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## DYSLIPIDEMIA IN PATIENTS WITH RHEUMATOID ARTHRITIS DEPENDS ON COMORBID PATHOLOGY AND GENETIC PREDICTORS

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The purpose of the study was to investigate the dynamics of the blood lipid spectrum under the influence of treatment depending on comorbid pathology and polymorphism of the gene T-786C endothelial nitric oxide synthase in patients with rheumatoid arthritis. 110 patients with rheumatoid arthritis and 20 practically healthy people were examined and treated. In the study, the concentration of high-density lipoprotein cholesterol decreased in patients with rheumatoid arthritis – by 22.3 %, rheumatoid arthritis, arterial hypertension – by 29.27 %, rheumatoid arthritis, arterial hypertension, abdominal obesity – by 33.61 %, rheumatoid arthritis, arterial hypertension, abdominal obesity, type 2 diabetes mellitus – by 44.55 %. The increase in total cholesterol, low-density lipoprotein cholesterol and triglycerides depending on the gene polymorphism is found in 87.5 %, 62.5 %, 100 % of patients with *CC* genotype, in 56.52 %, 47.83 %, 78.26 % of patients with *TC* genotype, 56.52 %, 37.93 % and in 75.86 % of patients with TT genotype. A comprehensive treatment of rheumatoid arthritis with comorbid pathology was proposed by adding telmisartan, rosuvastatin and L-arginine to the basic therapy.

**Key words:** rheumatoid arthritis, comorbid pathology, dyslipidemia, polymorphism of the T-786C gene of endothelial nitric oxide synthase, rosuvastatin, telmisartan, L-arginine

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## ДИСЛІПІДЕМІЯ У ХВОРИХ НА РЕВМАТОЇДНИЙ АРТРИТ ЗАЛЕЖНО ВІД КОМОРБІДНОЇ ПАТОЛОГІЇ ТА ГЕНЕТИЧНИХ ПРЕДИКТОРІВ

Метою роботи було вивчити динаміку ліпідного спектру крові під впливом лікування залежно від коморбідної патології та поліморфізму гена Т-786С ендотеліальної оксиду азоту синтази у хворих на ревматоїдний артрит.У роботі обстежено та проліковано 110 хворих на ревматоїдний артрит та 20 практично здорових осіб. При дослідженні концентрація холестерол ліпопротеїдів високої щільності знижувалась у пацієнтів із ревматоїдним артритом – на 22,3 %, ревматоїдним артритом, артеріальною гіпертензією – на 29,27 %, ревматоїдним артритом, артеріальною гіпертензією, абдомінальним ожирінням – на 33,61 %, ревматоїдним артритом, артеріальною гіпертензією, абдомінальним ожирінням, цукровим діабетом типу 2 – на 44,55 %. Підвищення вмісту загального холестеролу, холестерол ліпопротеїдів низької щільності та тригліцеролів залежно від поліморфізму гена виявляється відповідно у 87,5 %, 62,5 %, 100 % хворих *CC*-генотипом, у 56,52 %, 47,83 %, 78,26 % хворих *TC*-генотипом, у 56,52 %, 37,93 % та 75,86 % хворих ТТ-генотипом. Запропоновано комплексне лікування ревматоїдного артриту з коморбідною патологією шляхом додаванням до базисної терапії телмісартану, розувастатину і L-аргініну.

**Ключові слова:** ревматоїдний артрит, коморбідна патології, дисліпідемія, поліморфізм гена Т-786С ендотеліальної оксиду азоту синтази, розувастатин, телмісартан, L-аргінін.

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A timely diagnosis of rheumatoid arthritis (RA) and the earliest possible appointment for adequate therapy significantly improves the course of the disease. It contributes to the achievement of long-term clinical remission [13].

The interaction of genetic and environmental factors leads to a cascade of immune responses, which ultimately lead to the development of synovitis, joint destruction and structural bone damage. This, in turn, leads to pain, disability, and emotional, social, and economic problems [9].

The European Alliance of Associations for Rheumatology (EULAR) has identified 6 phases for risk factors for RA: Phase a – genetic risk factors for RA; Phase B – Environmental Risk Factors; Phase C – systemic autoimmune factors associated with RA; phase D – symptoms without clinical arthritis; Phase E – undifferentiated arthritis; Phase F – RA [2].

The presence of arterial hypertension (AH), abdominal obesity (AO), and type 2 diabetes mellitus (DM2) in RA patients double the risk of fatal and non-fatal cardiovascular complications and events regardless of age and sex. It worsens the functional status of the patient [7]. This is associated with accelerated atherogenesis and coronary heart disease (CHD) development. Therefore, RA is considered a predictor of coronary heart disease. In addition to these pathological factors, dyslipidemia also affects the development of cardiovascular events in RA patients [3]. According to studies, the development of obesity, hypertension and impaired glucose and lipid metabolism occurred in 15–45 % of cases [12].

According to modern ideas, the increase in the incidence of cardiovascular pathology among patients with RA is associated with accelerated atherogenesis. It is based on disorders of lipid metabolism and transport [14] and local inflammation of the vascular wall [10] against the background of the ongoing autoimmune inflammatory process [15].

**The purpose** of the study was to access the dynamics of the blood lipid spectrum under the influence of treatment depending on comorbid pathology and polymorphism of the gene *T-786C* endothelial nitric oxide synthase in patients with rheumatoid arthritis.

**Material and methods.** The study presents the results of the examination and treatment of 110 patients with RA. 40 patients had RA without comorbid pathology, 30 had RA with AH, 20 had RA in combination with AH and AO, and 20 had RA in combination with AH, AO and DM 2. The inpatient treatment was provided in the Rheumatology Department of the "Chernivtsi Regional Clinical Hospital", Chernivtsi "City Clinical Hospital No. 3" and "Chernivtsi Regional Endocrinology Center". The control group consisted of 20 healthy individuals.

Anthropometric surveys were performed: height (m), body weight (kg), BMI (kg/m$^{2)}$ and the degree of obesity were determined according to the WHO classification (1997). The waist-to-hip ratio determined the type of obesity.

Determination of the blood lipid spectrum by the content of total cholesterol (TH), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol was performed using diagnostic standard kits (PZ Cormay S.A., Poland) on the ACCENT 200 spectrophotometer. The atherogenicity index (AI) was determined.

Molecular genetic testing was performed by isolating a genomic section of DNA from peripheral blood using the commercial innuPREPBlood DNA MiniKit test system (AnalytikJena, Germany) by centrifuge filters by polymerase chain reaction (PCR).

All patients with RA received essential therapy: methotrexate (MT) – 10 mg per week, folic acid – 5 mg not earlier than a day and not later than a day before taking MT; methylprednisolone – 20 mg per day with a gradual dose reduction lasting up to 1 month. If necessary, meloxicam 15 mg was used IV.

Given the presence of concomitant pathology (AH, AO and DM-2), telmisartan – 80 mg per day, rosuvastatin – 10 mg per day and L-arginine aspartate – 5 ml were added to essential therapy of patients with RA 3 times a day for one month.

Statistical processing was performed using Microsoft Office Excel applications® 2007™, IBM SPSS Statistics® 23.0. During statistical analysis of the quantitative results of the study, the arithmetic mean values (M) and standard error (m) were calculated. The data are given as M±m. The probability of data for independent samples was calculated using Student's parametric T-test or non-parametric Mann-Whitney U-test.

**Results of the study and their discussion.** To determine changes in the lipid spectrum of blood in patients with RA depending on the concomitant pathology and polymorphism of the *eNOS* gene (rs 2070744), we analysed the content of TH, HDL cholesterol, LDL cholesterol and TG in the blood, followed by AI calculation.

Changes in the blood lipid spectrum in patients with RA depending on comorbid pathology are shown in Table 1.

We observed a higher content of TH, TG and AI in all studied groups of patients with RA than in the control group by 1.17–2.39 times ($p \leq 0.04–0.001$), at a lower concentration of HDL cholesterol – by 20.75–30.19 % ($p \leq 0.026–0.001$). The level of TH was significantly higher in the group of patients with RA in combination with AH, AO and DM-2 than in the control group – by 48.37 % ($p<0.05$), with isolated RA – by 31.47 % ($p<0.05$), with RA with AH – by 30.71 % ($p<0.05$) and RA with AH and AO – by 28.25 % ($p<0.05$). An increase in the TH content was found in all study groups: in patients with RA by 1.7 times ($p<0.05$), RA with AH – by 1.8 times ($p<0.05$), in RA with AH and AO – by 1.89 times ($p<0.05$), and in patients with RA

with AH, AO and DM-2 – by 2.27 times (p<0.05). At the same time, in RA, in combination with AH, AO and DM-2, its level exceeded that in RA without comorbid pathology by 33.81 % (p<0.05). HDL cholesterol concentrations decreased in patients with RA – by 22.3 % (p<0.05), with RA and AH – by 29.27 % (p<0.05), with RA, AH and AO – by 33.61 % (p<0.05) and in patients with RA, AH, AO and DM-2 – by 44.55 % (p<0.05). However, in patients with RA with AH, AO and DM-2, this index was lower by 18.18 % (p<0.05) than in patients with isolated RA. The LDL cholesterol level in all study groups exceeded the control, but in AH, AO and DM-2, it was higher – by 16.94 % (p<0.05) than in RA without concomitant pathology. In patients with RA associated with AH, AO, and DM-2, AI was 46.61 % (p<0.05) higher than that of isolated RA.

Table 1

**Blood lipid spectrum before and after treatment in patients with rheumatoid arthritis depending on comorbid pathology**

| Disease | | TH, mmol/L | LDL cholesterol, mmol/L | HDL HS, mmol/L | TG, mmol/L | AI, c.u. |
|---|---|---|---|---|---|---|
| Control | | 4.59±0.35 | 2.94±0.26 | 1.59±0.12 | 0.82±0.13 | 2.27±0.56 |
| RA with AH, n=30 | before treatment | 5.21±0.24 p=0.055 | 3.32±0.18 | 1.23±0.09 p=0.01 | 1.48±0.12 p<0.001 | 4.10±0.5 p=0.01 |
| | after treatment | 4.62±0.21 | 3.08±0.18 | 1.37±0.09 $p_1$<0.05 | 1.27±0.11 $p_1$<0.05 | 3.02±0.32 $p_1$<0.05 |
| RA with AH and AO, n=20 | before treatment | 5.31±0.28 p<0.05 | 3.24±0.29 | 1.19±0.11 p=0.01 | 1.55±0.16 p<0.001 | 3.97±0.37 p=0.003 |
| | after treatment | 4.66±0.25 | 2.91±0.28 $p_1$<0.05 | 1.33±0.11 $p_1$<0.05 | 1.33±0.15 $p_1$<0.05 | 3.13±0.33 $p_1$<0.001 |
| RA with AH, AO and DM-2, n=20 | before treatment | 5.81±0.18 p<0.001 | 3.59±0.29 | 1.10±0.09 p<0.001 | 1.86±0.23 p<0.001 | 5.01±0.56 p<0.001 |
| | after treatment | 4.93±0.19 $p_1$<0.05 | 3.14±0.28 $p_1$<0.05 | 1.28±0.09 $p_1$<0.05 | 1.47±0.23 $p_1$<0.05 | 3.95±0.40 $p_1$ $p_2$<0.05 |

Note. p – the probability of differences compared to the control group; $p_1$ – the probability of differences between indicators before and after treatment; $p_2$ – the probability of differences between the indices with the 1st group.

The dynamics of the blood lipid spectrum after treatment are characterized by a decrease in the level of TH and TG: in patients with RA with AH – by 12.77 % and 16.54 % (p<0.05); RA with AH and AO – by 13.95 % and 16.54 % (p<0.05) and in patients with RA with AH, AO and DM-2 – by 17.85 % (p<0.05) and 26.53 % (p<0.05), respectively. HDL levels increased by 11.38 %, 11.76 %, and 16.36 % (p<0.05), respectively.

After treatment, AI decreased in patients with RA with AH by 1.36 times (p<0.05), RA with AH and AO, and in patients with RA with AH, AO and DM-2 by 1.27 times (p<0.05). On the other hand, in patients with RA, associated with AH, AO, and DM-2, AI remains 30.79 % (p<0.05) and 26.2 % (p<0.05) higher than in patients with RA with AH and patients with RA with AH and AO.

The distribution of RA patients depending on the polymorphic variants of the eNOS gene (rs 2070744) is shown in table 2.

Table 2

**Blood lipid spectrum in patients with rheumatoid arthritis before and after the treatment depends on polymorphic variants of the eNOS gene (rs2070744)**

| Genotypes of the eNOS gene | | TH, mmol/L | LDL cholesterol, mmol/L | HDL HS, mmol/L | TG, mmol/L | AI, c.u. |
|---|---|---|---|---|---|---|
| Control | | 4.59±0.35 | 2.94±0.26 | 1.59±0.12 | 0.82±0.13 | 2.27±0.56 |
| TT, n=21 | before treatment | 5.53±0.42 p=0.01 | 3.38±0.30 | 1.21±0.14 p=0.006 | 1.25±0.09 p<0.001 | 4.13±0.76 p=0.002 |
| | after treatment | 4.72±0.23 $p_1$<0.05 | 3.16±0.20 $p_1$<0.05 | 1.38±0.09 p<0.05 | 1.06±0.18 p<0.001 | 3.35±0.34 $p_1$<0.05 |
| TC, n=15 | before treatment | 5.31±0.48 p=0.025 | 3.49±0.33 | 1.14±0.13 p<0.001 | 1.53±0.16 p=0.001 | 5.01±0.85 p=0.003 |
| | after treatment | 4.45±0.16 $p_1$<0.05 | 3.25±0.20 $p_1$<0.05 | 1.20±0.91 p=0.004 | 1.30±0.17 p. $p_1$<0.001 | 3.92±0.36 $p_1$<0.05 |
| CC, n=6 | before treatment | 5.97±0.26 p<0.001 | 3.76±0.28 p=0.022 | 1.26±0.11 p=0.026 | 2.01±0.30 p=0.049 | 4.11±0.52 p=0.009 |
| | after treatment | 5.11±0.30 $p_1$<0.05 | 3.64±0.36 $p_1$<0.05 | 1.35±0.13 $p_1$<0.05 | 1.76±0.09 $p_{TT}$<0.001 | 3.45±0.43 $p_1$<0.05 |

Notes: p – the probability of differences in indices with the control group; $p_1$ – the probability of differences between indices before and after treatment; $p_{TT}$ – the probability of differences after treatment with carriers of the *TT* genotype.

Changes in the blood lipid spectrum depending on variants of the eNOS gene (rs 2070744) showed an increase in the content of TH, LDL cholesterol and TG in blood serum in 87.5 %, 62.5 %, 100 % of patients with CC genotype, in 56.52 %, 47.83 %, 78.26 % of patients with TC genotype, and in 56.52 %,

37.93 % and 75.86 % of patients with TT genotype. In contrast, among TT genotype carriers, individuals with a lower content of antiatherogenic HDL cholesterol were found more often – by 31.04 % (p=0.018) and in TC genotype carriers – by 30.44 % (p=0.039) than among CC genotype carriers. TH and TG levels in carriers of the CC genotype exceeded this figure in carriers of the TT genotype by 28.36 % and 75 %, and in carriers of the TC genotype – by 30.04 % and 31.54 % (p<0.05), respectively.

Lipid metabolism disorders are associated with higher levels of TG and TH in carriers of the mutant C-allele. At the same time, wild-type T-allele carriers are more likely to have lower levels of anti-atherogenic HDL.

The content of TH after the proposed therapy decreased in carriers of the TT genotype – by 17.16 % (p<0.05), in carriers of the TC genotype – by 19.33 % (p<0.05) and in carriers of the CC genotype – by 16.83 % (p<0.05). It was found that the content of TG among carriers of the TT genotype after treatment was the lowest in comparison with carriers of the TC genotype – by 22.64 % (p<0.05) and carriers of the CC genotype – by 66.04 % (p<0.05). In contrast, the concentration of HDL cholesterol increased in TT genotype carriers by 14.05 % (p>0.05) without a significant difference among C-allele carriers.

After the essential therapy with telmisartan, rosuvastatin and L-arginine, there was a decrease in AI by 23.28 % in carriers of the TT genotype, by 27.81 % – in carriers of the TC genotype and by 19.13 % – in carriers of CC genotype.

Based on modern aspects of the pathogenesis of RA development in combination with AH, AO and DM-2, a significant role belongs to pro-inflammatory cytokines that directly affect the blood lipid spectrum. Increased TH, LDL cholesterol, TG levels, and decreased HDL levels in RA patients correlated with systemic inflammation [8]. Many studies have shown a higher level of dyslipidemia in patients with RA with increased inflammatory activity and DAS28 index [6].

In recent years, the anti-inflammatory effect of statins and their efficacy in the treatment of RA have been proven [4]. The ANDROMEDA study compared the efficacy and safety of atorvastatin 10–20 mg to rosuvastatin 10–20 mg in patients with diabetes mellitus 2. As a result, the TH and LDL cholesterol levels were lower with rosuvastatin compared to atorvastatin in equivalent doses [1].

A 6-week open-label randomized STELLAR study found that low-dose rosuvastatin (10–40 mg) reduced LDL cholesterol levels by 52–63 %, TG levels by 34 %, and HDL cholesterol levels by 10 %. It surpassed all other statins in high doses. [11].

Thus, numerous studies (STELLAR, MERCURY I, SOLAR) have shown that rosuvastatin is the most effective statin. It blocks the activity of the critical enzyme of biosynthesis of cholesterol 3-hydroxy-3-methylglutaryl-coenzyme A-reductase (HMG-CoA). It activates synthesising the main HDL protein – apolipoprotein A-I (apo A-I). It increases from 5 % to 15 % at low and medium doses of 10–20 mg, reaching the target levels of LDL cholesterol at an earlier date. And the tolerability and safety of rosuvastatin are comparable to other statins [5]. Therefore, we used rosuvastatin in our study.

These data correspond to the studies on the occurrence of dyslipidemia in RA, which is one of the main factors in the development of CVD and exacerbates systemic inflammation in patients with RA.

## Conclusions

1. The course of rheumatoid arthritis is accompanied by dyslipidemia, which is aggravated by its combination with arterial hypertension, abdominal obesity and type 2 diabetes mellitus.

2. The expediency of including Telmisartan, rosuvastatin and L-arginine in the basic therapy (with dose adjustment, rosuvastatin 20 mg per day, L-arginine 30 ml per day in carriers of CC genotype) was justified. This permitted to avoid the progression of the disease, reduce the lipid profile, increase the duration of clinical remission and improve the patient's quality of life.

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## SEVERITY OF ADENTIA AS A RISK FACTOR OF REPEATED DENTAL IMPLANT OPERATIONS

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Risk factors for dental implantation can be divided into general and local, early and late. Our experience shows that the length of the edentulous jaw affects the quality and predictability of the first stage of dental implantation. Conducted a retrospective analysis of data from clinical journals of dentistry. To facilitate the data accounting process, we have introduced conditional definitions of dentition defects by their length: mild, moderate and severe defects of the dentition, complete adentia. Found that the value of the relative risk of re-dental implantation in the group of dentitions with severe defects and with complete adentia (OR=0.36) is approximately 4.2 times less than in the group with mild defects (OR=1.5), p<0.05. Total 157 (17.1 %) edentulous areas out of 917.

**Key words:** dental implants, risk factor, osseointegration, dental implantation.

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## ПРОТЯЖЕНІСТЬ ДЕФЕКТУ ЗУБНОГО РЯДУ КАК ФАКТОРИ РИЗИКУ ПОВТОРНОЇ ОПЕРАЦІЇ З ДЕНТАЛЬНОЇ ІМПЛАНТАЦІЇ

Фактори ризику імплантації зубів можна розділити на загальні та місцеві, ранні та пізні. Наш досвід вказує, на наявність впливу довжини беззубої щелепи на якість і передбачуваність першого етапу дентальної імплантації. Проведений ретроспективний аналіз даних клінічних журналів стоматології. Для полегшення процесу обліку даних ми ввели умовні визначення дефектів зубних рядів за їх довжиною: «дрібні», «середні», «значні» дефекти зубних рядів, повна адентія. Встановлено, що значення відносного ризику повторної імплантації зубів у групі зубних рядів з «великими» дефектами та з повною адентією (OR=0,36) приблизно в 4,2 рази менше, ніж у групі з «дрібними» дефектами (OR=1,5). ), p<0,05. Всього 157 (17,1 %) беззубих ділянок із 917.

**Ключові слова:** зубні імпланти, фактор ризику, остеоінтеграція, імплантація зубів

*The study is a part of the research project: "Dynamic changes in morphological and biomechanical properties of maxillofacial tissues in the rehabilitation of patients with adentia", state registration No. 0118U007136.*

Dental implants have become a common choice among treatment options in the rehabilitation of secondary adentia. Cases of failed implantation according to various data range from 1 % to 19 % [2, 3]. To date, peri-implantitis is the leading cause of implant loss (81.9 %). Implantation in previously failed sites, regardless of early or late failure, results in survival of 71 % to 100 % for 5 years [13].