies in the first two weeks [9].

Clinical urinalysis demonstrated the following: color - yellow, transparency – moderate, urine ratio 1020, pH – 5.5, glucose – 1.7, ketone bodies ++, protein – no, leukocytes – 3–5.

Instrumental investigations

The oxygen saturation using pulse oximeter was 93 %.

X-ray with no syndromes on it is shown in *fig. 1*.

**Fig. 1.** X-ray film

Two days later, chest CT scan without intravenous contrast was performed which demonstrated low-intensity compaction centers looking like ground glass opacities (GGOs) with fuzzy contours, places of drainage. In the segments on the left and in the basal sections of both lungs, there were the signs of linear fibrosis. Lung tissue damage made 27% (*fig. 2*).

The key point of COVID-19 is bilateral presence of patchy ground glass opacities (GGOs) that may coalesce into dense, consolidated lesions, with a predominantly peripheral distribution under the pleura and along the bronchovascular bundles. In addition to GGOs and consolidations, COVID-19

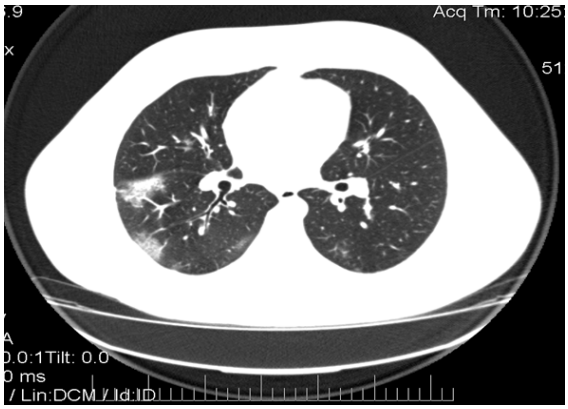


**Fig. 2.** Chest CT without contrast

pneumonia may show other CT findings or patterns such as interstitial thickening, crazy-paving pattern, "reversed halo sign", "halo sign", and airway and vascular changes. These may help to differentiate COVID-19 pneumonia from other forms of pneumonia [10].

Electrocardiography (ECG) showed sinus tachycardia, 117 beats per minute, electrical axis deviation to the left (*fig. 3*).

The blood saturation was maintained at 97 % using oxygen therapy. Comparison of the saturation with the respiratory rate showed that tachypnea correlated with the saturation. Adequate water balance up to 1.5 liters per day was maintained.

The treatment was performed according to the Guidelines for diagnosis and treatment of COVID-19 cases (the Order of Ministry of Health of Ukraine No. 762). The patient was administered empirical antibiotic treatment based on the level of procalcitonin, i.e. third-generation cephalosporin 1 g tid IV and azithromycin 500 mg po once/day as well as a preventive doze of low-molecular heparin (anticoagulants) 0.4 tid because of increased risk of a blood clot development, the doze was calculated with accordance to D-Dimer [12]. Systemic corticosteroids included dexamethasone 8 mg IV per day due to respiratory failure. Additionally, he received antioxidant therapy such as L-arginine aspartate 100 ml IV, ascorbic acid 4 ml IV and rheosorbilact solution 200 ml IV to reduce intoxication. Treatment of comorbid pathology included combination of

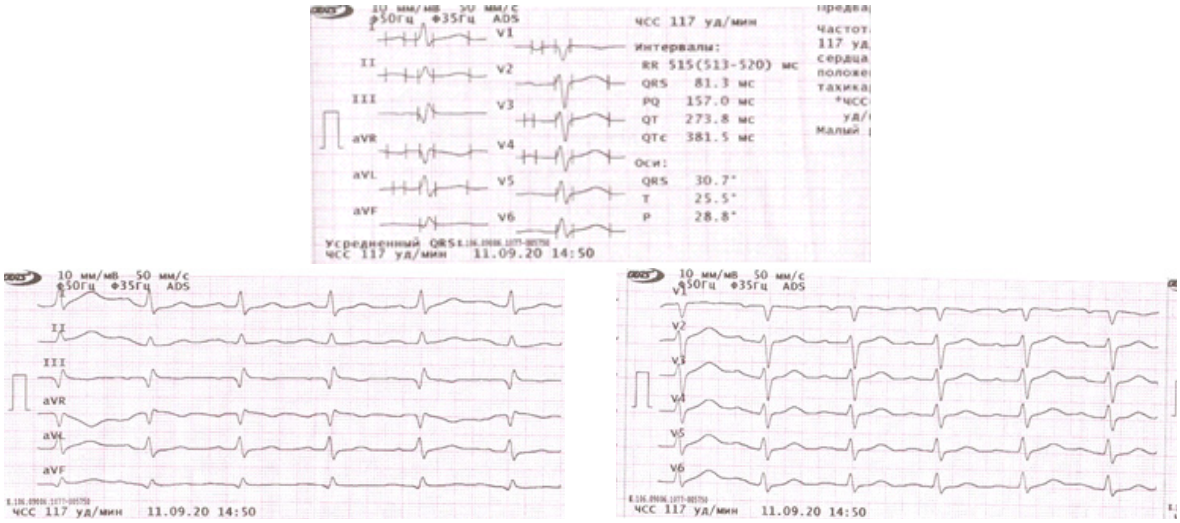


**Fig. 3.** ECG

Final diagnosis

Bilateral polysegmental interstitial moderate COVID-19 pneumonia with stage 2 respiratory failure was made. SARS-Co-2 RNA were identified on 11.09.2020.

The patient was diagnosed with coronary heart disease, cardiosclerosis, grade 2 hypertension of high risk, II A heart failure, stage 2 type 2 diabetes mellitus.

Treatment

The patient required oxygen supply on the first day of hospitalization because of hypoxemia. Supplemental oxygen was administered through a nasal cannula at a rate of 5 liters per minute. Perindopril/Indapamide/Amlodipine 8/2.5/10 po once/day (hypertension), Metformin 1,000 mg tid (type 2 diabetes mellitus). The patient was placed in the prone position in bed.

Outcome

The following 2 days, his fever elevated to 39.2°C. Chills, cough persisted; dyspnea increased; headache, diarrhea developed. The rate of supplemental oxygen was increased to 10 liters per minute. On the third day the initial antibiotic treatment was changed to fluoroquinolones (levofloxacin) 500 mg IV without any other changes. Normal blood glucose level at about 6.1 mmol/l was maintained using Metformin, because

typically glucose level in COVID-19 patients with type 2 diabetes mellitus rises above 14 mmol/l requiring insulin correction. After 10 days of low-molecular heparin therapy, the patient was switched to tableted anticoagulants, rivaroxabanum 15 mg po. Dexamethasone was used during the whole period of respiratory failure.

On day 12 of the treatment, positive dynamics was observed: the body temperature was constantly normal (36.5°C), weakness reduced, but still persisted, there was no cough and bilateral chest pain during it.

Laboratory findings demonstrated reduction of the cytokine storm (C-reactive protein, IL-6, procalcitonin and ferritin), normal white blood cells 9.0 *109/l, monocytosis 13.7 % proving that inflammatory process comes to an end.

Pulse oximetry showed 98% oxygen saturation. X-ray on 21st day of the disease (*fig. 4*) demonstrated positive development in complete decomposition of the obscure regions on the both sides with preservation of the diaphragm fibrosis.

Chest CT (*fig. 5*) findings on the 8th day after recovery showed single spots of pulmonary tissue on both sides according to the type of GGO, the total failure area of 5% in the sub-pleural sections of the lungs.

Despite the comorbid pathology, taking account absence of treatment at the pre-hospital stage, there was no major lung tissue damage. Thus, the inpatient treatment proceeded without any complications and negative dynamics.

After recovery, pulmonary rehabilitation was recommended. Physical activity should be dosed and only in the comfort zone without feeling fatigue and shortness of breath. Vaccination against pneumococcal infection once every five years and against influenza annually was recommended.

After all, numerous uncertainties remain in our understanding of the spread of COVID-19

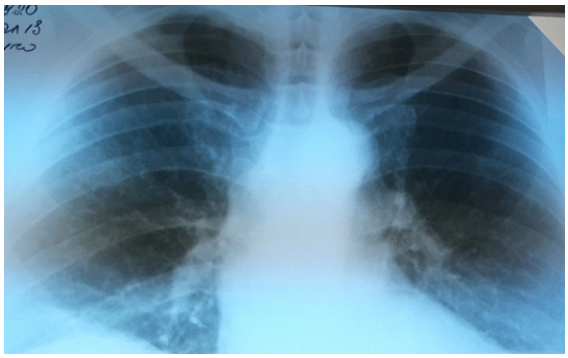

**Fig. 4.** X-ray

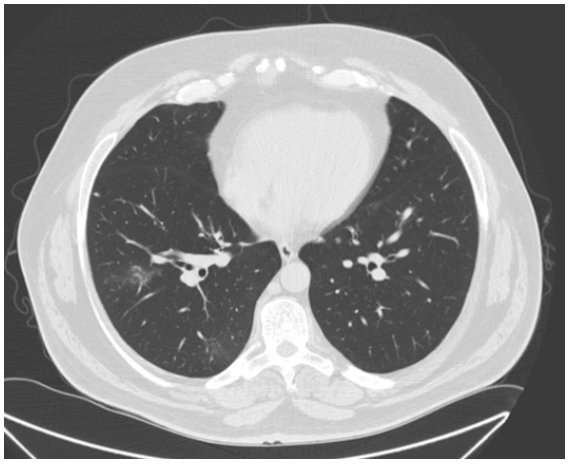

**Fig. 5.** Chest CT

and its management. There are limited data about reinfection with SARS-CoV-2 after recovery from COVID-19.

Acute lung injury and hyperinflammation in COVID-19 disease is associated with the presence of pulmonary fibrosis [12]. A pharmacological approach for reducing the risk of SARS-CoV-2 infection-associated pulmonary fibrosis or prevention of fibrotic status is investigated.

**Conflict of interests**

The authors of the article declare no conflict of interest.

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# MANIFESTATION OF COVID-19 IN THE FORM OF ACUTE MYOCARDIAL INFARCTION (CASE REPORT)

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**Abstract**

Acute myocardial infarction is necrosis of any myocardial mass due to ischemia. COVID-19 can be complicated by thrombosis and myocardial damage, which can lead to the deployment of a clinical picture similar to acute myocardial infarction. The material of this article is presented on the example of a clinical case. A woman aged 37 was diagnosed with an acute myocardial infarction, which later turned out to be a manifestation of a complicated course of coronavirus COVID-19 infection. This case drew attention to the absence of a clinical picture specific to this infection in the form of a damage to the respiratory system or intoxication. The case is also distinguished by the presence of a single uncharacteristic clinical manifestation of COVID-19 in the form of a cardiovascular event with elevations of the ST segment on the cardiogram and other objective data and additional research methods characteristic of acute myocardial infarction. The work also analyzed the pathogenetic mechanisms of acute myocardial infarction and cardiovascular complications of COVID-19, examined the general links of pathogenesis of these two pathological units and analyzed the causes of difficulties in their differential diagnosis. In this regard, there are unquestionably complications of differential diagnosis and the prescription of timely correct therapy. A deeper understanding of these data may improve the algorithms for diagnosing acute myocardial infarction and cardiovascular complications of COVID-19.

***Keywords:*** *COVID-19, acute myocardial infarction, thrombosis, "cytokine storm".*

## Introduction

At present, COVID-19 cannot be considered solely a respiratory disease that leads to severe acute respiratory distress syndrome (SARS-CoV-2) [1]. Today, there is also evidence of additional inclusion of immunopathogenetic mechanisms in its pathogenesis [2]. Hypreproduction of tumor necrosis factor-α, interleukin-1 and interleukin-6 leads to development of a "cytokine storm" and multiple organ failure. Other important pathogenetic links of the infectious process can also be defined in this process: activation of the hemostasis system, intravascular coagulation and, as a result, thrombosis of vessels of mainly small caliber in the organs providing vital functions, primarily in the lungs [3].

Thus, acute myocardial infarction (AMI) is the necrosis of any myocardial mass due to ischemia of different origin, including thrombosis of coronary arteries. Key pathogenetic mechanisms include formation of stenosing atherosclerotic plaque, endothelial inflammation, disruption of fibrinolysis system, activation of bradykinin system, activation of platelet adhesion and aggregation, vasospasm, activation of renin-angiotensin-aldosterone system (RAS), NO blockade, which forms the occlusion of the coronary vessel, resulting in cardiomyocyte death and formation of the morphological equivalent of AMI, the focus of myocardial necrosis [4].

In turn, myocardial damage is often registered in patients with COVID-19 disease [5]. The question of the classification of myocardial damage at COVID-19 is still disputable. Some scientists consider. that it is the morphological equivalent of myocarditis, and the others believe

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that it is a form of lesion morphologically similar to inflammation [6]. The issue of the pathogenesis of this damage is also being investigated. It is believed to be a direct consequence of the effects of the virus on the myocardium. There is also a view that this damage occurs indirectly through a number of enzymatic, hemostatic and hormonal transformations [7; 8].

The pathogenetic mechanisms of myocardial damage in case of COVID-19 are the development of multiple organ failure due to a "cytokine storm", dysregulation of RAS, oxide stress due to hypoxia, prothrombogenic effect and microvascular inflammation [9].

Myocardial damage by COVID-19 is also largely due to the co-exchange of the angiotensin-converting enzyme-2 (ACE-2). As it has already been mentioned, at the initial stages of development of SARS-CoV-2 in coronavirus infection, activation of RAS occurs, resulting in pathological enzyme ACE-2 expression primarily in the lungs and in the myocardium. In addition, there is evidence of increased expression of endothelial fraction of ACE-2 [10]. It leads to dysregulation of peptide fractions, which ultimately leads to increased fibrosis of the pulmonary parenchyma, and in the vasocardial system ACE-2 enhances endothelial dysfunction and thrombosis. All this factors cause positioning of the heart and vessels as target organs for the COVID-19 [11].

Special attention should also be paid to development of the "cytokine storm." The pathology of ACE-2 exchange and active replication of the virus lead to the hyperproduction of a number of immunocompetent molecules, among which the key roles belong to proinflammatory cytokines [12]. Activation of cytokines normally should trigger a number of immunological mechanisms and enhance the immunological response to infection of the virus. But in the case of massive replication of the virus, the cytokine response can change according to a pathological scenario. Classical cys-transmission causes the formation of gp130 complexes, which, when bound to the membranes, can be expressed in almost any tissues and organs, primarily in the organs of the cardiovascular system. This leads to increased inflammation at the sites of expression, which, in combination with hypoxia, leads to the development of insufficient function of target organs, the development of symptoms of sepsis and multiple organ failure [13; 14].

It should be noted that the excessive uncontrolled production of cytokines triggers a cascade of secretion of other biologically active substances, the final effect of which is the pathological changes in the coagulation units of homeostasis towards hypercoagulation and thrombophilia [15]. There is also an increase in vascular permeability due to hypoproduction of nitric oxide and inhibition of fibrinolysis. All these disorders of the hemostatic balance cause both the COVID-19 vascular and myocardial damage [16–18].

Thus, there are some common links of pathogenesis, which lead to a common clinical picture of myocardial damage in COVID-19 infectious process and in AMI [19–21]. In this regard, there are unquestionably complications of differential diagnosis and the prescription of timely correct therapy [22–25].

In order to clearly demonstrate the possibility of developing cardiovascular disorders in patients with COVID-19, an illustrative clinical case is reported. The patient agreed for publishing the data, about which the informed consent of the patient was obtained.

**Clinical case**

A 37-year old nonobese woman (BMI 23,2 kg/m$^2$) with no hypertension and cardiovascular problems in history, non-smoker admitted to the cardiology ICU with a complaints at burning pain in the sternum area, radiating into her left arm, shoulder, lasting for 1 hour, general weakness. Anginal pains appeared for the first time on the day of admission during sleep, when, due to the high intensity of pain syndrome, the patient woke up and called an ambulance. According to the ECG findings, acute coronary syndrome was diagnosed and she was hospitalized. Prehospital care was provided in full in accordance with the Unified clinical protocol for emergency, primary, secondary (Specialized) and Tertiary (Highly Specialized) care and medical Rehabilitation "Acute coronary syndrome with ST segment elevation", Order of the Ministry of Health of Ukraine № 455 (02.07.2014).

Vital signs: body temperature – 36.5°C; peripheral O 2 saturation 98 % on room air; respiratory rate of 16 breaths/min, heart rate of 105 beats/min, blood pressure of 110/70 mmHg.

Physical examination: Patient was concious and well oriented in time and space. Skin and mucous membranes were normal. No particular changes were found in body systems.

Laboratory findings: leukocytosis; elevated ALT (102.5 U/L), creatine phosphokinase (4859.7 U/L) and myocardial fraction creatine phosphokinase (619.4 U/L).

ECG: sinus rhythm and elevation of ST segment in V1–V6 leads up to 6 mm. Acute stage

of anterior myocardial wall infarction was diagnosed.

Ultrasonography of the heart (Echo-CG): end diastolic volume 94 $cm^3$, end systolic volume – 51 $cm^3$, interventricular septum thickness – 0.9 cm; left ventricular posterior wall thickness 0.9 cm; hypoakinesia zones were installed, no dyskinesia zones were found. Aorta was 2.9 cm, right atrium – 3.1 cm and right ventricle – 2.3 cm.

The diameter of the inferior vena cava – 1.5 cm, collaborates on breath more than 20 %. The pericardium was normal. The pulmonary artery valve was 1.7 cm. Ejection fraction was 45 %. Restrictive type of diastolic dysfunction.

Coronarography: thrombotic occlusion of the middle segment anterior descending artery (TIMI 0). After stenting procedure – TIMI – III.

On the 10-th day after ECG normalized, the patient was discharged with the supervision of a cardiologist. During outpatient consultation it was decided to hospitalize the patient to the cardiology department to continue the treatment. According to the standards of delivery of health care all patients must pass COVID-19 test to be hospitalized. Patient's PCR test result was positive. Thus, acute myocardial infarction turned out to be a complication of the infectious process and its only clinical manifestation.

Similar clinical data have been described in the literature. Thus, a group of researchers led by Kevin J. Clerkin describes cases COVID-19 mainly with cardiac clinical manifestations in the form of ST-segment elevation on ECG and changes in the cardiac panel of serum biochemical analysis [26].

The data on myocardial damage in COVID-19 patients have also been published by a group of researchers (Masataka Nishiga et al.), which describes the markers of myocardial damage in such patients [27].

The findings of the group of researchers from Italy show that STEMI may represent the first clinical manifestation of COVID-19, and 85 % of such patients did not have a COVID-19 test result at the time of coronary angiography. They have also published the data about approximately 40 % of patients with COVID-19 with STEMI, in whom a culprit lesion is not identifiable by coronary angiography [28].

This case deserves a particular attention because of the young age of the patient with MI (37 years old female) and cardiovascular events that occurred against a background COVID-19 with no clinical presentation specific for this infection, which significantly aggravated the diagnostic algorithm.

**Conflict of interests**

The authors of the article declare no conflict of interest.

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# VITAMINS B1 AND B12 DEFICIENCY AS A PREDICTOR OF TUBERCULOSIS SEVERITY AND PERIPHERAL NERVOUS SYSTEM DAMAGE

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**Abstract**
It is known that vitamin status plays one of the leading roles in the normal functioning of the immune system. Vitamins deficiency leads to weakening of immunity and can provoke occurrence of severe infectious diseases, including tuberculosis. **The purpose** of the study was to investigate the role of vitamins B1 and B12 deficiency as a predictor of tuberculosis severity and development of peripheral nervous system damage. **Materials and methods.** 89 patients with pulmonary tuberculosis and 12 healthy persons were included in the study. The patients were examined and treated according to current guidelines of the Ministry of Health of Ukraine. Additionally, the concentration of vitamins B1 and B12 was measured by ELISA in blood serum in all the patients at the treatment onset and in all healthy persons. To find the damage of peripheral nervous system we performed stimulation electroneuromyography of lower limbs. **Results.** The level of vitamin B12 was 0.19±0.01 nmol/L (median – 0.19 nmol/L) in patients with destruction of the lung tissue and 0.22±0.01 nmol/L (median – 0.21 nmol/L) in patients without destruction, $p < 0.05$. MNCV was 49.25±0.80 mm/s (median – 49.40 mm/s) in patients with destruction of the lung tissue and 53.41±0.99 mm/s (median – 53.10 mm/s) in patients without destruction, $p < 0.01$. SNCV was 43.41±1.14 mm/s (median – 42.05 mm/s) in patients with destruction of the lung tissue and 45.91±0.94 mm/s (median – 46.00 mm/s) in patients without destruction, $p < 0.05$. **Conclusions.** Pulmonary tuberculosis leads to the disturbances in the metabolism of vitamins B1 and B12, causing their deficiency and the associated violation of impulse conduction along peripheral nerve fibers. More severe tuberculous lesions with destruction of lung tissue and massive bacterial excretion are associated with a more pronounced deficiency of vitamins B1 and B12, as well as decrease of motor and sensory conduction velocity.
***Keywords:*** *tuberculosis, vitamins, electroneuromyography, diagnosis.*

## Introduction

It is known that vitamin status plays one of the leading roles in the normal functioning of the immune system. Vitamins deficiency leads to weakening of immunity and can provoke occurrence of severe infectious diseases, including tuberculosis [1].

Some anti-tuberculosis drugs can affect vitamin metabolism, especially group B vitamins. Isoniazid, one of the most effective first-line drugs, is a derivative of hydrazine, which is classified as a highly toxic substance of convulsive action. It inhibits synthesis of gamma-aminobutyric acid by inhibiting glutamic acid decarboxylase by antagonism with pyridoxal phosphate. By disrupting the exchange of vitamins of group B and glutamic acid, Isoniazid penetrates the blood-brain barrier and produces a pronounced neurotoxic effect, which is manifested by the symptoms of damage to the central and peripheral nervous system [2]. Linezolid, an anti-tuberculosis drug widely used in the treatment of drug-resistant tuberculosis, causes adverse reactions in about 60 % of cases. The most common of these are thrombocytopenia, irreversible peripheral neuropathy and optic neuropathy [3].

Meanwhile, group B vitamins play an important role in the pathogenesis of tuberculosis

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and the mechanisms of the anti-tuberculosis immune response formation. Thus, the study by Hu S et al. [4] describes the important role of vitamin B1 in formation of the immune response, which shortens *M. tuberculosis* survival time in macrophages and in vivo through regulation of the proliferation activator receptor by gamma peroxide. Accordingly, vitamin B1 deficiency is associated with long-term survival, growth and reproduction of *M. tuberculosis*.

The study by S. Rempel et al. [5] shows that *M. tuberculosis* actively imports vitamin B12 which is necessary for its growth and development, thereby deepening its deficiency in patients with tuberculosis. Thus, the study of the deficiency of group B vitamins, namely vitamins B1 and B12, in tuberculosis patients, as well as the associated lesions of the peripheral nervous system, is an urgent issue.

**2. Purpose, subjects and methods:**

**2.1. The purpose** of the study was to investigate the role of vitamins B1 and B12 deficiency as a predictor of tuberculosis severity and development of peripheral nervous system damage.

**2.2. Subjects & Methods**

89 patients with pulmonary tuberculosis and 12 healthy persons were included in the study. The patients were examined and treated according to the current guidelines of the Ministry of Health of Ukraine. Additionally, the concentration of vitamins B1 and B12 was measured by ELISA in blood serum in all the patients at the treatment onset and in all healthy persons. To find the damage of the peripheral nervous system we performed stimulation electroneuromyography of lower limbs. The function of n. tibialis – m. abductor hallucis (arch of the foot, stimulation at the level of the tarsus and popliteal fossa) and n. peroneus – m. extensor digitorum brevis (the outer edge of the dorsum of the foot, stimulation at the level of the tarsus and popliteal fossa) was assessed. To assess motor and sensory conduction we measured motor nerve conduction velocity (MNCV), terminal motor latency (TML), sensor nerve conduction velocity (SNCV), terminal sensory latency (TSL). Statistical data processing was carried out using Statistica 8.0 with calculation of Mann–Whitney criterion and Spearman correlation coefficient.

**Conflict of interests**

The authors of the article declare no conflict of interest.

**3. Results & discussion**

Comparison of vitamin B1 levels showed its significantly lower level in the tuberculosis patients (28.51±0.66 nmol/L, median – 27.85 nmol/L) than in the control group (56.37±2.11 nmol/L, median – 56.45 nmol/L), $p < 0.001$. When comparing the levels of vitamin B12, significantly lower values were also found in tuberculosis patients (0.22± 0.01 nmol/L, median – 0.20 nmol/L) than in control group (0.29±0.01 nmol/L, median – 0.29 nmol/L), $p < 0.001$. The decrease in the level of vitamins B1 and B12 in patients with tuberculosis was accompanied by a decrease in the MNCV, which was 52.94±0.77 mm/s (median – 51.00 mm/s) in tuberculosis patients and 60.87±0.91 mm/s (median – 60.10 mm/s) in control group, as well as a decrease in the SNCV, which was 44.79± 0.66 mm/s (median – 43.70 mm/s) in patients with tuberculosis and 57.22±1.61 mm/s (median – 59.50 mm/s) in control group, $p<0.001$. Tuberculosis patients also had an increased TML up to 2.35±0.07 ms (median – 2.33 ms) and TSL up to 2.37±0.08 ms (median – 2.40 ms) compared with the control group in whom the TML and TSL were 1.84±0.10 ms (median – 1.80 ms) and 1.71±0.11 ms (median – 1.75 ms) respectively, $p < 0.001$.

When studying the dependence of the changes in the level of vitamins B1 and B12, as well as the degree of disturbances in the nerve fiber conduction, it was found that in the presence of destruction of the lung tissue, there is a significant decrease in the level of vitamin B12, as well as in the speed of conduction of the nerve impulses along the motor and sensory fibers compared with the patients without destruction of the lung tissue. Thus, the level of vitamin B12 was 0.19±0.01 nmol/L (median – 0.19 nmol/L) in patients with destruction of the lung tissue and 0.22±0.01 nmol/L (median – 0.21 nmol/L) in patients without destruction, $p < 0.05$. MNCV was 49.25±0.80 mm/s (median – 49.40 mm/s) in patients with destruction of the lung tissue and 53.41±0.99 mm/s (median – 53.10 mm/s) in patients without destruction, $p<0.01$. SNCV was 43.41±1.14 mm/s (median – 42.05 mm/s) in patients with destruction of the lung tissue and 45.91±0.94 mm/s (median – 46.00 mm/s) in patients without destruction, $p<0.05$. The data are presented in *fig. 1*.

Correlation analysis showed significant negative correlations between the level of vitamin B1 and the massiveness of bacterial excretion detected by sputum microscopy ($r = -0.40$) and culture ($r = -0.34$), $p<0.05$. That is, the lower is the level of vitamin B1, the more massive is the bacterial excretion in the patient.

A negative correlation of the average strength ($r = -0.58$, $p<0.05$) was revealed between MNCV and glucose level in patients with tuberculosis, *fig. 2*.

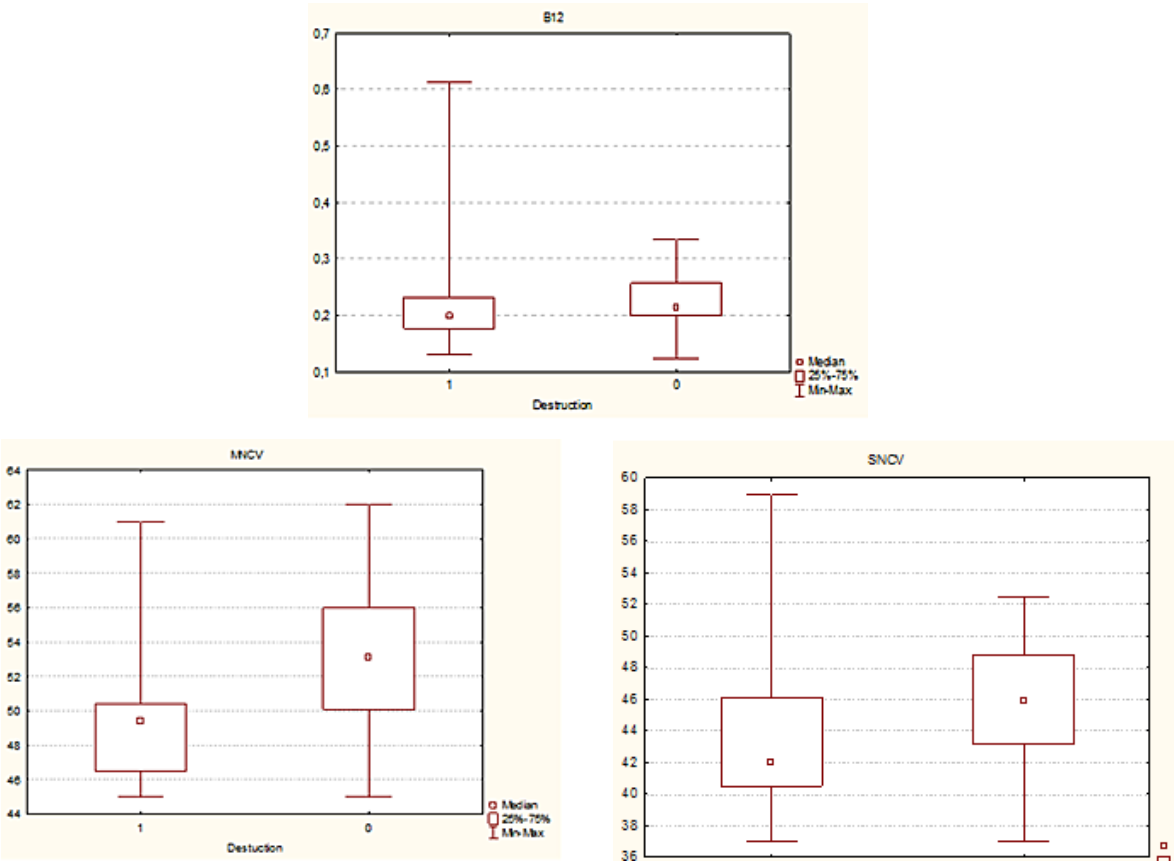


**Fig. 1.** Comparison of vitamin B12 levels and motor and sensory conduction velocity in patients with destruction of pulmonary tissue (1) and without it (0)

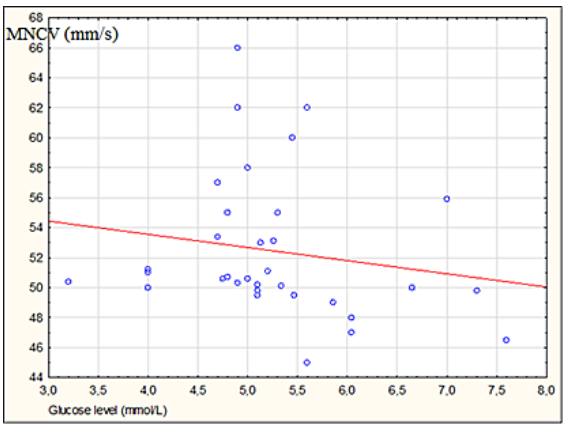


**Fig. 2.** Correlation between motor speed of conduction and glucose level in tuberculosis patients

Vitamin B1 takes part in oxidative decarboxylation of keto acids (pyruvic and lactic), synthesis of acetylcholine, which takes part in carbohydrate metabolism and associated energy, fat, protein, water-salt metabolism, in providing axonal transport, determines the regeneration of nervous tissue and the activity of the nervous system [6; 7]. Vitamin B12 is essential in the formation of protein and fatty structures of the protective myelin layer of nerve fibers [8; 9]. Thus, according to the literature, vitamins B1 and B12 are important components that ensure the normal functioning of the peripheral nervous system.

Our study revealed a significant decrease in the levels of vitamins B1 and B12 in tuberculosis patients compared with healthy individuals. This decrease was accompanied by reduction in the motor and sensory conduction velocity and an increase in terminal motor and sensory latency. These can signal the onset of peripheral neuropathy in tuberculosis patients. With the neurotoxic effect of anti-tuberculosis drugs, it can be assumed that these disorders will further worsen during the treatment.

A correlations were found between the levels of vitamins B1 and B12, the motor and sensory conduction velocity and the severity of tuberculosis lesions (destruction of lung tissue and massive bacterial excretion). The correlation showed that the presence of destruction of the lung tissue is associated with a decrease in the level of vitamin B12 and is accompanied by a decrease in motor and sensory conduction velocity. Decreases level

of vitamin B1 is associated with more massive bacterial excretion at the beginning of treatment.

Of particular interest is negative correlation between motor and sensory conduction velocity and the glucose level. In other words, the higher is the glycemic level, the slower the impulse is conducted in the peripheral nerve fibers. Previously, we have already identified a violation of the parameters of carbohydrate metabolism in patients with tuberculosis [10]. The combination of this factor with the neurotoxic effect of anti-tuberculosis drugs and the direct action of *M. tuberculosis* suggests the problem of vitamin deficiency and impaired functioning of the peripheral nervous system in patients with tuberculosis, aggravated during treatment, and recommends the appointment of vitamins of group B, in particular B1 and B12, as an additional pathogenetic therapy in patients with pulmonary tuberculosis.

**Conclusions**

Pulmonary tuberculosis leads to the disturbances in the metabolism of vitamins B1 and B12, causing their deficiency and associated violation of impulse conduction along the peripheral nerve fibers. More severe tuberculous lesions with destruction of the lung tissue and massive bacterial excretion are associated with a more pronounced deficiency of vitamins B1 and B12, as well as a decrease of motor and sensory conduction velocity. The data obtained allow us to advise additional administration of vitamins B1 and B12 in the pathogenetic therapy of tuberculosis in order to prevent peripheral neuropathy development.

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# PHYSICAL THERAPY OF PATIENTS AFTER AUTOPLASTY OF THE ANTERIOR CRUCIATE LIGAMENT AT THE FOLLOW-UP STAGE

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**Abstract**

Background: despite the large number of works covering the rupture of the anterior cruciate ligament of the knee joint, today there are no generally accepted tactics of physical therapy after this injury. The issue of staged rehabilitation of persons after autoplasty of the anterior cruciate ligament needs to be clarified. Objective: to develop an effective program of complex physical therapy for persons after autoplasty of the anterior cruciate ligament at the follow-up stage based on comparisons of rehabilitation programs of the two medical centers. Materials and Methods. The clinical trial involved 26 patients of different ages and genders from two medical centers (by 13 subjects) at the follow-up stage after autoplasty of the anterior cruciate ligament. Original rehabilitation program with using crossovers, balancing platforms, massage rollers, kinesiotaping and CPM was developed. Amplitude of knee flexion and extension, manual and muscular testing and some cardiovascular parameters (heart rate, systolic and diastolic blood pressure) were analyzed before and after the rehabilitation program in all participants from medical center 1 (original program) and for all participants from medical center 2 (standard program). Standard statistics was used to describe and compare the results. Results: after the course of therapy, the patients in both centers achieved the same rates of active flexion and extension of the knee, but patients from the 1 medical center reached them on average 5–6 weeks after the start of therapy. Conclusions: there is an advantage of using a comprehensive program of physical therapy (with using multi-function simulators, balancing platforms, massage rollers, kinesio-taping and CPM simulators) for individuals after autoplasty of the anterior cruciate ligament at the follow-up stage.

***Keywords:*** *anterior cruciate ligament; autoplasty; follow-up stage; physical therapy; rehabilitation.*

Introduction

Anterior cruciate ligament rupture is the most common ligament injury in the knee joint, which without proper treatment can lead not only to the end of the sports career (in an athlete), but also to irreversible injuries in the knee joint in the long term and even greater injuries from repeated injuries. Even in non-athletes, this injury significantly impairs the quality of life [9, 12, 18].

Anatomically, women are more prone to rupture of the anterior cruciate ligament (2-8 times), but due to the more active participation of men in sports in which the anterior cruciate ligament is more often damaged, the majority of patients with this injury are men [3, 7, 22].

A torn anterior cruciate ligament does not grow on its own. It can either be reconstructed by surgery (plastic), or left as it is. Under normal circumstances, the knee can work without the anterior cruciate ligament. Many patients in their thirties who do not exercise will not experience discomfort even if the ligament is damaged. In turn, the rupture of the anterior cruciate ligament in athletes needs to be restored to sports as soon as possible, because the anterior cruciate ligament is an important stabilizer of the knee joint. Therefore, plastic surgery is required in this case [10, 15, 21].

In Ukraine, anterior cruciate ligament plastic surgery ranks the 7th out of all surgical operations. The number of plastic operations, and hence revision plastic operations, is growing every year.

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Negative results of cruciate ligament plastic surgery occur only in 10–20 % of cases [13].

Circuate ligaments are important passive stabilizers of the knee joint, and the anterior cruciate ligament is its most important stabilizer [10, 22]. The most popular practice is the use of tendons from the patellar ligament and the tendons of the semitendinosus muscles (*fig. 1*) [10].

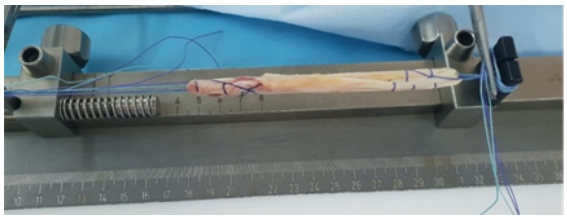

**Fig. 1.** Tendon graft of semitendinosus muscle ("new" ligament) of the anterior cruciate ligament, folded in four

A review of the literature and scientific sources has shown that today there are many methodological developments and works on special rehabilitation measures for the patients with anterior cruciate ligament rupture. But there is no single clear tactic for physical therapy after anterior cruciate ligament autoplasty, and only a few issues have been covered. The issue of physical therapy for persons after autoplasty of the anterior cruciate ligament at the follow-up stage needs to be clarified.

**2. Purpose, subjects and methods:**

**2.1. The purpose** of the work was to develop an effective program of complex physical therapy for persons after autoplasty of the anterior cruciate ligament at the follow-up stage based on comparison of rehabilitation programs of the two medical centers.

**2.2. Subjects & Methods**

The clinical trial involved 26 patients of different ages and genders at the follow-up stage after autoplasty of the anterior cruciate ligament. Rehabilitation process was conducted in two medical centers (kinesitherapy center "KinesisLife" and rehabilitation center "Your Health" in 13 patients from each center). Each patient provided informed consent to participate in the study and in the subsequent publication of the results. All studies met ethical requirements.

The selection of research methods took into account the symptoms of the injury, the course and possible complications according to the age and type of injury. Research methods included drawer test and Lachman's test, autoplasty, accurate diagnosis, anthropometry, manual muscle testing, flexion and extension amplitude in the knee joint after autoplasty. These complex methods were necessary for defining the goals of physical therapy and choosing the right rehabilitation program that can give a quality and long-term result [6, 17, 21].

Physical therapy at the follow-up stage begins 5 weeks after the surgery and lasts for up to 6 months. An important task during this period is to return the person to a normal lifestyle. When the anterior cruciate ligament is ruptured, 3 periods (motor modes) are distinguished in patients at the follow-up stage. It is on the basis of periodization by stages that we created a comprehensive individual program of physical therapy, where each of these motor modes has its own tasks, methods and means (*fig. 2*).

When performing physical therapy for persons after autoplasty of the anterior cruciate ligament at the dispensary stage, a clear sequence should be followed, which will allow to assess the need for certain procedures (*fig. 3*).

For comparison of effectiveness of the original rehabilitation program with the traditional one, we implemented them in the rehabilitation procedure for all participants from medical center 1 (original program) and for all participants from medical center 2 (standard program).

Particular attention was paid to exercises on the "crossover" simulator (*fig. 4*) [19].

Differences in the conduct of physical therapy after autoplasty of the anterior cruciate ligament at the dispensary stage in two medical centers (*table 1*).

The studied indicators were compared and analyzed. Standard statistics was used to describe and compare the results. Difference was considered to be statistically significant if two-way P was less than 0.05.

**Conflict of interests**

The authors of the article declare no conflict of interest.

**3. Results & discussion**

There was no significant difference between the parameters of the patients from different centers during the background survey (*table 2*). Thus, background flexion amplitudes in the patients from medical center 1 were 115.7 ± 1.92, medical center 2 – 115.1 ± 2.15 ($p>0.05$).

Cardiovascular parameters after the complex therapy were lower in both medical centers.

The final systolic blood pressure in patients from the medical center 1 was 121.1 ± 1.3 mm Hg, diastolic blood pressure – 71.2 ± 1.84 mm Hg, which is slightly lower than in patients 2 medical center, where the systolic blood pressure was

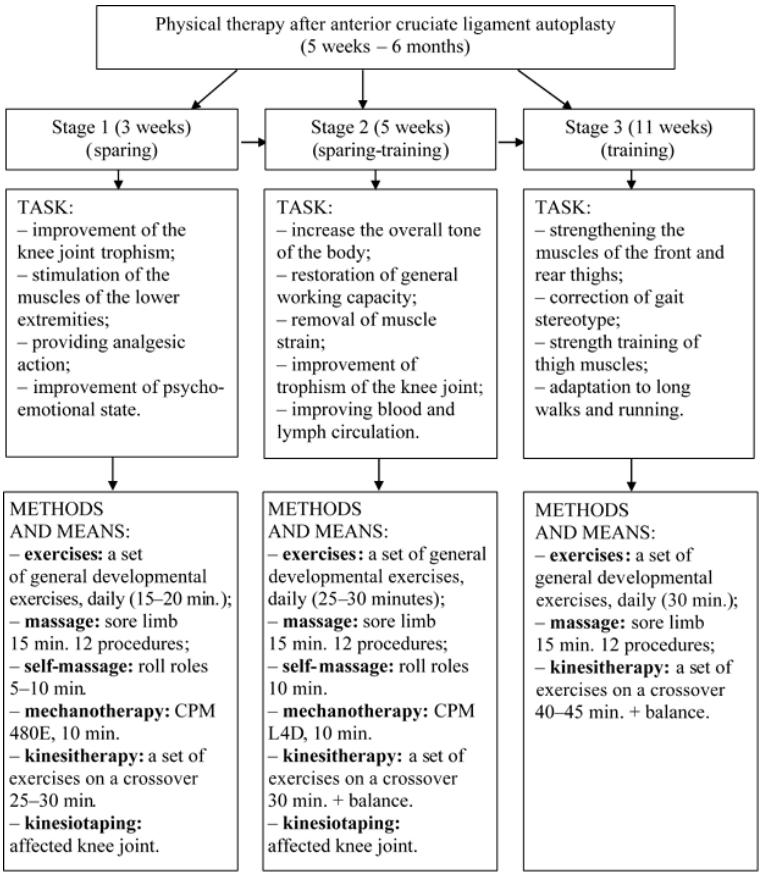


**Fig. 2.** The program of complex physical therapy after autoplasty of the anterior cruciate ligament at the follow-up stage

122.4 ± 1.76 mm Hg, and the diastolic blood pressure was 76.3 ± 2.71 mm Hg.

Diastolic blood pressure in medical center 1 patients after the rehabilitation course was lower than in those from medical center 2 patients (71.2 ± 1.84 vs. 76.3 ± 2.71 mm Hg).

After the introduction of the proposed approaches to physical therapy, the heart rate in 1 medical center patients was 3.9 beats/min lower than the background; in patients 2 medical center – 2.1 beats/min.

The indicators of the amplitude of knee flexion in patients of both centers were significantly higher after the rehabilitation with no difference between centers. Indicators of the muscle strength in flexion and extension of the knee (according to the manual muscle test) before rehabilitation in patients of both groups were evaluated at 2 points, after therapy – at 4 points.

After the course of therapy, the patients in both centers achieved the same rates of active flexion and extension of the knee, but patients from the 1 medical center reached them on average 5-6 weeks after the start of therapy, while patients in the comparison group – 6–7 weeks, i.e. patients 1 medical center reached the goal 1–2 weeks faster than patients 2 medical center.

Tendon grafts use the patellar ligament, semitendinosus tendon, quadriceps femoris tendon, and synthetic tendon [1, 4]. There is still a dispute between orthopedists and traumatologists about the choice of tendon graft; it is historically believed that the tendon of the knee ligament is stronger, but this technique has several disadvantages, mostly esthetic (a large scar on the front of the knee), pain during movements, longer recovery time [2, 11, 16]. The autograft from the tendons of the semitendinosus muscle meets all the strength characteristics of the ligament, allows different options for fixation, and this is the least traumatic method of reconstruction [8, 14].

The method of application of physical exercises in each case depends on the diagnosis and stage of the disease, individual characteristics of the patient, his level of physical fitness, age and comorbidities, based entirely on the principle of individual approach [5].

The technique is based on exploratory causes based on manual muscle testing, kinesiological correction and therapeutic movement aimed at

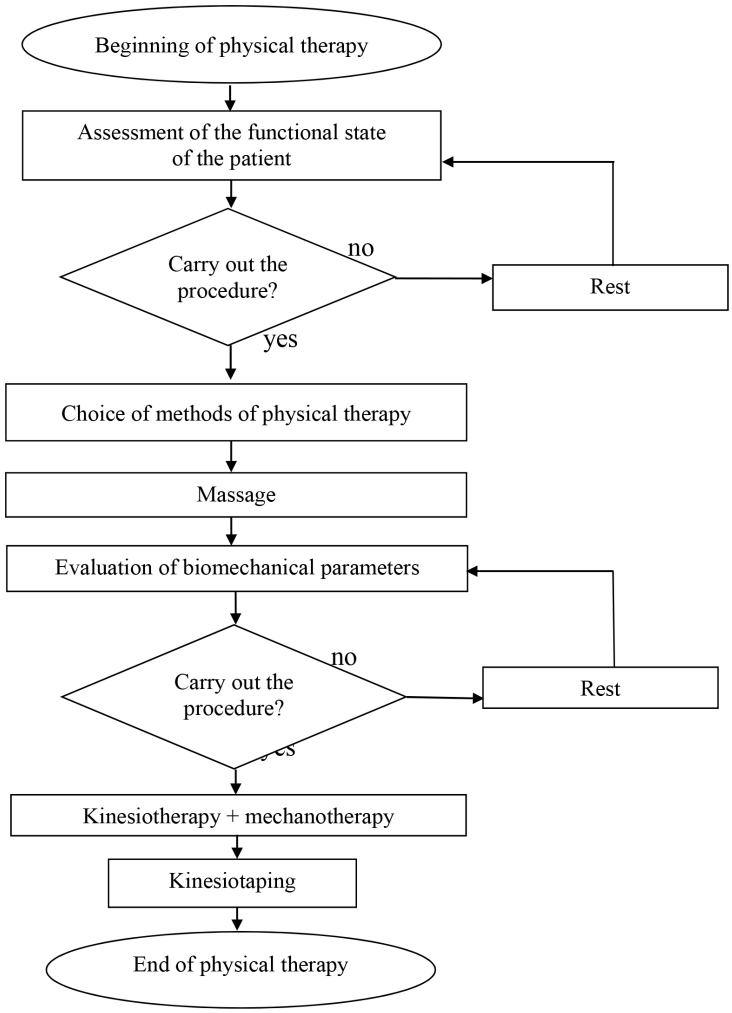


**Fig. 3.** The sequence of procedures of the physical therapy program after autoplasty of the anterior cruciate ligament at the dispensary stage

**Fig. 4.** General view of the multifunctional simulator "Crossover"

eliminating muscle imbalance, forming an optimal motor stereotype, restoring blood flow and innervation [19] with is a fine background for the long-term results [21].

Kravchenko B. M. described the method of rehabilitation of patients after autoplasty of the anterior cruciate ligament only with the help of a crossover and massage, without the use of additional modern means of physical therapy [19].

Physical therapists find a solution to the problem of recovery and stabilization of the knee by using only coordination exercises [20, 23].

The use of additional modern means of physical therapy can significantly accelerate the recovery of patients after autolpastic anterior cruciate ligament.

The proposed program of physical therapy can be used in practice by specialists in physical therapy, physiotherapists in the work of rehabilitation centers and on the basis of sports clubs.

***Table 1***

*Comparison of rehabilitation programs of two medical centers*

| Structural element | Physical therapy programs | |
|---|---|---|
| | 1 medical center | 2 medical center |
| Kinesiotherapy with a specialist in physical therapy | 5 times a week 40–45 min. | 3 times a week 30–45 min. |
| Mode of kinesitherapy | Passive, passive-active, active | Passive, passive-active, active |
| Equipment | Rollers, rubber, crossovers, CPM, balls, Blackroll, various balancing platforms | Rollers, balls, rubber, crossovers, percussion portable massager |
| Exercises | A set of exercises of general and special orientation | A set of general developmental exercises |
| Therapeutic massage | Sick limb | Sick limb |
| Kinesiotaping | Sick limb | – |
| Mechanotherapy | CPM 480E, CPM L4D | – |

***Table 2***

*Comparative dynamics of the studied parameters of the state of the musculoskeletal system and the general condition of the patient's body after autoplasty of the anterior cruciate ligament in two medical centers*

| Indicators | Medical center | Background survey X±m | Final survey X±m | Changes, % | Difference, P |
|---|---|---|---|---|---|
| Amplitude of knee flexion | 1 | 115.7±1.92 | 135±2.42 | 22.31 | < 0.0001 |
| | 2 | 115.1±2.15 | 135±1.81 | 22.1 | < 0.0001 |
| Amplitude of knee extension | 1 | 0 | 0 | 0 | |
| | 2 | 0 | 0 | 0 | |
| MMT, points | 1 | 2 | 4 | 100 | |
| | 2 | 2 | 4 | 100 | |
| HR, beats/min | 1 | 65±2.16 | 61±1.97 | 3.9 | < 0.0001 |
| | 2 | 65±2.1 | * 63±1.27 | 2.1 | 0.0072 |
| Systolic BP, mm Hg | 1 | 124.9±1.2 | 121.1±1.3 | 3 | < 0.0001 |
| | 2 | 124.9±1.31 | *122.4±1.76 | 1.5 | 0.0004 |
| Diastolic BP, mm Hg | 1 | 76.6±1.54 | 71.2±1.84 | 7 | < 0.0001 |
| | 2 | 77.7±1.97 | *76.3±2.71 | 1.8 | 0.1450 |

## Conclusions

Physical therapy program at Medical Center 1 using crossovers, balancing platforms, massage rollers, kinesiotaping and CPM was more effective than the standard program used for patients at Medical Center 2.

The results of the research may indicate that our program of physical therapy for patients after the anterior cruciate ligament autoplasty is more effective than the standard program. We can assume that the proposed individual physical therapy program can allow people to recover more quickly and efficiently from the negative effects of autoplasty of the anterior cruciate ligament of the knee joint at the follow-up stage.

The proposed program of physical therapy can be used in practice by specialists in physical therapy, physiotherapists, occupational therapists, in the work of rehabilitation centers and on the basis of sports clubs.

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# THE USE OF 3-PLANE SCHROTH GYMNASTYCS IN THE TREATMENT OF GRADE 2 SCOLIOSIS

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**Abstract**

**Background.** Scoliosis is defined as deformity of the spinal column and torso in three dimensions. The cause of scoliosis remains unknown. Therefore, such scoliosis is called idiopathic. Adolescent idiopathic scoliosis is one of the most common structural deformities of the spine in adolescents, which aggravates during an active growth. Physical rehabilitation plays an important role in the system of complex conservative treatment of scoliotic disease. The most effective conservative treatment is 3-plane gymnastics according to the method of C. Schroth and brace therapy according to Abbott-Cheneau principle. **Objective.** Improving a comprehensive program of physical rehabilitation for adolescents with scoliotic disease of the second degree by Schroth method and determining its effectiveness. **Methods.** We examined 14 patients aged 11–15 years with scoliotic disease of the second degree. These patients were divided into 2 groups: main and control (7 persons in each, respectively). In patients of the main group the complex treatment of scoliosis that included Schroth's method in combination with massage and brace therapy was used. In the control group comprehensive rehabilitation treatment included restorative and preventive measures according to the generally accepted program. **Results.** The use of Schroth technique in a comprehensive physical rehabilitation program better reduced Cobb's angle of deviation of the spine, increased strength endurance of the back and abdominal muscles, improved formation of the muscular corset, largely eliminated cosmetic defects. **Conclusion.** Schroth's technique had a positive effect on Cobb's angle and other parameters in adolescent girls with a grade 2 scoliosis. The multi-component Schroth technique, which includes passive correction, self-stretching and corrected breathing creates conditions for is necessary to be widely implemented in clinical practice.

***Keywords.*** *Schroth's gymnastics, scoliosis, scoliotic disease, orthopedic devices, Cobb's angle.*

## Introduction

At present medical check-ups of preschool and school children frequently reveal children with posture disorders. Increase in the number of children and adolescents with the consequences of scoliosis progression is one of the main concerns of pediatric orthopedics. Scoliotic disease causes both physical and psychological problems. Therefore, it is important to distinguish pathology of posture and scoliosis as early as possible [7].

Scoliotic disease is a genetically caused problem of the human musculoskeletal system characterized by multiplanar deformity of the spinal column and chest, accompanied by dysfunction of the organs and systems of the body. Scoliosis is not only medical, but also a complex social problem that requires a comprehensive approach [1].

Scoliosis prevalence in the world varies from 3.2 to 20.0 % of the general population and from 2–5 to 13.3 % in pediatric one. Over the recent 20 years, the number of patients with scoliosis has increased from 6.4 to 17.0 % [15].

Despite of the high frequency, the diagnosis of scoliosis in adolescents is problematic as there is no pain or other inconvenience until a pronounced cosmetic defect develops [3].

The diagnostic procedure usually includes history taking, visual examination, special tests to determine the mobility of the spinal column, evaluation of Cobb's angle of the spinal column deviation.

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Among the numerous methods of determining the curvature angle, the most widespread is Cobb's method, based on determining the angle formed by the two end vertebrae of the curvature arc [14]. For this purpose two lines are drawn of the x-ray film, in parallel with the planes of the neutral vertebrae and a wide intervertebral space. At the point of intersection of these lines the angle of scoliosis is measured. At small curvatures the additional angle between the perpendiculars to these lines is determined (*fig. 1*).

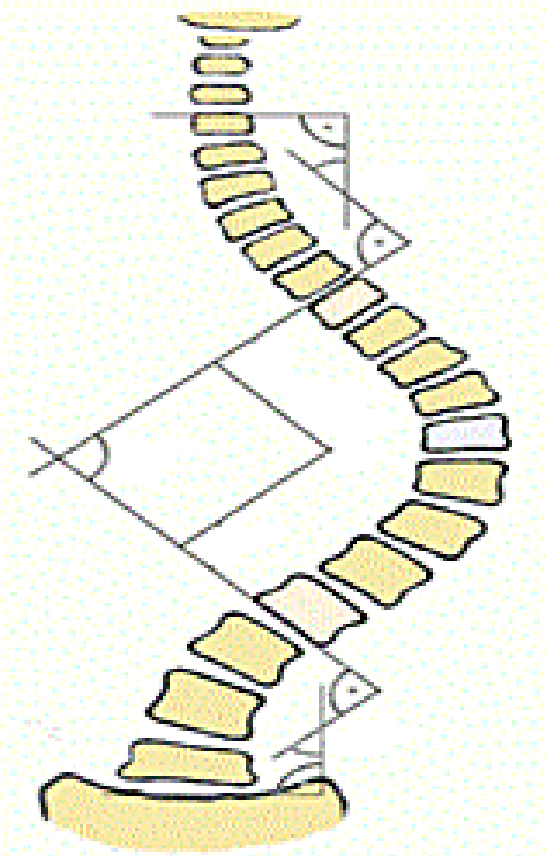


**Fig. 1.** Determining the angle by Cobb's method [9]

Based on Riesser's test, the prognosis of scoliotic deformity is made, as well as the possibility of wearing a back brace is assessed. This test can be performed using x-ray films (*fig. 2*). The principle of this test consists in the fact that ossification of the iliac bones begins at the anterior upper edge and moves to the end. The iliac crest is divided into 4 parts. The degree of maturity is determined by the number of squares that have been ossified. For example, grade 3 according to Riesser means that 75 % of the iliac crest has been ossified. Grade 4 means that all four parts have been ossified. Grade 5 according to Riesser means that all four parts have been ossified and merged with the iliac bone. When a child reaches

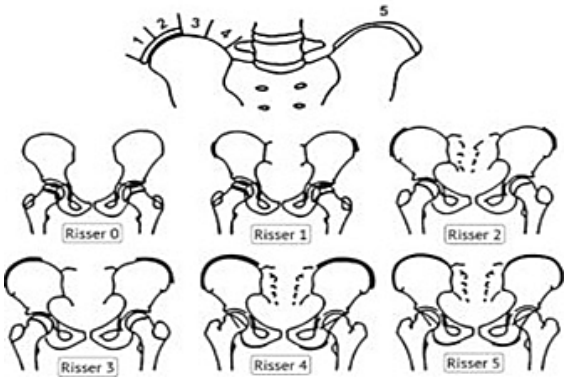



**Fig. 2.** Scheme for determining the bone age. Riesser's test [6]

ossification of grade 5, it makes no sense to wear a back brace, because the growth zones are closed and the growth of the spinal column and its mobility have stopped [12].

The most popular and effective method of physical rehabilitation of patients with scoliosis in European countries is 3-plane anti-scoliotic gymnastics according to Schroth and brace therapy by the principle of Abbott-Cheneau. Such programs are currently used in hospitals of Germany and Spain and include courses lasting for 3–5 weeks 4–6 hours a day [12].

Schroth's method is a conservative gymnastics based on 3-plane correction with alignment of the torso in the typical for each type of scoliosis position and correct breathing. The goal is to develop the internal muscles of the chest and ribs in order to change the shape of the upper torso and correct any abnormalities of the spinal column.

Proper breathing is the main part of Schroth's gymnastics as in scoliotic patients the thorax participates in breathing asymmetrically. It is due to the spinal column rotation and the thorax deformity. Thus, intercostal spaces from the side of the concavity are diminished and o the opposite side they are enlarged, that is why with every inhalation the greater volume of air comes in lungs from the convex side, and less from the concave one. This is one of the causes of rib hump formation and falling in of the ribs on the opposite side. The correct breathing is directed opposite to the curvature side, i.e. inhalation is done by the falling in zones of the thorax [14].

Another main feature is development of a new "correction position". All exercises in the program are mostly static, providing different loads on different muscles depending on the type of curvature and severity of scoliotic disease. Their main goal is to stabilize the corrected position in all three planes of the spinal column and to form a muscular core [14].

However, prolonged wearing of the brace relaxes the paravertebral muscles by maintaining the body with the brace, and therefore performing exercises for the back muscles is necessary to strengthen them, give them the right shape and keep them in the corrected position.

**2. Purpose, subjects and methods:**

**2.1. The purpose** of the work was to determine the most effective rehabilitation program for adolescents with grade 2 scoliosis.

**2.2. Subjects & Methods**

14 female patients aged 10–15 years with grade 2 scoliosis were examined. The examination program included generally recommended diagnostic methods [2, 4, 5, 11, 13]:

- functional examination (determination of the static strength endurance of the muscles of the back, abdomen and oblique muscles of the abdomen in the child);
- clinical and instrumental examination (visual inspection and palpation, measurement of the height and length of the lower extremities, measurement of vertebral torsion, level of the upper arms, shoulders, waist triangles, lumbar lordosis, pelvic level, feet. Vital capacity of the lungs and some cardiovascular system parameters were also assessed.

Several forms of scoliosis were diagnosed in the examined subjects:

- right thoracic – left lumbar scoliosis (n=5),
- right cervical-thoracic – left lumbar scoliosis (n=2),
- right thoracolumbar scoliosis (n=3),
- left-cervical-thoracic – right thoracolumbar scoliosis (n=2),
- left thoracolumbar scoliosis (n=2).

The original physical rehabilitation program was developed based on the forms and methods of kinesiotherapy, focused on both tonic effect and targeted preventive and corrective effects. The following methodological principles were used in the program:

1. The degree and type of disorders in the spatial organization of the child's body, as well as the degree of scoliotic deformity were taken into account.

2. The character of the exercises, dosage of physical activity, sequence of exercises, starting positions, intensity corresponded to the general health, physical development and fitness level of the patient.

3. Each training was based on the principle of comprehensive influence on the body and all muscle groups. Special corrective exercises were alternated with static exercises, self-stretching exercises, exercises with objects and on balancing platforms and balls to improve proprioception.

4. Principles of gradualness and consistency were used both to teach the correct posture (for each type of deformity) as well as correction of the posture disorder and in dosing each exercise and the complex of exercises as a whole.

5. When selecting the exercises, the emphasis was placed to strengthening (training) the weakened, overstretched muscles and relaxation, stretching of the muscles with relatively high tone against a background of uniform training of other muscle groups.

6. Each session necessarily included an exercise to relax tense muscles.

7. Performing respiratory cycles (inhalations and exhalations in the fallen in and convex areas) was necessary to expand the intercostal spaces and reduce them, respectively, on the opposite side.

8. Great attention was paid to maintaining a positive emotional background during the lessons which contributed to the effectiveness of the correct posture skills, correcting scoliotic deformity and decreased the program efficacy.

To compare the effectiveness of the developed rehabilitation program, the examined patients were divided into 2 groups: the main group (MG) (girls aged 11–15 years, n=7) and the control group (CG) (girls aged 10–14 years, n=7).

Physical rehabilitation program for children from the main group included the methods of the original program (namely exercises for 3-plane correction of scoliosis by the method of C.Schroth in combination with massage and brace therapy).

Children from the control group were treated with restorative and preventive measures according to the generally accepted program of scoliotic deformity correction. Duration and intensity of the programs matched to each other. The comparative characteristics of the exercises included in the rehabilitation program of the main and control groups are presented in *table 1*.

The investigation was carried out according to the standard principles of bioethics.

The findings of the study were evaluated by the methods of mathematical statistics. Mathematical processing of numerical data was carried out using the methods of variation statistics. The significance of the difference was assessed using Mann–Whitney test. Differences not exceeding the probability level $p < 0.05$ at a given number of degrees of freedom were considered statistically significant. Statistica 7.0 application program was used for mathematical processing of the numerical data.

***Table 1***

*Comparative characteristics of exercises*

| Main group | Control group |
|---|---|
| Basic | |
| 1. Static exercises in the position of "correction" with correctly selected inhalations and exhalations, performed in different starting positions, w ith objects and without objects | 1. Exercises for formation of skills of correct posture: started from adoption of the correct posture near the wall and with each lesson expanded to perform exercises in different positions with the correct posture |
| 2. Static exercises aimed at strengthening the muscles of the back, abdomen and lateral muscles of the torso. The number of repetitions for each exercise was different and was selected individually depending on the functional capabilities of the body | 2. Symmetrical and asymmetrical adjusted exercises |
| 3. Exercises for relaxation, stretching of spasmodic and tense muscles. Exercises to coordinate and stabilize the spine in the correct position | 3. Exercises to relax the muscles of the back (namely the muscular embankments), the lateral muscles of the torso (concave side), the muscles of the legs and arms |

**Conflict of interests**

The authors of the article declare no conflict of interest.

**3. Results & discussion**

3-plane correction exercises according to the method of C.Schroth improved the body position and evenly distributed the load to al muscles due to adhering to the characteristic individual "posture of correction", increasing strength endurance of the muscles of the back and abdomen, i.e. formation of strong muscular core, which is a guarantee of effective stabilization of the scoliotic process (*fig. 3–5*). This also stopped progression of scoliotic disease.

All the above testifies to the effectiveness of the developed comprehensive program of physical rehabilitation for adolescent girls and allows to recommend it for practical implementation.

The results of re-examination of girls with scoliotic disease demonstrated the effectiveness of the developed rehabilitation program and its advantages over the standard method (*table 2*).

The scheme shows that the developed comprehensive rehabilitation program is more effective in reducing the angle of spine deviation in comparison with the standard method (*fig. 3, 4*).

Functional test findings show that the use of static exercises in a comprehensive rehabilitation program increased strength endurance of the back muscles (from the initial 60 sec. to 150 sec.) and abdominal muscles endurance (from 45 sec. to 120 sec.), i.e. the formation of a strong muscular core, which is necessary for effective stabilization of the scoliotic process (*fig. 5*).

In our study, the results of spinal correction using Schroth's method combined with brace therapy were significantly better than those observed after the standard rehabilitation.

Researchers at Columbia University in New York conducted a study of the effect of one yoga exercise (including respiratory technique) on the patients with idiopathic scoliosis. A few months later, a significant clinical effect was observed, which depended on the nature of the disease and the regularity of exercises. The majority of non-surgical methods of scoliosis treatments are based on changes in the shape of the back and spine as a result of muscle and ligament relaxation. However, these methods have not been sufficiently evaluated in systematic studies. But the authors concluded that asymmetric strengthening of the back muscles on the side of the convex part of the curvature within several months considerably reduces the size of the arch [3]. A common form of rehabilitation for scoliosis is gymnastics according to Lana Paley, which she

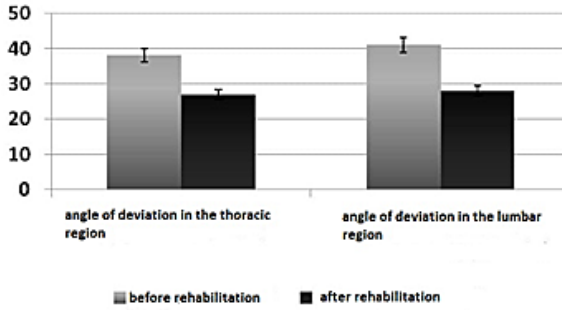



**Fig. 3.** Main group

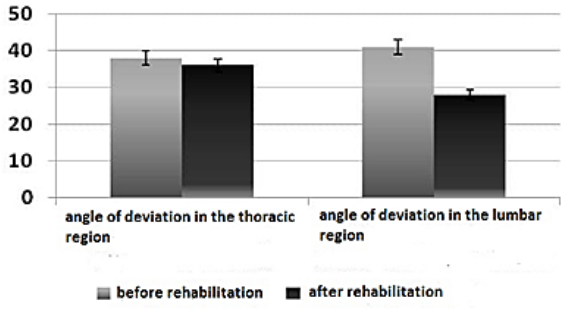


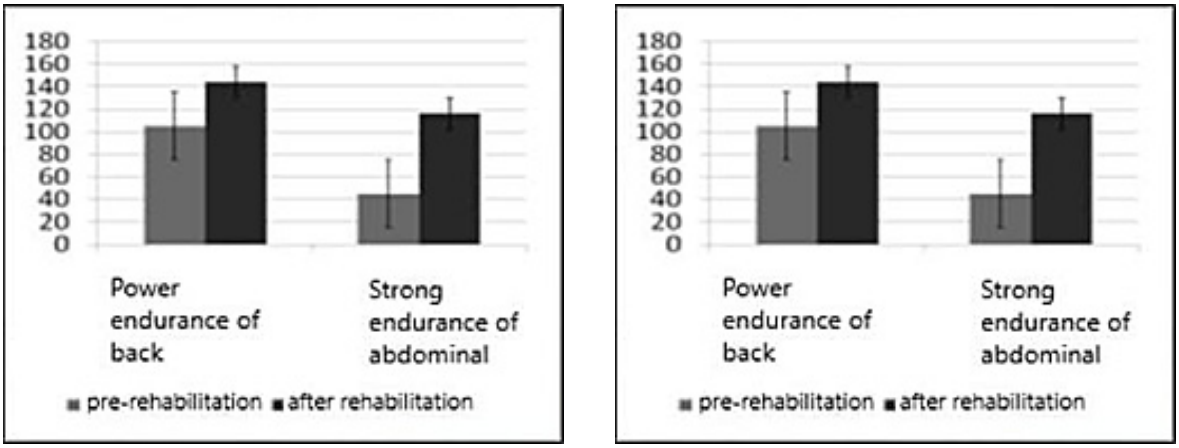

**Fig. 4.** Control group

***Table 2***

*Dynamics of clinical and functional parameters in patients from MG and CG under the influence of rehabilitation*

| Patient | Body length, cm | | Length of the lower extremities **, cm | | Strength endurance of back muscles, s | | Strength endurance of abdominal muscles, s | | Deviation angle *** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | before | after | before | after | before | after | before | after | before | after |
| Main Group | | | | | | | | | | |
| I- M. | 162 | 164 | 79/79 | 80/80 | 150 | 180 | 120 | 150 | 45/0 | 40/0 |
| H-L. | 163.5 | 163.5 | 79/80 | 79/80 | 120 | 150 | 60 | 120 | 20/25 | 17/16 |
| R- T | 160.5 | 161 | 77/78 | 77/78 | 150 | 180 | 120 | 150 | 30/37 | 26/20 |
| R- N. | 165 | 166 | 78/79 | 78/79 | 90 | 150 | 90 | 120 | 50/0 | 46/0 |
| U- D. | 171 | 173 | 85.5/86 | 86.5/87 | 120 | 150 | 120 | 150 | 32/30 | 30/16 |
| T- V. | 163 | 165 | 79/79 | 80/80 | 120 | 180 | 90 | 150 | 30/38 | 28/24 |
| I- A. | 168 | 168 | 82.5/82 | 82.5/82 | 150 | 180 | 90 | 150 | 0/27 | 0/9 |
| mean±mean-square | 164.7±3.6 | 165.8±3.8 | 80.0±3.0/ 80.4 ±2.8 | 80.4±32/ 80.9 ±3.0 | 128.6±22.7 | 167.1±16.0 | 98.6±22.7 | 141.4±14.6 | 29.6±6.5/ 22.4±16.0 | 26.7±15.1/ 12.1±9.4 |
| probability | p <0.05* | | p >0.05* | | p <0.05 | | p <0.05 | | p <0.05* | |
| Control Group | | | | | | | | | | |
| I- A. | 153.7 | 155 | 73.5/73 | 74/73.5 | 150 | 180 | 60 | 120 | 0/22 | 0/9 |
| K-A. | 159.7 | 160 | 62/62.5 | 62/62.5 | 150 | 180 | 60 | 120 | 40/25 | 28/15 |
| Sh. A. | 171 | 173 | 84/83 | 85/84 | 90 | 150 | 40 | 90 | 42/28 | 38/18 |
| U-K. | 176 | 176.5 | 85/86 | 85/86 | 90 | 150 | 60 | 90 | 24/12 | 20/09 |
| K- K. | 155 | 155 | 71/72.5 | 72/73.5 | 90 | 120 | 60 | 90 | 27/30 | 20/09 |
| V- P. | 144.5 | 146.3 | 60/61 | 61/62 | 60 | 90 | 40 | 60 | 50/44 | 50/40 |
| G- D. | 163.4 | 163.6 | 79/80 | 79/80 | 150 | 180 | 120 | 150 | 43/40 | 37/27 |
| mean±mean-square | 160.5±10.7 | 161.3±10.6 | 73.5±9.9/ 74.0 ±9.7 | 74.0±9.9/ 74.5± 9.6 | 111 .4±37.6 | 150.0±34.6 | 62.9±26.9 | 102.9±29.3 | 32.3±16.9/ 29.3± 11.4 | 27.6±16.2/ 18.1±11.7 |
| probability | p <0.05* | | p >0.05* | | p <0.05 | | p <0.05 | | p <0.05* | |

* reliable according to the criteria of Mann-Whitney
** left / right
*** according to Cobb.




*a* *b*

**Fig. 5.** Comparative characteristics: *a* – the main group, *b* – the control group

developed in co-operation with a rheumatologist, P.V. Yevdokimenko. This technique combines strength and stretching exercises, as well as static positions, which are similar to yoga asanas and are performed at a slow pace [10]. Compared to this technique, 3-plane correction exercises seem to be more effective due continuous improvement.

**Conclusion**

Our findings demonstrate that the use of Schroth's technique in a comprehensive physical rehabilitation program helps to reduce the angle of deviation of the spine better than the conventional technique. It also increases strength endurance of the back and abdominal muscles, promotes formation of a strong muscular core, largely eliminates cosmetic defects. Effective stabilization of the scoliotic process after including Schroth's technique to the original correction method allows recommending it for wide a practical implementation.

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# FEATURES OF ENDOMETRIAL RESTRUCTURING IN HIV INFECTION

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**Abstract**

**The purpose** of our study was to evaluate the features of endometrial restructuring when infected with the human immunodeficiency virus. **Materials and methods:** The study involved sectional material taken from 60 women of reproductive age from 20 to 40 years. Group 1 (30 women) consisted of women who were diagnosed with HIV infection. The control group comprised women (30) without concomitant HIV infection. **Results.** An average diameter of the endometrial glands (proliferative type) was 8% smaller in HIV infection than in the comparison group. The minimum diameter of the endometrial glands (proliferative type) decreased by 1.73 %, the maximum was 5.24 % less in the HIV-infected group than in the comparison group. The wall thickness was reduced by 0.5 % in HIV infection. The relative volume of the epithelium decreased by 2.4 % (proliferative type). There were also significant changes in the structure of the glands and endometrium in secretory phase, as in the proliferative type. Thus, the average diameter of the glands decreased by 5%, the minimum volume of the glands by 5.01 %, the maximum by 11.2 %, the wall thickness by 1.5 %, the relative volume of the epithelium by 9.5 %, less in the group HIV-infected than in the comparison group. The thickness of the epithelium increased by 4.5 % in the HIV-infected group compared with the comparison group. **Conclusion.** The study evaluated features of endometrial restructuring in the presence of concomitant HIV infection in women.

***Keywords:*** *uterus, endometrium, HIV, glands.*

## Introduction

Many different studies have investigated the immunological and hormonal aspects of hyperplastic diseases of the uterus (HDU) [1–3]. Many authors have shown a violation of the supervisory functions of the immune system, which regulate the processes of cell proliferation [4–7]. These changes can be both hereditary and acquired during the expression or mutations of the corresponding genes during life [8]. The results of other studies have suggested that there is a genetic predisposition to the development of HDU, and genetic determinants are the main risk factors triggering pathogenic mechanisms of proliferative processes in the uterus [9, 10].

HIV (AIDS) today occupies a leading position among the causes of death of women of reproductive age all over the world. The disproportionate impact of HIV on young women may be due not only to social inequality, but also to biological patterns of heterosexual transmission of the virus [11–13]. HIV infection is a disease that affects all organs and systems of a patient. Approximately 60–90 % of HIV transmission occurs through sexual contact.

Globally, women make up more than half of the population living with HIV. The majority of women become infected during sexual intercourse, when the mucous membrane is most vulnerable to HIV infection [14, 15]. It has a special effect on the human reproductive system. Being an entrance gate, this pathological condition starts a cascade of pathological reactions, causing various changes in all organs of the reproductive system.

The first line of defense against HIV infection in the female genital tract is the mucous membrane of the epithelial barrier [14]. Consequently, the expected maximum pronounced changes can occur precisely in the endometrium.

**2. Purpose, subjects and methods:**

**2.1. The purpose** of our study was to evaluate the features of endometrial restructuring when infected with the human immunodeficiency virus.

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**2.2. Subjects & Methods**

The study involved the sectional material taken from 60 women of reproductive age from 20 to 40 years. All the subjects were divided into two groups. Group 1 (30 women) consisted of women who were diagnosed with HIV infection.

The control group comprised women (30) who died from diseases not associated with reproductive disorders without concomitant HIV infection (deaths as a result of traffic and other accidents).

The material was fixed in 10 % neutral buffered formalin, after which the selected samples were embedded in paraffin. At the next stage, sections with a thickness of $5r10^{-6}$ m were made from the prepared paraffin blocks. Subsequently, staining with hematoxylin and eosin was performed. Microscopic examination was carried out on an Olympus BX41 microscope, followed by morphometric examination using the Olympus DP-soft 3.12 software.

The following indicators were determined: average diameter of the endometrial glands (proliferative type), minimum diameter of the endometrial glands (proliferative type), maximum diameter of the endometrial glands (proliferative type), wall thickness (proliferative type), relative volume of the epithelium (proliferative type), average diameter of the glands (secretory type), minimum diameter of the glands (secretory type), maximum diameter of the glands (secretory type), relative volume of the epithelium (secretory type), thickness of the epithelium.

Statistical processing was performed using the methods of variation statistics. Correspondence of the distribution to normal was determined by Shapiro-Wilk's test, which showed that the samples were close to the normal distribution. Statistical indicators are presented in the format $M\pm\sigma$, where M is the arithmetic mean, $\sigma$ is the standard deviation. Student's t-test was used. Correlation analysis was carried out using Spearman's rank correlation coefficient. The statistical difference between the studied parameters was considered significant at $p$ less than 0.05.

The procedure was done strictly in compliance with the Helsinki Declaration after approval from the Regional Ethical Review Board at Odessa National Medical University, protocol No. 3 dated 17th October 2011.

**Conflict of interests**

The authors of the article declare no conflict of interest.

**3. Results & discussion**

Results of performed morphometric study are shown in the *table*.

Thus, the study showed that the average diameter of the endometrial glands (proliferative type) was 8 % smaller in HIV infection than in the comparison group. The minimum diameter of the endometrial glands (proliferative type) decreased by 1.73 %, the maximum was 5.24 % less in the HIV-infected group than in the comparison group. The wall thickness was reduced by only 0.5 % in HIV infection.

The relative volume of the epithelium decreased by 2.4 % (proliferative type) in the HIV-infected group compared with the comparison group.

*Indicators of the structure of endometrium in HIV infection and in the comparison group*

| Parameter under study | Comparison group | HIV-infected women |
|---|---|---|
| The average diameter of the endometrial glands (proliferative type), $\times10^{-6}$ m | 51.71±2.90 | 47.62±2.29 |
| The minimum diameter of the endometrial glands (proliferative type), $\times10^{-6}$ m | 32.47±1.83 | 31.88±1.92 |
| The maximum diameter of the endometrial glands (proliferative type), $\times10^{-6}$ m | 72.14±2.21 | 68.36±3.15 |
| Wall thickness (proliferative type), $\times10^{-6}$ m | 15.18±1.60 | 15.10±1.04 |
| The relative volume of the epithelium (proliferative type), % | 54.43±1.79 | 53.12±2.41 |
| The average diameter of the glands (secretory type), $\times10^{-6}$ m | 101.55±3.12 | 96.34±4.26 |
| Minimum diameter of glands (secretory type), $\times10^{-6}$ m | 33.86±1.17 | 32.14±1.67 |
| Maximum diameter of glands (secretory type), $\times10^{-6}$ m | 127.98±2.10 | 113.64±3.51 |
| Wall thickness (secretory type), $\times10^{-6}$ m | 13.02±1.36 | 12.82±1.26 |
| The relative volume of the epithelium (secretory type),% | 61.24±1.11 | 55.43±1.70 |
| Epithelial thickness, $\times10^{-6}$ m | 49.14±1.44 | 51.33±1.23 |

At the next stage the indicated indicators (secretory type) were investigated.

There were also significant changes in the structure of the glands and endometrium, as in the proliferative type. Thus, the average diameter of the glands decreased by 5 %, the minimum volume of the glands by 5.01 %, the maximum by 11.2 %, the wall thickness by 1.5 %, the relative volume of the epithelium by 9.5 %, less in the group HIV-infected than in the comparison group.

The thickness of the epithelium increased by 4.5 % in the HIV-infected group compared with the comparison group. Our study identified the changes in the endometrium due to the presence of concomitant HIV infection in women. Based on the data obtained, it can be assumed that concomitant HIV infection stimulates the development of hyperplastic changes in the endometrium.

There are reports in the literature on the "inflammatory" origin of HDU [16–18]. It is known that in the presence of long-term [19, 20], often exacerbated inflammatory processes of the genital organs, the risk of endometrial cancer increases 20 times, and against a background of HDU – 15 times [21–22]. Long-term persistent infection of the genital organs leads to a change in the receptors of estradiol and progesterone in the tissue of the endo- and myometrium.

Nevertheless, it is probably fair to consider the fact that in the development of hyperplastic processes, the main role is traditionally assigned to an increase in the concentration of estrogens [23].

Changes of the HER (human epidermal growth factor receptor) expression should be considered the most frequent problem of the state of the endometrium and as a consequence of the actual problem in the female population and oncological alertness due to its high prevalence [24, 25]. Today HDU is officially recognized to be one of the most important and potentially health-damaging medical problems that challenge doctors around the world. The steady increase in the number of patients with HDU, unclear etiology, variable clinical manifestations and a high relapse rate and risk of malignancy, as well as low treatment efficacy have led to a significant increase in scientific interest in this problem in recent years [26].

In Ukraine, the HIV-infected population is growing every year with the overwhelming majority (77.6% of people of young, reproductive and working age, i.e.15–49 years), the number of HIV-infected pregnant women is increasing [27], which is explained by the high proportion of women of reproductive age among the patients with HIV infection.

Currently, HDU is defined as a pathological process affecting the epithelial and stromal components of the endometrium and manifested by an increase in the total number of glands, as well as various changes in the phenotypic characteristics of cells [28]. Endometrioid, intraepithelial neoplasia is currently considered as a variant of atypical hyperplasia, a feature of which is the formation of foci more than 2 mm in diameter with a predominance of the parenchyma over the stroma, with pronounced atypia of the crowded gland cells and with loss of PTEN (phosphatase and tensin homolog) expression [29].

Currently, interesting and at the same time contradictory statistical data are given in relation to the combined pathological processes of the endo- and myometrium, which, to some extent, can be explained by a fairly frequent asymptomatic course [30]. HDU occupies 15–40 % in the structure of all gynecological diseases, and up to 80 %, when combined with adenomyosis. Contradictory data in the literature are also given in relation to the combination of HDU and uterine leiomyoma, the frequency of which ranges from 13 to 80 %. In the asymptomatic course of uterine leiomyoma in postmenopausal women, every sixth patient has HDU, at the same time, when uterine bleeding appears, concomitant development of HDU is determined in every second patient [30].

It should be noted that the least reliably ($p < 0.05$) variable indicator is the thickness of the endometrial wall (proliferative type), which significantly is decreased by only 8 mm on average in the presence of HIV infection.

The most pronounced significant changes affected the glands, especially the secretory type. Thus, at the same time the maximum volume of the glands changed at 14x106m. Subsequently, these findings can be confirmed by other additional studies.

Consequently, our study gives grounds to assume the possible development of hyperplastic processes in the endometrium in HIV-infected patients, which cannot but affect the peculiarities of the presentation, diagnosis and treatment of inflammatory and non-inflammatory processes of the reproductive system.

**Conclusions**

The study evaluated the features of endometrial restructuring in the presence of concomitant HIV infection in women. These changes are manifested by hyperplastic changes in the mucous membrane. The most pronounced changes were revealed in the endometrial glands (secretory type).

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