Monthly Reviewed International Journal

№3 March 2011

ISSN 1925-2188

# Innovative Medicine and Biology

**SECTORS:**
-Medicine
-Biology
-Zoology
-Veterinary
-Medical and Bio Technology

2011 - Canada

# INNOVATIVE MEDICINE AND BIOLOGY

Monthly reviewed, multi discipline international journal designed for the scientists of difference fields: Medicine, Morphology, Microbiology, Immunology, Physiology, Biochemistry, Pharmacy, Bio-Medical Physics, Genetic, Biology, Nano-medicine, Nano-Biology, Veterinary, Zoology, Plant Pathology etc.;

Innovative Medicine and Biology is the official journal of Innovative Bio Medical Technologies Ltd (*Canada, Toronto*), David Aghmashenebeli University of Georgia (*Georgia, Tbilisi*) and Health Sciences Faculty of Klaipeda University *(Lithuania, Klaipeda).* Journal publishes official papers of these institutions as well as independently submitted articles.

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# THE INFLUENCE OF ACTIVITY OF SYSTEMIC INFLAMMATORY PROCESS, LEPTIN AND ADIPONECTIN LEVELS ON INSULIN RESISTANCE DEVELOPMENT AND ATHEROSCLEROTIC AFFECTIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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**Abstract:**

The obtained data testify patients with rheumatoid arthritis (RA) without metabolic syndrome (MS) have higher level of adipokins compared with the patients of control group. There is statisticaly reliable correlation between the level of systemic inflammation and insulin resistance in patients with rheumatoid arthritis. This fact has proved the presence of systemic inflammation influence on the development of insulin resistance in patients with rheumatoid arthritis. There are correlations between the insulin resistance level and lipid metabolic disorders, the thickness of carotid intima-media (IM) complex, and the level of endothelium-dependent (EDVD) and non-endothelium-dependent vasodilatation (NEDVD). These above mentioned correlations prave the prevailing influence of insulin resistance on the development of atherosclerotic vascular affections in patients with rheumatoid arthritis.

**Key words:** rheumatoid arthritis, leptin, adiponectin, inflammation, insulin resistance, pioglitason, atorvastatin, intima-media.

## Introduction:

Leptin and adiponectin are signal hormones, which are synthesized by mature adipocytes and are of great importance in the regulation of energy balance of the human body [14]. Biological effects of leptin are realized in the central nervous system, where it activates the mechanisms blocking needs in food and participates in regulation of

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adenohypophysial hormone secretion. At the periphery leptin stimulates the fatty acid oxidation and glucose uptake by tissues [26].

The adiponectin content in blood plasma correlates negatively with obesity degree, severity of diabetic dyslipidemia, cardio-vascular pathology, and insulin resistance degree. It has been determined that low level of adiponectin in peripheral blood can be the independent risk factor for type II diabetes mellitus development [24]. Adiponectin reveals the definite anti-inflammatory action in addition to the energy metabolism regulation. It depresses macrophage and myelomonocyte activity, inhibits the synthesis of anti-inflammatory cytokine of TNF-α with macrophages. It is possible to assume the cytokine participates in the organism protection against atherosclerosis development due to its anti-inflammatory action and its action as insulin sensitizator [30]. The investigations on humans and animals have demonstrated that some cytokines (e.g. TNF-α, IL-1, IL-6) increase an expression of ribonucleic acid (RNA) and the level of leptin circulated in the blood. Furthermore, it is known that leptin modifies T-cell balance, induces T-cell activation, changes production of cytokines for differentiation of I type helpers [23]. The same changes in immune system are typical for patients with rheumatoid arthritis [6]. On the other hand a dyslipoproteinemia, complex of carotid intima-media thickness (cIMT), endothelial dysfunction, rapid progression of atherosclerotic vascular affections [12], and susceptibility to metabolic syndrome development [15] are marked in patients with rheumatoid arthritis against a background of systemic inflammation. It is well known that systemic inflammation causes insulin resistance development.

The mechanism of its onset is caused by blocking of subsequent signal transmission from insulin receptor due to direct influence of TNF-α, IL-6, free adipose acids and glucose, activation of serine/threonine kinases, to kinase of NF-kB inhibitor especially, which leads to insulin resistance development and NF-kB activation. This

nuclear factor of transcription stimulates the formation of many pro-inflammatory substances including TNF-α and IL-6. Furthermore, the influence of these cytokines causes disbalance in adipocytokines secretion increasing leptin synthesis, one of the effects of which is a synthesis of TNF-α and IL-6 in adipose tissue. The increasing of TNF-α and IL-6 levels leads to inhibition of adiponectin synthesis, which decreases pro-inflammatory cytokines formation and insulin resistance. There are data, which need the standardization concerning the pathogenetic value of systemic inflammatory activity influence, levels of leptin and adiponectin for insulin resistance development in patients with rheumatoid arthritis, their influence on development of atherosclerosis and metabolic syndrome in these patients, and possible ways for correction for revealed changes.

**Material and Methods:**

The first stage of our research is the study of basic rheumatoid arthritis therapy influencing on the development and progressing of atherosclerosis and insulin resistance. For this purpose we have checked 64 patients with RA (54 women and 10 men) who had not been treated with the basic rheumatoid arthritis therapy before our research (mean age 48.5±2.7 years old). These patients have been included into research during the first year of their disease. The activity of RA before investigation in 25% (16 patients) has corresponded to the 1$^{st}$ degree; in 56.2% (36 patients) it has corresponded to the 2$^{nd}$ degree; and in 8.8% (12 patients) the activity has corresponded to the 3$^{rd}$ degree. Seropositive patients according to the rheumatoid factor constituted 65.5% of patients. The patients with severe accompanied pathology and acute or aggravated chronic diseases were the candidates for our research. According to administered basic treatment we have formed the following groups: patients with RA who received methotrexate in a dose of 7.5 to 15 mg/week (32patients); patients who received leflunomide in a dose of 20 mg/week (24

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patients); and 10 patients who had not been treated with basic therapy as a result of various reasons (intolerance to basic treatment, absence of compliance).

The researches for this group were carried out before the basic therapy and 6 months later after the treatment.

To determine the ways for correction of IA and atherosclerosis in patients with rheumatoid arthritis we formed the following groups of the patients:

I – control group – comprises 27 "conditionally healthy persons" (21 females and 6 males, mean age 44.2±1.3 years).

II – experimental group – includes 44 persons (33 females and 11 males, mean age 49.4±2.1years) with ischemic heart disease (IHD), stable exertional angina pectoris of II functional class according to the classification of Canadian Cardiological Association. The patients were prescribed medical therapy according to the underlying disease. The therapy included angiotensin-converting enzyme (ACE) inhibitors, ß-blockers, and nitrates when necessary. This clinical study excluded patients who had had myocardial infarction in past history, and suffered from heart failure, severe concomitant conditions, acute diseases or exacerbation of chronic diseases.

III group is divided into 2 subgroups (III A and III B). III A embraces 58 patients (15 males and 43 females) with signs of dyslipidemia and atherosclerotic lesions of blood vessels who took atorvastatin (20 mg daily) in the course of year in addition to the basic therapy (methotrexate 7.5-15 mg weekly**,** folic acid 0.001g daily when methotrexate was not taken; or leflunomide (20 mg daily), dexamethasone in a dose of 4-8 mg daily by intravenous infusion for 2-3 days which then changed with methylprednisolone in a dose 4-8 mg daily gradually reducing the dose to the withdrawal of the drug). III B group involves 27 patients with rheumatoid arthritis (6 males and 21 females) who were prescribed standard therapy (methotrexate 7.5-15 mg weekly, folic acid 0.001g daily when methotrexate

was not taken; or leflunomide (20 mg daily), dexamethasone in a dose of 4-8 mg daily by intravenous infusion for 2-3 days which then changed with methylprednisolone in a dose 4-8 mg daily gradually reducing the dose to the withdrawal of the drug). The patients showed dyslipidemia as well as atherosclerotic lesions of blood vessels, but for various reasons (drug intolerance, the absence of compliance) they were not prescribed to take atorvastatin.

IV group comprises 28 females and 9 males both with rheumatoid arthritis and signs of metabolic syndrome (mean age 45.9±2.1 years). This group in its turn is divided into 2 groups: IV A formed by 26 patients who in addition to the conventional therapy took agonist PPARγ pioglitazone in a dose of 15 mg daily in the course of year, and IV B formed by 11 patients who for various reasons (drug intolerance, the absence of compliance) were not prescribed to take pioglitazone.

Rheumatoid arthritis was diagnosed according to the unified diagnostics in accordance with unified diagnostic criteria established by the American Rheumatism Association (1987) and on the basis of comprehensive physical examination of the patients. Verification of IHD (ischemic heart disease) and its forms was carried out in compliance with WHO classification (1999) and recommendations of European Society of Cardiology **(**2007**)**. The metabolic syndrome was diagnosed in accordance with criteria of the World Health Organization (1998), ATP III (2001)**,** the International Diabetes Federation (IDF) (2005). Lipoperoxidation was assessed by malonic dialdehyde (MDA) concentration. To evaluate antioxidant status we determined catalase and ceruloplasmin [3]. The total cholesterol content (TCC), total triglycerides and high-density lipoprotein (HDL) cholesterol, and total lipid in blood serum were measured by the standard methods ("Lahema" reagents were used).

The level of C-reactive protein (CRP), C-peptide**,** leptin, and adiponectin has

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been estimated by ELISA method. IR (insulin resistance) level and pancreatic ß-cells' function were calculated by HOMA 2 model taking into account C peptide level and using Microsoft Excel® based HOMA 2 calculator [17]. Ultrasound imaging (USI) of blood vessels was performed using an ultrasound scanner Mindray DP6600. We investigated EDVD and NEDVD of the brachial artery under conditions of reactive hyperemia produced by occluding the arm circulation with a pressure cuff [12], and evaluated the indices of the dysfunction [7]. Carotid intima-media complex thickness (IMT) was assessed by conventional methods [9]. The patients filled in the Finnish Diabetes Risk Score (FINDRISC) questionnaire and American Diabetes Association Questionnaire (ADAQ) tests. The Kettle's index, waist /hip circumference ratio**,** total mass of general adipose tissue (GAT), and visceral adipose tissue (VAT) were measured by Durnin-Womersley method [17] for all the patients.

Electronic statistical data processing was carried out by application of Analysis Soft Stat Plus (2006). The data distribution normality was analyzed by using Shapiro-Wilk and Lilliefors criteria. Variances of character distribution were assessed by F-criterion during the ANOVA procedure. To calculate the normality we used the p value ($p<0.05$). The arithmetic mean value (M) and quadratic mean error (m) were evaluated under the normal data distribution. The difference in probability between the indices compared was calculated by Student t-test. Pearson's correlation coefficient was used to analyze the correlation. When there was no normal data distribution the main tendencies and variances of characteristics under the observation were described by median value (Me) and interquartile range (25 and 75 percentiles). For the further investigation we used Mann-Whitney test, non-parametric Kolmogorov-Smornov and Wald-Wolfowitz criteria as well as Spearman and Kendal's correlation methods. To analyze binomial characteristics the determination of $\chi 2$ was

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applied. Differences meaning $p<0.05$ were considered to be statistically significant [2].

**Research results:**

During estimation of the insulin resistance HOMA 2 model, where the percentage β-cells of the pancreas activity (HOMA 2 % B), tissue sensitivity to insulin (HOMA 2 % S) and level of insulin resistance (HOMA 2 % IR) is represented, we have obtained the following results (Tab.1):

Table1. Insulin resistance in patients with rheumatoid arthritis, rheumatoid arthritis and metabolic syndrome and patients with ischemic heart disease according to the HOMA 2 model.

| | Patients with rheumatoid arthritis | Patients with rheumatoid arthritis and metabolic syndrome | Patients with ischemic heart disease | Control group |
|---|---|---|---|---|
| HOMA2 % B | 156,95±7,21 | 224,62±8,15 | 156,03±7,54 | 113,6±9,25 |
| HOMA2 % S | 85,89±6,31 | 54,06±6,39 | 82,09±5,02 | 160,85±9,88 |
| HOMA2 IR | 1,39±0,02 | 2,39±0,06 | 1,93±0,08 | 0,71±0,09 |
| C peptides, ng/ml | 1,97±0,07 | 3,34±0,03 | 2,68±0,08 | 1,03±0,09 |

Thus, the level of insulin resistance in patients with rheumatoid arthritis, rheumatoid arthritis and metabolic syndrome, and in patients with ischemic coronary heart disease was quite higher than in the control group. The highest level of insulin resistance was marked in the group of patients with rheumatoid arthritis and the metabolic syndrome and it was validly higher than in the group of patients with rheumatoid arthritis and the group of patients with metabolic syndrome. At the same time, indices of peripheral tissue sensitivity to insulin (HOMA 2 % S) and pancreatic β-cells

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activity (HOMA 2 % B) had not statistically significant differences between groups of patients with rheumatoid arthritis and patients with ischemic heart disease and they validly ($p<0,01$) differed from the similar indices in the patients with rheumatoid arthritis and metabolic syndrome.

Positive correlation between the level of HOMA2 insulin resistance and level of C reactive protein ($r=0,67$, $p<0,05$), level of insulin resistance and leptin levels ($r=0,34$, $p<0,05$) was observed in the patients, who have rheumatoid arthritis with metabolic syndrome. Similar tendency was observed in the group of patients with rheumatoid arthritis ($r=0,65$, $p<0,05$; $r=0.32$, $p<0,05$ accordingly) and in patients with ischemic heart disease ($r=0,53$, $p<0,05$; $r=0,31$, $p<0,05$). Therefore, the level of insulin resistance both in patients with rheumatoid arthritis and in patients with coronary artery disease is directly connected with the level of systemic inflammation process.

Studying the about connection between insulin resistance level and therapy we found out the following results (figure 1, fig. 2).

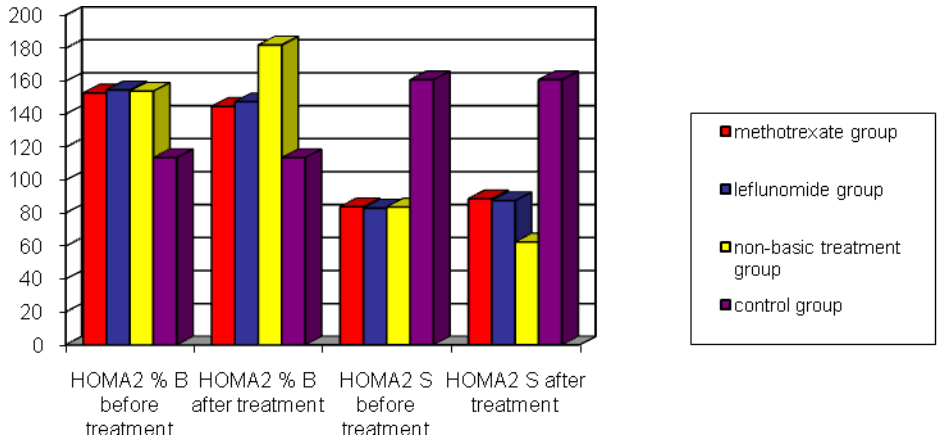


Fig. 1 Indices of pancreatic B-cells activity (HOMA2 % B) and the sensitivity of peripheral tissues (HOMA2 % S), depending on the received basic treatment

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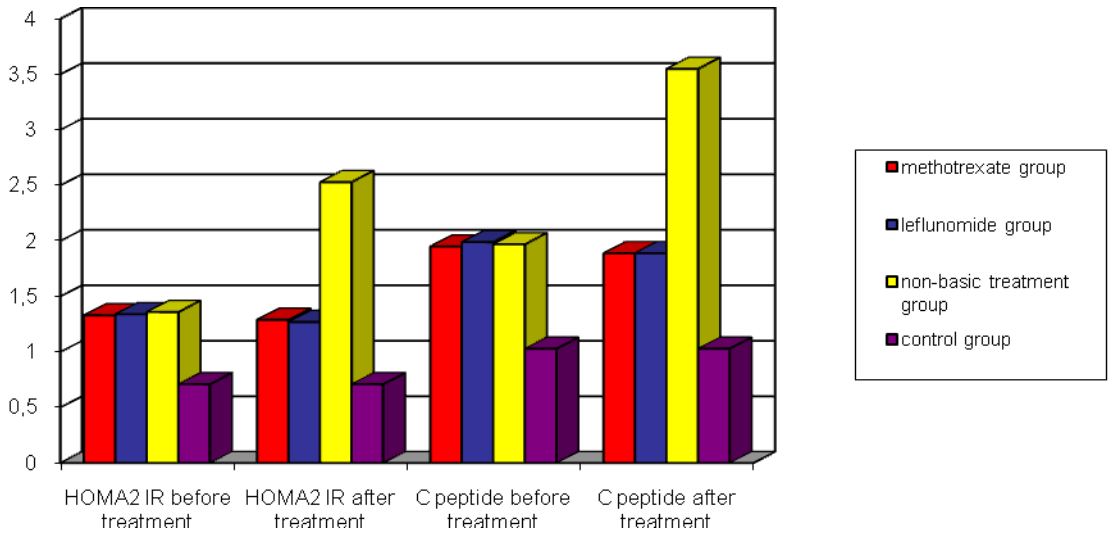


Fig. 2 Indices of insulin resistance (HOMA2 IR) and C peptide level, depending on the obtained treatment

Thus, invalid ($p<0,05$) tendency to decrease insulin resistance, increase peripheral tissue sensitivity to insulin, and to reduce of pancreatic B-cells activity was observed in patients with rheumatoid arthritis after a six-month course of basic therapy with methotrexate or leflunomide.

Valid differences between indices of methotrexate group and indices of leflunomide group were not found. At the same time, the reliable increase of insulin resistance, pancreatic B-cells activity, reduced peripheral tissue sensitivity to insulin was marked in the group of patients who have not received basic treatment. This group difference after six months of treatment from groups of patients, who received basic therapy was significantly in all the indications.

From the obtained findings we can suggest that the basic therapy stabilizes the insulin resistance progression in patients with rheumatoid arthritis. At the same time, the

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level of insulin resistance does not depend on the usage of leflunomide or methotrexate.

Analyzing the changes of insulin resistance in patients with rheumatoid arthritis under the influence of therapy with atorvastatin we received the following results (fig. 3).

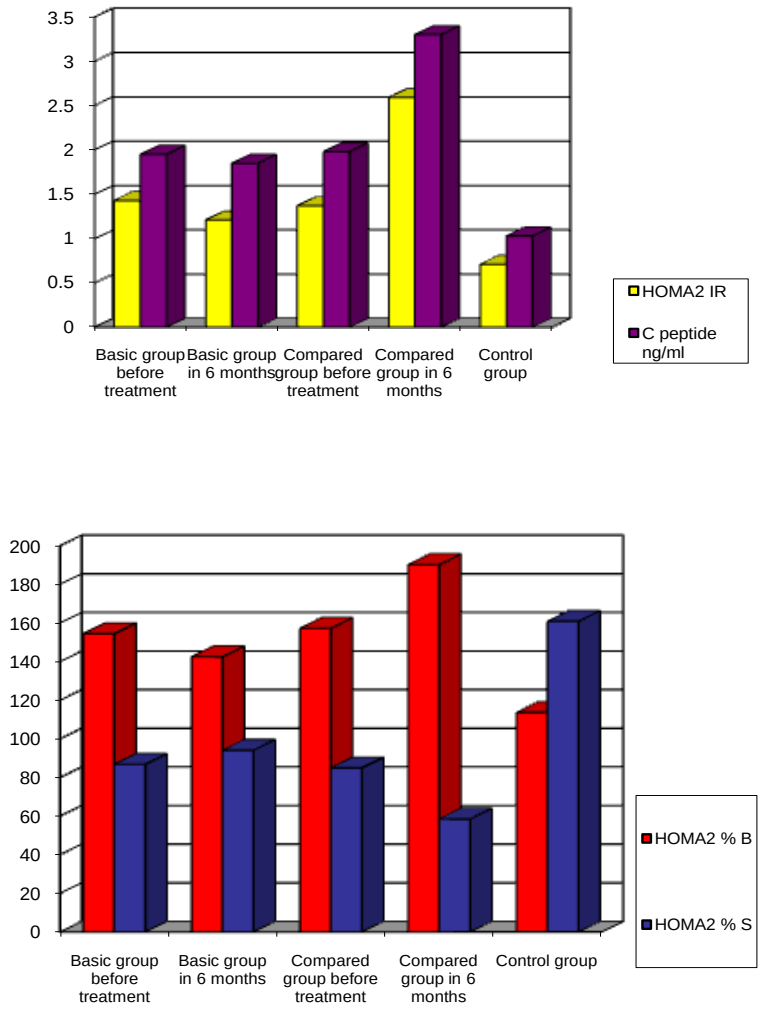


Fig. 3 Dynamics of indices in the β-cells of the pancreas activity (HOMA2 % B), the sensitivity of peripheral tissues (HOMA2 % S) (upper graph) and insulin resistance indices (HOMA2 IR) and the level of C peptide during atorvastatin therapy (lower graph).

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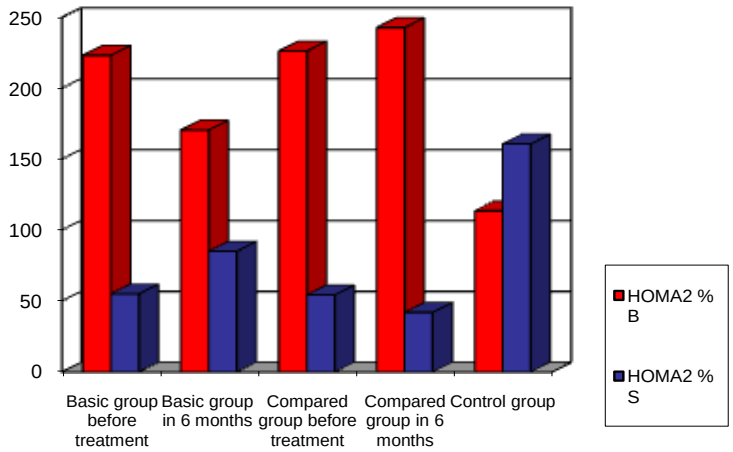
Valid ($p<0,05$) decreasing the level of insulin resistance, increasing peripheral tissues for insulin sensitivity, and increasing the level of β –cells activity in thyroid gland have been noted in 6 month therapy of atorvastatin's patients. At the same time, it was marked the increasing the insulin resistance level, β – cells activity of thyroid gland, increasing peripheral tissues for insulin sensitivity in patients that haven't athorvastatine. We consider that decreasing the level of insulin resistance during atorvastatin's therapy was resulting from reducing of blood's plasma lipids. It is possible that reducing of free fatty acids and triglycerides in patients with rheumatoid arthritis can lead to growth of consumption and glucose oxidation by peripheral tissues. The main factor of insulin resistance development is hyperlipidemia equally with systemic inflammation, as one considered [7]. In studying of pioglitazone's influence on insulin resistance course in rheumatic arthritis's patients such results have been taken (fig.4).



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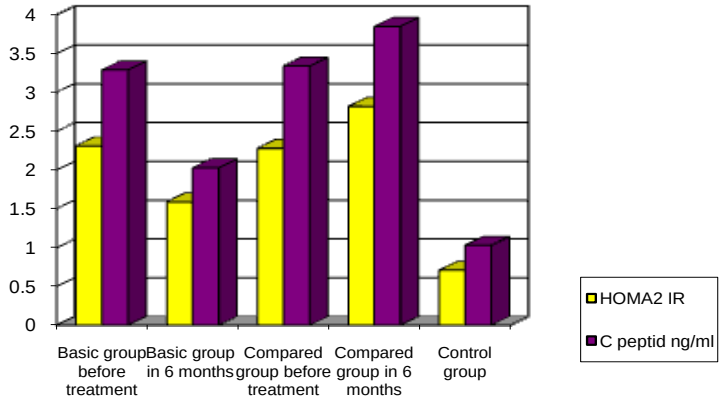


Fig. 4 Indices of β –cells activity dynamics (HOMA2 % B), peripheral tissues sensitivity (HOMA2 % S) (upper figure) and indices of insulin resistance (HOMA2 IR) and C- peptide -level during pioglitazone therapy (lower figure).

Decreasing the level of insulin resistance, increasing the level of sensitivity in peripheral tissues for insulin, and decreasing the level of β –cells activity in thyroid gland have been noted in 6 month therapy of pioglitazone's patients. At the same time, increasing the insulin resistance level, β – cells activity of thyroid gland, decreasing peripheral tissues for insulin sensitivity have been marked in patients that haven't pioglitazone.

With the purpose of estimation for prediction possibility insulin resistance and MS development in routine practice without C peptide or insulin levels estimation we have used FINDRISK (Finnish Diabetes Risk Score) Questionnaire and Questionnaire-Test of American Diabetic Association (ADA) (tab. 2)

In spite of difference in group's index that have been examined, correlative connection between insulin resistance level, FINDRISK data and ADA was absent in the group of RA

patients and MS (r=0,01, p<0,05) and (r=0,03, p<0,05) and in the group of RA patients (r=0,04, p<0,05) and (r=0,02, p<0,05) accordingly. At the same time, with the group of patients with IHD positive correlation between insulin resistance has been noted and FINDRISK polling date (r=0,32, p<0,05) and ADA (r=0,35, p<0,05), that can prove high role of routine risk factors in insulin resistance development in IHD patients and minor part in RA patients.

With the aim of prediction of adipose tissues influence on insulin resistance development, we have calculated index of Ketle (BWI), correlation of waist size to thigh size, have calculated the mass of general adipose tissue (GAT) and visceral adipose tissue (VAT) (tab.3)

Table 2. Possibility of II type diabetes mellitus development in patient with RA, RA and MS and in patient with IHD according to FINDRISK Questionnaire and Questionnaire-Test (ADA) dates.

| | RA patients | RA patients with MS | IHD patients | Control group |
|---|---|---|---|---|
| FINDRISK (max.= 26) | 6,86±0,83 | 13,33±0,75 | 7,24±0,99 | 5,37±0,89 |
| ADA(max.= 27) | 7,23±0,94 | 11,22±1,12 | 8,24±0,68 | 2,71±0,56 |

Table 3. Distribution of lipid tissue in RA patients, RA and MS patients with IHD

| | RA patients | RA patients with MS | IHD patients | Control group |
|---|---|---|---|---|
| BWI, kg/м$^2$ | 24,5±0,64 | 30,53±0,76 | 25,7±0,87 | 23,49±0,55 |
| waist size/thigh size | 0,86±0,04 | 1,03±0,01 | 0,95±0,07 | 0,81±0,04 |
| GAT, kg | 12,89±0,76 | 27,59±1,66 | 17,24±0,89 | 11,52±0,57 |
| VAT, kg | 6,78±0,49 | 11,46±0,56 | 8,21±0,75 | 7,78±0,66 |

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Correlation between BWI level and insulin resistance, which consist of r=0,37 in p<0,05 have been marked. Correlation between insulin resistance and BWI mass (r=0,44 p<0,05), between insulin resistance and VAT mass (r=0,49 p<0,05) have been noted. Relation between waist size/thigh size ratio and insulin resistance is r=0,33 p<0,05.

Table 4. The level of leptin and adiponectin in RA patients, RA and MS and IHD patients

| | RA patients | RA patients with MS | IHD patients | Control group |
|---|---|---|---|---|
| Leptin, ng/ml | 6,65±1,6 | 12,57±3,38 | 13,81±1,65 | 4,58±1,47 |
| Adiponectin, mkg/ml | 20,91±1,02 | 25,42±1,81 | 29,56±1,34 | 11,05±2,13 |

Validly differences between leptin level in RA and RA with MS groups (p<0,01) have been determined (tab. 4). At the same time the difference between leptin level in RA with MS groups of patients and IHD patients has not significant (p<0,05). Increased level of leptin and adiponectin in the group of IHD patients in comparison with the group of RA with MS patients has increased interest as BWI and visceral and general adipose tissue level is higher in the group RA with MS patients.

Table 5. Dynamics of leptin and adiponectine levels in RA patients under atorvastatin therapy

| | Basic group | | Compared group | | Control group |
|---|---|---|---|---|---|
| | Initial index | In 6 months | Initial index | In 6 months | |
| Leptine, ng/ml | 6,43±1,31 | 4,42±1,22*$^{1,2,3}$ | 6,54±1,08 | 6,65±3,65 | 4,58±1,47 |
| Adiponectin, mkg/ml | 21,31±3,21 | 26,45±3,64*$^{1;2,3}$ | 20,86±2,11 | 19,35±3,27 | 11,05±2,13 |

Notes: * p<0,05; **p<0,01 ; *$^{1}$ - comparing with initial indices, *$^{2}$ - comparing with compared group, *$^{3}$ - comparing with control group.

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Valid (p<0,05) leptin level reduction and adiponectin level increase in group of patients who were given atorvastatin have been marked under atorvastatin therapy (tab. 5).

There was valid (p<0,01) increase of leptin, adiponectin levels compared with primary data as well as with comparative group (figure 5) in case of pyoglitazone treatment. Simultaneously there was valid (p<0,01) BWI increase due to subcutaneous fat while visceral fat level has been unchanged in patients who were given pioglitazone. Leptin and adiponectin levels increase in these patients can be explained just by peripheral fat weight increase due to PPARγ receptors activation [4].

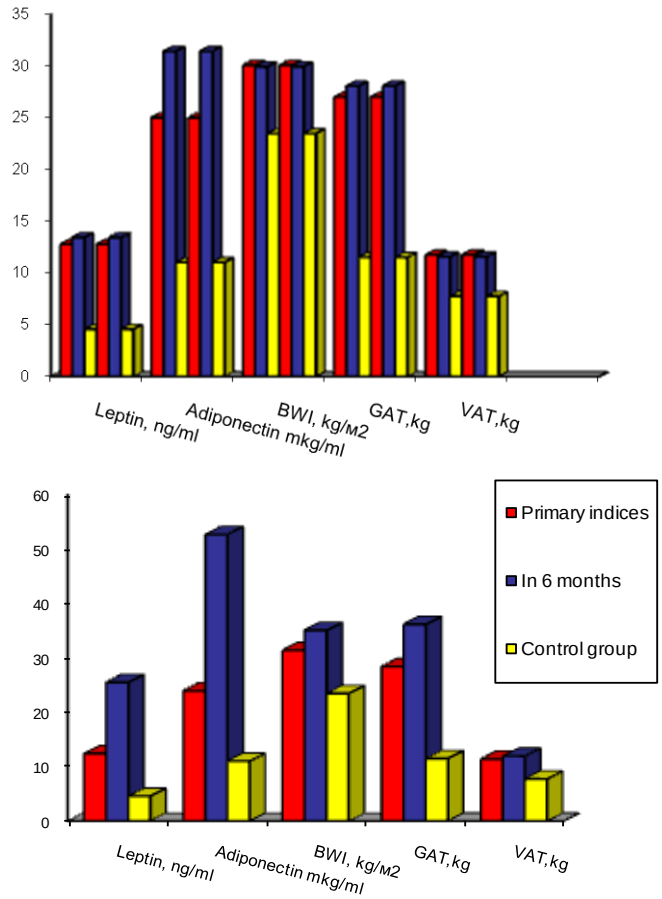


Fig. 5 Dynamics of leptin and adiponectin, BWI, GAT and VAT levels in RA with MS patients in case of pioglitazone administration. The left table shows control group indices, the right table shows the basic group indices.

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While studying IM-complex and endothelium function in RA with MC patients in case of PPARγ activation in main group after pioglitazone intake within 6 months there was valid decrease of this index in bifurcation as well as along common carotid artery. It demonstrates anti-atherosclerotic effect of PPARγ activation not only for patients with "pure" metabolic syndrome, that was proved by randomized multicentered investigations of CHICAGO and PERISCOPE, but in patients with MS and RA too. There was significant (5,3%) improvement of EDVD results, that testifies to qualitative endothelium functions improvement, as well as the improvement of NEDVD results, that testifies to vessels muscular layer function improvement (tab. 6, fig. 6,fig. 7). In 6 months of atorvastatin receiving by patients with RA to compensate revealed lesions the following results have been obtained: during investigation noticeable and valid decrease of IM-complex thickness in bifurcation as well as along CA have been marked (fig.8, fig.9).

Considerable EDVD improvement (4,5% due to absolute value, or at 47, 52% ) has been observed, that testifies to qualitative endothelium functions improvement, as well as the improvement of NEDVD results, that testifies to vessels muscular layer function improvement; at that time in most cases EDVD indices as well as NEDVD indices reach standards (tab. 7). On the investigation of the thickness of complex IM both in patients with RA and at patients with IHD there was noted the marked and reliable lowering of this index both on bifurcation and extension of common carotid artery. Paying no attention on the reliable difference between the carotid artery intima-media thickness in patients with RA and IHD the results of primary therapy by athorvastomin were almost equal in both groups of patients: decreasing of carotid artery intima-media thickness at 13.6% while in patients with RA and at 17% in patients with IHD and decreasing of thickness of IM on bifurcation at 15.2% and 14% correspondingly (Tab. 8).

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Table 6. Dynamics of IM thickness (IMT), EDVD and NEDVD in patients with RA and MS under pioglitazone therapy

| | Basic group | | Compared group | | Control group |
|---|---|---|---|---|---|
| | Initial indices | In 6 months | Initial indices | In 6 мic | |
| c IMT , mm | 0,92±0,09 | 0,73±0,08*[1;2;3] | 0,94±0,07 | 0,93±0,06 | 0,62±0,03 |
| IMT of CA bifurcation, mm | 1,15±0,06 | 0,92±0,07*[1;2;3] | 1,18±0,05 | 1,21±0,08 | 0,66±0,02 |
| EDVD, % | 4,91±0,87 | 10,2±0,92*[1;2;3] | 4,81±0,46 | 5,7±0,81 | 11,2±0,5 |
| NEDVD, % | 8,11±0,58 | 18,2±0,61**[1;2] | 9,24±0,86 | 11,2±0,54 | 23,2±0,7 |

Notes: * p<0,05; **p<0,01 ; *[1] - comparing with primary indices, *[2] - comparing with compared group, *[3] - compared with control group.

Table 7. Dynamics of IM-complex thickness EDVD and NEDVD in RA patients depending on atorvastatin receiving

| | Basic group | | Compared group | | Control group |
|---|---|---|---|---|---|
| | Initial indices | In 6 months | Initial indices | In 6 months | |
| c IMT , mm | 0,81±0,04 | 0,69±0,06*[1;2;3] | 0,82±0,05 | 0,75±0,06 | 0,62±0,03 |
| IMT of CA bifurcartion, mm | 0,92±0,07 | 0,78±0,09*[1;2;3] | 0,91±0,03 | 0,86±0,07 | 0,66±0,02 |
| EDVD, % | 5,3±0,6 | 9,8±0,9*[1;2;3] | 5,2±0,4 | 6,7±0,8 | 11,2±0,5 |
| NEDVD, % | 10,1±0,5 | 20,2±1,1**[1;2;] | 10,2±0,8 | 12,3±0,9 | 23,2±0,7 |

Notes: * p<0,05; **p<0,01 ; *[1] - comparing with primary indices, *[2] - comparing with compared group, *[3] - comparing with control group.

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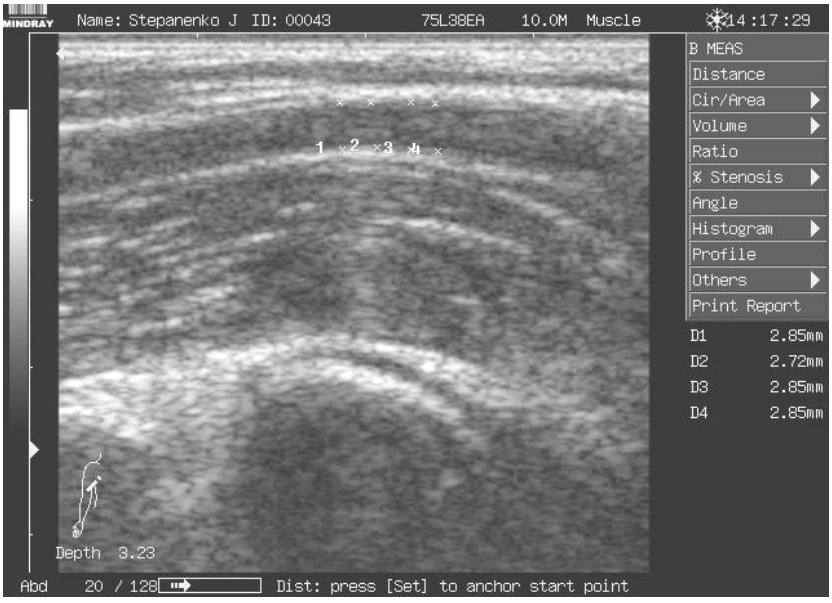


Fig. 6 Endothelium dependent vasodilatation in patient S., group RA with MS.

The sonogram included into investigation.

1 – lumen of vessel; 2 – measurement findings.

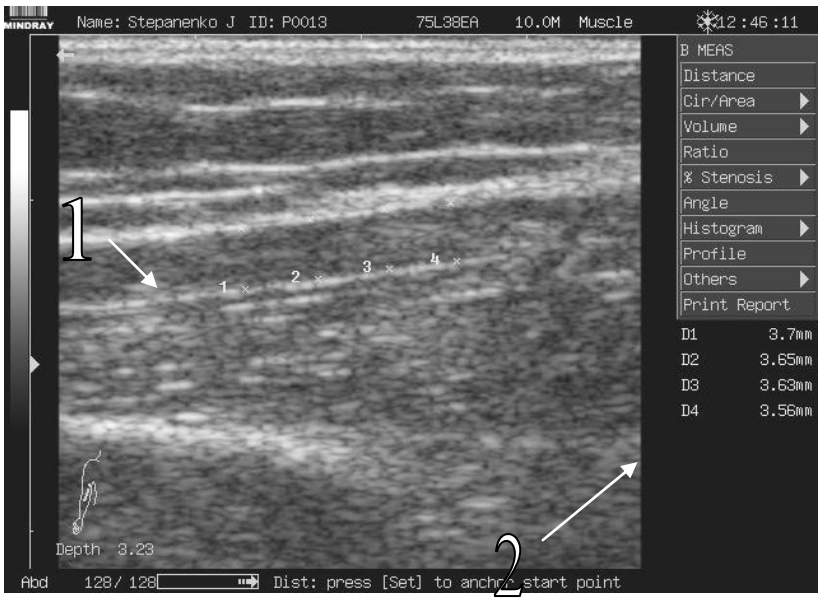


Fig. 7 Endothelium dependent vasodilatation in patient S., group RA with MS.

The sonogram in 6 months of therapy.

1 – lumen of vessel; 2 – measurement findings.

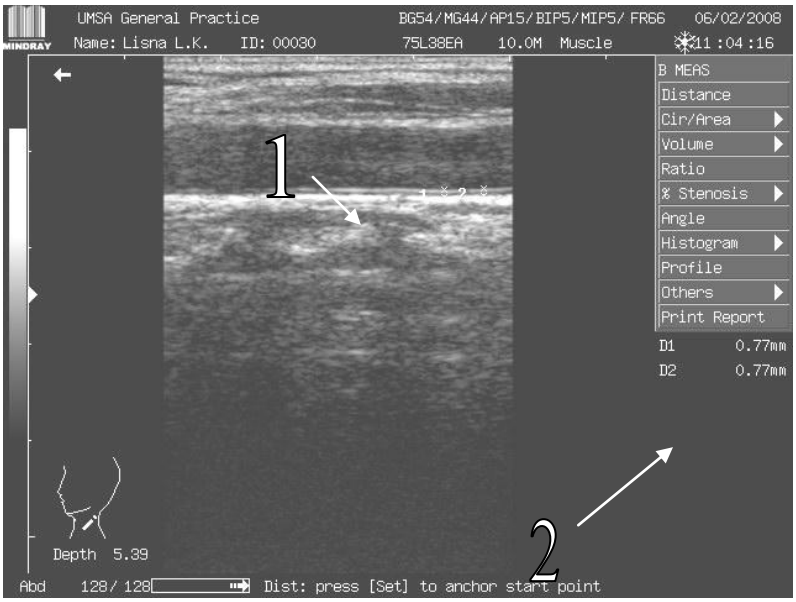


Fig. 8 IM-complex thickness in patient L, main group.

The sonogram included into investigation.

1- IM-complex; 2- measurement findings.

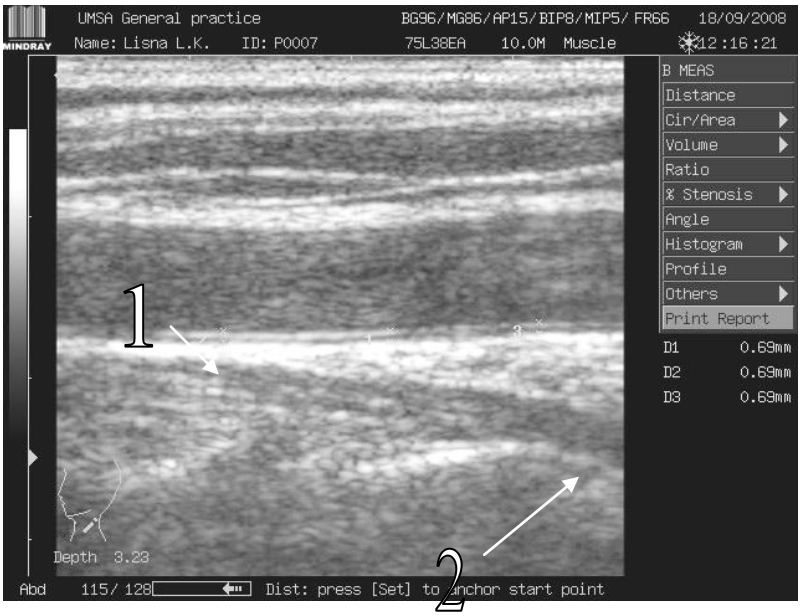


Figure 9 IM-complex thickness in patient L, main group.

The sonogram in 6 months of atorvastatin therapy.

1-complex IM; 2- measuring results

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There were supposed the significant improvement of the results both EDVD and NEDVD. At the some time in patients with IHD there was noted the reliable lower percentage of improvement comparing with the patients with RA (2% against 4,5% correspondingly). That may be cleared by more severe injuring of the vessels in patients with IHD that is confirmed by the reliably higher carotid artery intima-media thickness. The indices of NEDVD had the stable tendency to normalization that testify on improvement of sensitivity of vessels to the influence of NO under the action of atorvastatin. At the time of conducting correlative analysis there was revealed that the level of leptin in patient with RA with MS had the positive correlation with the level CRP ($r = 0.41$; $p < 0.05$) that testify to the influence of inflammation activity on the development the violations of metabolism of adipose tissue hormones as a component MS in patients with RA. The level of C reactive protein in patients with RA with MS had positive correlation with the mass of visceral adipose tissue ($r = 0.42$; $p < 0.05$) and attitude to the amount of waist and the amount of hips ($r = 0.54$; $p < 0.05$), at the same time there was no correlation with BWI ($r = 0.05$; $p = 0.76$) that testify to the significant role of abdominal obesity in the development of inflammation in such patients. Also there was noted positive correlative connection between the leptin level and mass of visceral adipose tissue interrelation of waist amount/hip amount and body mass index ($r = 0.87$; $p < 0.05$; and $r = 0.75$; $p < 0.05$ and $r = 0.71$; $p < 0.05$ correspondingly). At the same time the level of adiponectin at correlation with the mass of visceral tissue and body mass index although had negative sense of purpose, had the low statistical meaning ($r = 0.25$; $p = 1.67$ and $r = - 0.18$; $p = 1.52$) that taking into account negative connection with the level C reactive protein testifies to oppression of synthesis of adeponectin at the high activity of inflammatory process in patient with RA with MS.

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Table 8. Comparative dynamics of thickness of IM (IMT),EDVD and NEDVD in patients with RA and IHD under therapy with athorvastomin.

| | Patients with RA | | Patients with IHD | | Control group |
|---|---|---|---|---|---|
| | Initial indexes | In 6 months | Initial indexes | In 6 months | |
| c IMT, mm | 0,81±0,04*[2;3] | 0,69±0,06*[1;2] | 0,94±0,07*[3] | 0,78±0,03*[3] | 0,62±0,03 |
| IMT of CA bifurcation, mm | 0,92±0,07*[2;3] | 0,78±0,09**[1;2;3] | 1,14±0,04*[3] | 0,98±0,09*[3] | 0,66±0,02 |
| EDVD, % | 5,3±0,6*[3] | 9,8±0,9*[1;2;3] | 5,4±0,2*[3] | 7,4±0,8*[3] | 11,2±0,5 |
| NEDVD, % | 10,1±0,5*[3] | 20,2±1,1**[1;2;] | 9,8±0,6*[3] | 21,7±0,5 | 23,2±0,7 |

Notes: *p< 0.05; **p< 0.01; *1 - comparing with initial indices, *2- comparing with the group of patients with IHD, *3 - comparing with control group.

Correlation between the level of leptin and the level of adiponectin and not noted (r = - 0.03; p = 0.01) that indicates an more influence of inflammation an oppression of synthesis of adiponectin than leptin.

Thus, high inflammation activity in patients with RA is pathogenetically connected with the development of MS in these patients.

There was noted positive correlation between thickness of cIMT and the level of C peptide (r = 0.51; p = 0.02) and negative correlation between thickness of cIMT and the level of adiponectin (r = - 0.47; p = 0.01). It have been noted negative correlation of low power between level of leptin, C peptide and EDVD (r = - 0.27; p = 0.01; r = - 0.22; p = 0.02 correspondingly) and positive

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correlation between the level of adiponectin and EDVD ($r = 0.52$; $p = 0.01$).

Thus, it is possible to come to the conclusion that in patients with RA even without MS there was noted on 31.1 % higher level of leptin and on 47.15% higher level of adiponectin than in control group not paying attention on 12.9% hightr level of visceral adipose tissue in the group of healthy. At the same time in patients with RA and MS the level of leptin at 1.89 times and in patients with IHD at 2,08 times higher than in patients with RA and at 2.74 times and at 3.02 times correspondingly higher than the indices of the control group.

Level of adiponectin in patients with RA and MS at 17.74% and in patients with IHD on 29.26% higher than in patients with RA and at 2.3 times and at 2.68 times correspondingly higher than indexes in control group.

Taking into account correlation of these indices with level of insulin resistance this testifies to occurrence of resistance to endogenic secreted leptin and adiponectin in patients with expressed insulin resistance. At the same time between the level of systemic inflammation and insulin resistance in patients with rheumatoid arthritis it is statistically reliable the correlative dependence ($r = 0.67$; $p < 0.05$ for group RA and MS) that support the presence of influence of systemic inflammation on the development of insulin resistance in patients with rheumatoid arthritis.

**Discussion:**

Undoubtedly there is the role of adipocytokins both in the development of dislipidemic, insulin resistance, atherosclerotic damages and in progressing arterial hypertension and hypertrophia of myocardium.

The level of leptin and adiponectin has been validly determined in patients with RA and MS. This level associated with the mass of visceral of the adipose tissue, BWI,

and the mass of general adipose tissue [29]. Much attention is paid to the level of leptin and adiponectin in the patients with IHD, comparatively in the group of patients with RA and MS, so BWI and the level of visceral and general adipose tissue was higher in the group of people with RA and MS.

The information base was obtained by us according to it, increase of the level of leptin has a negative influence on atherosclerosis, process of endothelium-dependent vasodilation, the increase of level of adiponectin assisted in the endothelium function normalization and a decrease of c IMT. We made a conclusion that a level of leptin and adiponectin connects with atherosclerosis.

Our conclusion is approved by researches, in which a leptin was shown as a marker of the primary risk of hemorrhagic stroke [20] and myocardial infarction [21]. Another research depicted that leptin deficiency in mice is associated with anti-atherosclerotic effect, despite a development of an expressed overweight [19].

It is necessary to indicate an appointment of adequate basic therapy influences on atherosclerosis in patients with RA mainly at the expense of an increase of inflammatory processes, an increase of peroxide lipids oxidation level and a decrease of the level of antioxidant protection.

Insulin-resistance, endothelium malfunction, dyslipidemia, which are the main parts of pathogenic development of atherosclerosis, can be noted both in patients with hyperactivity, and hypoactivity.

Some indices of endothelium malfunction in the group of patients with RA with basic methotrexate therapy can be explained that methotrexate assists in the formation of homocysteine which is a substance of endothelium [1]. From another hand, there is no valid improvement of endothelium function during basic leflunomid therapy.

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Analyzing the influence atorvastatin on RA, except normalization of lipid exchange, after six months atorvastatin therapy, patients have an increase insulin-resistance level, a decrease of sensitivity of perepheric tissues to insulin, an increase ß-cells activity of pancreas. Nowadays it is considered that hyperlipemia along with systemic inflammation is the main factor of insulin-resistance development [7].

Due to the atorvastatin activity the decrease of free fatty acids concentration and triglycerides leads to an increasing of the usage and oxidation of glucose by peripheral tissues and, accordingly insulin-resistance level that is approved by other researchers [5].

The decreased level of leptin and increase level of adiponectin during atorvastatin therapy testifies about balance adipocytokines normalization under atorvastatin's action and it does not contradict the information of other authors [27]. At the same time, there is information which testifies about the absence of insulin-resistance, leptin, adiponectin changes under atorvastatin therapy [11].

Received differences are explained by shorter duration of the research (3 months), much higher patients' average age (60,0 +_ 2,2 years), an expressed dyslipidemia on the background of type II diabetes mellitus in all patients.

Thickness decrease IM-complex of CA and improvement of results both EDVD and NEDVD according to the literature [10] testifies the qualitative endothelium functions and muscle sphere of vessels functions in patients, who took atorvastatin.

It is explained by nitricoxide normalization in the walls of vessels under atorvastatin's action [16].

Besides, statins inhibit the synthesis of important anti-inflammatory cytokines, such as TNF-α, IL-6, Il-1 and IL-28 [25]. It was demonstrated that statins, especially atorvastatin, prevent the development of

chronic paralysis which was caused in mice by artificial demyelinization. This associated with the immune response with switching over Th1 to Th2 [28]. Especially, it is important for patients with RA, that's why an immune response of Th1 type and synthesis of anti-inflammatory mediators play a fundamental role in RA immunopathogenesis [18].

During six months pioglitazone therapy, patients with RA and MS have valid increase insulin-resistance level, a decrease of sensitivity of peripheral tissues to insulin, an increase ß-cells activity of pancreas on the background of an increase level of systemic inflammation.

Anti-inflammatory activity PPARγ activators can be explained due to that they are TNF-α antagonists [9] and NFkB inhibitors, which are one of the main anti-inflammatory nuclear randomized factors [32]. The level of leptin, adiponectin increased validly comparatively both primary information and a group of comparison during treatment by pioglitazone.

It was indicated the valid increase of BWI in the group of patients, who took pioglitazone. It was done due to subcutaneous fat, at the same time the level of visceral fat remained without changes. According to the increase mass of peripheral fat in consequence of PPARγ [4] receptors activation can be explained by an increase level of leptin and adiponectin in these patients. Anti-atherosclerotic effect of PPARγ activation, which developed as a decrease of IM-complex, approves by randomized CHICAGO and PERISCOPE numerous researches.

**Conclusions:**

Thus, patients with RA have typical development of insulin-resistance on the background of systemic inflammation, which is shown as a disturbance of lipids exchange and its regulation, endothelium malfunction,

changes of exchange adipose tissue hormones. These changes are common in the patients with MS. The usage of statins and thiazolidinediones contribute to the correction of irregularities.

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**“Innovative Medicine and Biology” ISSN 1925-2188**

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