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Lipid-Lowering and Pleiotropic Effects of Statins in Patients with Osteoarthritis and Metabolic Syndrome

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Abstract

The purpose of the study was the evaluation of the effect of atorvastatin on the dynamics of the lipid spectrum of blood, indicators of inflammatory activity, and pain intensity in patients with osteoarthritis and metabolic syndrome (MS). The study included 70 patients with osteoarthritis and MS who were divided into two groups. The patients in the control group (35 people) took only pathogenetic treatment of osteoarthritis and antihypertensive drugs. Patients of the main group (35 people) also received atorvastatin at a dose of 10 mg per day for 12 months. In both groups kept track of the lipid spectrum of blood: total cholesterol, triglycerides, cholesterol of lipoproteins of high (HDL-C) and low (LDL-C) density, the values of erythrocyte sedimentation rate, C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) and the pain intensity on a scale visual analog scale (VAS) values Lequesne index and the Western Ontario and McMaster Universities Arthritis (WOMAC) at 1-3 days, 7-10 days, and after 3, 6, and 12 months. At follow-up among patients of the main group noted the positive dynamics in all lipid spectrum of blood, the lower the erythrocyte sedimentation rate (ESR), CRP, and TNF-α, a significant decrease in the intensity of the manifestations of pain syndrome at rest and during movement, and reduced severity of articular manifestations according to the Lequesne index and the WOMAC index.

Keywords

Metabolic syndrome; Osteoarthritis; Atorvastatin

Introduction

The term "metabolic syndrome" (MS), introduced in 1988 [1], has become part of modern science, which is associated not only with the prevalence of this disease in the adult population, reaching 25-30% [2], but also with pathogenetic mechanisms, allowing to generalize MS components, each of which represents an independent predictor of cardiovascular complications [3]. Thus, if timely diagnosis and treatment of MS will be possible to achieve a considerable reduction in the mortality from cardiovascular events, which, according to who estimates, occupy the first place among the causes of mortality of the population in industrialized countries [4,5].

Osteoarthritis, in turn, represents the most common form of joint disease, affecting at least 20% of the world population [6]. Late diagnosis and ineffective treatment lead to a decrease patients' quality of life, growth of temporary disability and early disability persons of working age. It is now known that the basis of the pathogenesis of osteoarthritis is the predominance of catabolic processes over anabolic, while under the influence of certain pulses of the chondrocytes begins to produce proinflammatory cytokines, which increases the catabolic activity of chondrocytes. The Central role is given interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-α), which leads to increased activity of metalloproteinases that contribute to the growth of osteophytes and increase the stiffness of the subchondral bone, which, in turn, stimulates the degradation of articular cartilage, closing the pathological range [7]. However, to date, received data on the relationship of osteoarthritis with metabolic disorders [8]. Insulin resistance, the underlying MS, causes increased formation of oxygen radicals causing endothelial dysfunction [9]. It is known that the damage caused by free radicals, make a significant contribution to the development of atherosclerosis and diseases of the joints [10]. Also, found a close correlation between triglycerides and the ability of phagocytes to synthesize TNF-α, the local production of which is in the focus of inflammation provides chemotaxis of neutrophils, increased phagocytosis, degranulation, production, and secretion of their active forms of oxygen [11]. The impact of MS in the development of osteoarthritis proves the high level of triglycerides in patients with complete loss of the cartilage according to arthroscopy and its correlation with circulating immune complexes (CIC) [9,12]. Also identified a relationship between dyslipidemia and oxidative stress with erosive changes in the cartilage, the relationship of MS with more severe lesions of the articular cartilage, according to arthroscopy in patients with osteoarthritis, is complicated by secondary synovitis [13]. Thus, the presence of symptoms of MS in patients with osteoarthritis is associated with a more severe loss of cartilage and recurrent synovitis [14], which proves the negative impact of MS on the course of osteoarthritis.

Currently, the "gold standard" for the correction of hypercholesterolemia is the use of statins, which are capable of blocking HMG-COA-reductase, the rate-limiting cholesterol biosynthesis. In addition, a number of synthetic statins, in particular atorvastatina, were noted a positive impact not only on the levels of total cholesterol and cholesterol of lipoproteins of low density (LDL-C) but also in relation to HDL-C and triglyceride levels [15]. In addition, there opened a number of pleiotropic effects of this group of drugs, including anti-inflammatory effects, vasodilation, antioxidant, and antiplatelet effects [16-18].

The purpose of the study was to evaluate the lipid-lowering and pleiotropic features of atorvastatin in relation to the inflammatory response and articular manifestations in patients with osteoarthritis and MS.

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Materials and Methods

The study included 70 patients of the white race with osteoarthritis and MS. All patients were hospitalized in the rheumatology department of the Lipetsk Regional Clinical Hospital in 2012-2014. The examined patients were divided into two groups. In the control group, consisting of 35 people, and included patients with osteoarthritis and MS – 27 women and 8 men aged from 47 to 74 yrs, receiving pathogenetic treatment of osteoarthritis. In the main group were 35 patients with osteoarthritis and MS – 27 women and 8 men aged 49-69 yrs, treated against the background of pathogenetic therapy of osteoarthritis and atorvastatin. Patients in the control group due to the presence of dyslipidemia were also recommended atorvastatin; however, patients themselves have refused taking statins for no apparent reason and had been warned about the consequences of such a decision.

When admitted to hospital, all patients included in the study were diagnosed with MS on the basis of criteria developed by the Committee of experts of the International Diabetes Federation (IDF, 2005):

- Central obesity – waist circumference $>$ 94 cm in men, $>$ 80 cm in women (other ethnic groups other specific features), and two of the following four factors:
    1. The increase in triglyceride $\geq$ 1.7 mmol/l (150 mg/Dl), or receive treatment about this condition.
    2. The decrease in HDL-C $<$ 1.0 mmol/l (40 mg/Dl) in men, HDL-C $<$ 1.3 mmol/l (50 mg/Dl) in women or receive treatment about this condition.
    3. The increase in blood pressure $\geq$ 130/85 mmHg, or taking antihypertensive drugs.
    4. The increase in blood glucose levels in fasting plasma $\geq$ 5.6 mmol/l (100 mg/Dl) or previously diagnosed type 2 diabetes.

Among patients, the duration of osteoarthritis of up to 5 yrs to 34.4% of patients, 5-10 yrs – from 38.7%, more than 10 yrs – 26.9% of patients. Chest X-ray changes art. II (I. Kellgren and I. Lawerens) were detected in 100% of patients. The presence of synovitis was detected clinically and confirmed instrumental (using ultrasound diagnostics of the joints). Among comorbidities were arterial hypertension (100%), obesity (100%), dyslipidemia (100%), and CHD (82.4%).

Assessment of the severity of articular syndrome was carried out by assessing pain intensity at rest and during movement on the visual analog scale (VAS) (mm). This test reflects the overall severity of articular pain assessment patient, using a 100 mm pain scale, where 0 mm means no pain and 100 mm is the maximum intensity of pain [19]. The intensity of the pain syndrome at rest and during movement was assessed separately. The Lequesne index included assessment of pain at rest and during walking (five questions), maximum passable distance (one question) and daily activity (four questions). Ball the score of each question was summed and ranged to account for the severity of the disease. Index WOMAC (Western Ontario and McMaster University) was determined with the help of a questionnaire for self-assessment by the patient, the severity of pain at rest and during walking (5 questions), the severity and duration of stiffness (2 questions), and functional disability in daily activities (17 questions). When this evaluation was conducted on the scale of VAS (in cm), and then all the scores were summed up [19].

During inpatient treatment, patients in both groups received nonsteroidal anti-inflammatory drugs (NSAIDs) (nimesulide 100 mg 2 times a day or meloxicam 15 mg in the morning), chondroitin 100 mg i/m, in the presence of intra-articular synovitis was administered to lornoxicam 8 mg after puncture of the joint. Ambulatory patients also received symptom-modifying drugs slow action (chondroitin sulfate 1,000 mg/day and glucosamine 1,500 mg/day; 3 months 2 courses per year). NSAIDs systematically for ambulatory patients in both groups did not accept. Patients received drugs acetylsalicylic acid and antihypertensives, and metabolically neutral – ACE inhibitors and calcium channel blockers. During the survey (after 3, 6, and 12 months) and the presence of synovitis patients were administered 8 mg lornoxicam after intra-articular puncture of the joint. Atorvastatin (liponorm®) was administered to the patients of the main group at 10 mg daily for 12 months. In the control and main groups were tracked lipid spectrum of blood: total cholesterol, triglycerides, HDL-C, and LDL-C. Also assessed the indicators of inflammatory activity: ESR (Westergren), C-reactive protein (CRP), TNF-α. The intensity of articular syndrome was assessed according to the scale of VAS at rest and during movement, the Lequesne index and the WOMAC 1-3, 7-10 days hospital treatment, and after 3, 6, and 12 months. Statistical data processing was performed on a personal computer using Microsoft Excell Microsoft Office 2003. We estimated the average, the average error. The significance of differences of studied parameters in the control and main groups was determined by student's criterion.

Results

On a background of atorvastatin in the main group of patients at follow-up adverse reactions of the drug, demanded its abolition, were not recorded.

In the control group of patients, statistically significant changes in total cholesterol were found. Against the backdrop of diets during inpatient treatment, a slight tendency was observed to decrease in the future reversed the growth trend of this indicator. Values of triglycerides had a similar trend to decrease by 7-10 days of treatment in hospital, with subsequent growth after 3, 6, and 12 months. Among patients receiving atorvastatin, there was a significant decrease in total cholesterol with 6.03 $\pm$ 0.15 mmol/l to 5.16 $\pm$ 0.12 mmol/l ($p < 0.001$), in the future, this figure was reduced, making 4.42 $\pm$ 0.10 mmol/l ($p < 0.001$) after 3 months, or 4.31 $\pm$ 0.11 mmol/l ($p < 0.001$) after 6 months, 4.14 $\pm$ 0.10 mmol/l ($p < 0.001$) by the end of the study. The triglyceride level was significantly decreased from 2.42 $\pm$ 0.14 mmol/l up to 2.06 $\pm$ 0.10 mmol/l ($p < 0.01$) after 6 months and up to 2.0 $\pm$ 0.11 mmol/l ($p < 0.01$) after 12 months. When comparing the values of total cholesterol and triglycerides in the control and main groups revealed significant differences in the levels of total cholesterol by 7-10 days ($p < 0.01$), after 3, 6, 12 months ($p < 0.001$). The level of triglycerides in the study group had significantly lower values after 6 months ($p < 0.05$) and 12 months ($p < 0.01$) (Table 1). In the control group patients tended to increase for 7-10 days HDL-C; however, after 3 and 6 months was marked by the opposite tendency to the decrease of this indicator. By the end of the study, a significant decrease of this indicator 1.04 $\pm$ 0.04 mmol/l to 0.91 $\pm$ 0.02 mmol/l ($p < 0.01$) was showed. The values of LDL-C during inpatient treatment also tended to decrease, after 3 and 6 months was observed a reverse trend to grow, and by the end of the study, it was noted a significant increase in this indicator from 3.99 $\pm$ 0.11 mmol/l up to 4.41 $\pm$ 0.09 mmol/l ($p < 0.01$).

Among patients treated with atorvastatin, at 7-10 days was marked by the growth trend of this indicator in the future managed to achieve a significant increase in the level of HDL-C with the 1.06 $\pm$ 0.04 mmol/l and 1.20 $\pm$ 0.04 mmol/l after 3 months ($p < 0.05$); 1.23 $\pm$ 0.03 mmol/l

Indicator	Group	1-3 days	7-10 days	After 3 months	After 6 months	After 12 months
Total cholesterol (mmol/l)	Control	5.7 ± 0.15	5.67± 0.13	5.72 ± 0.14	5.77 ± 0.15	5.9 ± 0.13
	Study	6.03 ± 0.15	5.16 ± 0.12	4.42 ± 0.10	4.31 ± 0.11	4.14 ± 0.10
p		Not reliably	<0.01	<0.001	<0.001	<0.001
Triglycerides (mmol/l)	Control	2.33 ± 0.13	2.27 ± 0.12	2.37 ± 0.12	2.44 ± 0.13	2.5 ± 0.13
	Study	2.42 ± 0.14	2.23 ± 0.13	2.11 ± 0.12	2.06 ± 0.10	2.0 ± 0.11
p		Not reliably	Not reliably	Not reliably	<0.05	<0.01
HDL-C (mmol/l)	Control	1.04 ± 0.04	1.07 ± 0.03	0.99 ± 0.03	0.98 ± 0.03	0.91 ± 0.02
	Study	1.06 ± 0.04	1.15 ± 0.04	1.20 ± 0.04	1.23 ± 0.03	1.26 ± 0.03
p		Not reliably	Not reliably	<0.001	<0.001	<0.001
LDL-C (mmol/l)	Control	3.99 ± 0.11	3.66 ± 0.10	4.09 ± 0.09	4.2 ± 0.09	4.41 ± 0.09
	Study	4.08 ± 0.13	3.31 ± 0.12	2.66 ± 0.12	2.6 ± 0.10	2.50 ± 0.08
p		Not reliably	Not reliably	Not reliably	<0.01	<0.001

Table 1: Dynamics of lipid spectrum in the control and study group patients for 12 months

($p < 0.01$) after 6 months; 1.26 ± 0.03 mmol/l by the end of the study. Values of LDL-C decreased 4.08 ± 0.13 mmol/l to 3.31 ± 0.12 mmol/l already for 7-10 days ($p < 0.001$), and further continued to decline, amounting to 2.66 ± 0.12 mmol/l ($p < 0.001$) after 3 months; 2.6 ± 0.10 mmol/l ($p < 0.001$) after 6 months; 2.50 ± 0.08 mmol/l ($p < 0.001$) by the end of the study (Table 1). When comparing HDL-C and LDL-C among patients of both groups was found that in the main group the values of HDL-C were significantly higher after 3, 6 and 12 months of therapy ($p < 0.001$) compared to patients in the control group. The LDL-C level was significantly lower in the study group of patients for 7-10 days ($p < 0.05$), after 3, 6, and 12 months ($p < 0.001$).

Among the patients in the control group on the background of complex, in-patient treatment was significantly decreased in the values of the sedimentation rate from 17.1 ± 0.65 mm/h to 14.7 ± 0.41 mm/h ($p < 0.01$) for 7-10 days of treatment. However, in the future, in the absence of regular use of NSAIDs this index tended to increase and 17.7 ± 0.56 mm/h after 3 months and 18.4 ± 0.57 mm/h after 6 months. By the end of the study, the values of erythrocyte sedimentation rate in the control group patients were significantly increased to 18.9 ± 0.59 mm/h ($p < 0.05$). When this indicator CRP also significantly decreased from 14.4 ± 0.62 mg/l to 6.5 ± 0.23 mg/l ($p < 0.001$) for 7-10 days of treatment, and further had a tendency to increase, amounting to 14.1 ± 0.38 mg/l after 3 months; 14.8 ± 0.54 mg/l after 6 months; 16.2 ± 0.72 mg/l after 12 months. The values of TNF-α were significantly decreased from 8.3 ± 0.54 PG/ml to 6.7 ± 0.33 PG/ml ($p < 0.05$) for 7-10 days and had a tendency to increase in the future until the end of the study, amounting to 7.8 ± 0.27 PG/ml after 3 months; 8.1 ± 0.28 PG/ml after 6 months; 8.4 ± 0.31 PG/ml at 12 months (Table 2).

In the main group of patients, the average sedimentation rate is also significantly decreased for 7-10 days from 17.9 ± 0.74 mm/h to 14.2 ± 0.43 mm/h ($p < 0.001$) and further continued to decline, amounting to 13.9 ± 0.37 mm/h ($p < 0.001$) after 3 months, 13.5 ± 0.32 mm/h ($p < 0.001$) after 6 months; 12.2 ± 0.34 mm/h ($p < 0.001$) after 12 months. A similar pattern was the nature and prevalence of CRP, which was significantly decreased from 13.7 ± 0.61 mg/l to 6.2 ± 0.21 mg/l ($p < 0.001$) for 7-10 days, amounting to 5.7 ± 0.20 mg/l ($p < 0.001$) after 3 months; 5.1 ± 0.23 mg/l ($p < 0.001$) after 6 months; 4.4 ± 0.22 mg/l ($p < 0.001$) after 12 months. The values of TNF-α during the study were also significantly lower than the original 8.6 ± 0.49 PG/ml, amounting to 6.5 ± 0.40 PG/ml ($p < 0.01$) for 7-10 days; 6.1 ± 0.33 PG/ml ($p < 0.001$) after 3 months; 5.7 ± 0.28 PG/ml ($p < 0.001$) after 6 months; 5.1 ± 0.26 PG/ml ($p < 0.001$) by the end of the study (Table 2). When comparing the ESR, CRP, and TNF-α in the control and main groups was that all three of these indexes were significantly lower in the study group patients after 3, 6, and 12 months ($p < 0.001$).

Patients in both groups during hospital treatment were selected with adequate therapy, the result of which was marked by significantly reducing the severity of pain on a scale in VAS rest and during movement for 7-10 days ($p < 0.001$). However, both indicators in the future a control group of patients did not have significant changes compared with the initial values, whereas in the group of patients treated

Indicator	Group	1-3 days	7-10 days	After 3 months	After 6 months	After 12 months
ESR (mm/h)	Control	17.1 ± 0.65	14.7 ± 0.41	17.7 ± 0.56	18.4 ± 0.57	18.9 ± 0.59
	Study	17.9 ± 0.74	14.2 ± 0.43	13.9 ± 0.37	13.5 ± 0.32	12.2 ± 0.34
p		Not reliably	Not reliably	<0.001	<0.001	<0.001
CRP (mg/l)	Control	14.4 ± 0.62	6.5 ± 0.23	14.1 ± 0.38	14.8 ± 0.54	16.2 ± 0.72
	Study	13.7 ± 0.61	6.2 ± 0.21	5.7 ± 0.20	5.1 ± 0.23	4.4 ± 0.22
p		Not reliably	Not reliably	<0.001	<0.001	<0.001
TNF-α (PG/ml)	Control	8.3 ± 0.54	6.7 ± 0.33	7.8 ± 0.27	8.1 ± 0.28	8.4 ± 0.31
	Study	8.6 ± 0.49	6.5 ± 0.40	6.1 ± 0.33	5.7 ± 0.28	5.1 ± 0.26
p		Not reliably	Not reliably	<0.001	<0.001	<0.001

Table 2: Dynamics of ESR, CRP, and TNF-α in the control and study group patients for 12 months

Indicator	Group	1-3 days	7-10 days	After 3 months	After 6 months	After 12 months
VAS movement (mm)	Control	56.5 ± 0.67	30.6 ± 0.55	53.3 ± 1.86	55.2 ± 1.54	57.1 ± 1.55
	Study	57.9 ± 0.68	31.4 ± 0.43	51.9 ± 0.83	49.7 ± 0.77	46.2 ± 0.83
p		Not reliably	Not reliably	Not reliably	<0.01	<0.001
VAS alone (mm)	Control	20.6 ± 1.49	10.7 ± 0.6	18.9 ± 1.57	20.1 ± 1.54	21.5 ± 1.62
	Study	23.3 ± 1.52	11.2 ± 0.73	13.1 ± 0.86	11.4 ± 0.68	10.8 ± 0.44
p		Not reliably	Not reliably	<0.01	<0.001	<0.001
Lequesne (points)	Control	10.5 ± 1.17	7.2 ± 0.2	9.1 ± 0.47	10.3 ± 0.3	10.6 ± 0.29
	Study	11.1 ± 0.41	7.7 ± 0.21	9.0 ± 0.24	8.7 ± 0.25	7.9 ± 0.21
p		Not reliably	Not reliably	Not reliably	<0.001	<0.001
WOMAC (cm)	Control	104.1 ± 1.77	65.7 ± 1.47	99.7 ± 3.12	107.0 ± 1.77	111.0 ± 1.82
	Study	110.3 ± 1.97	69.3 ± 0.91	98.7 ± 0.99	94.7 ± 0.82	92.1 ± 0.21
p		<0.05	<0.05	Not reliably	<0.001	<0.001

Table 3: Dynamics of articular status in the control and main groups of patients for 12 months

with atorvastatin, the severity of pain at rest and during movement throughout the study was significantly lower than values obtained at 1-3 days ($p < 0.001$) (Table 3).

When comparing the severity of pain among patients of the control and main groups, it was found that the severity of pain at rest, among patients receiving siofor, was significantly lower after 3 months ($p < 0.01$), 6 and 12 months ($p < 0.001$), and pain in this group of patients when the movement was significantly less pronounced after 6 months ($p < 0.01$) and 12 months ($p < 0.001$) compared to patients in the control group (Table 3).

In both groups of patients were able to achieve significant reduction in the Lequesne index and the WOMAC for 7-10 days ($p < 0.001$), but in the control group patients in the future, these indicators did not differ significantly from the original, and the WOMAC index was significantly increased by 6.7% by the end of the study ($p < 0.01$). Patients of the main group were able to achieve a significantly lower values of both indicators throughout the study ($p < 0.001$).

When comparing the Lequesne index and the WOMAC in patients of both groups, it was found that the WOMAC index initially and for 7-10 days in the control group patients was significantly lower ($p < 0.05$), but after 6 and 12 months, patients taking atorvastatin had significantly lower values of both indices ($p < 0.001$) (Table 3).

Discussion

Currently in the world, statins have taken a strong place in therapy of cardiovascular diseases in connection with a reduction in mortality and improvement of prognosis in patients with ischemic heart disease and other manifestations of atherosclerosis, as well as in the treatment of disorders of lipid metabolism [20]. MS itself is a set of components, each of which is an independent risk factor for cardiovascular events. This fact confirms the need for inclusion of statins in the treatment of MS patients. In addition, the data obtained on the pleiotropic effects of this group of drugs can be judged and favorable effects on endothelial dysfunction, circulation, and anti-inflammatory effects of statins [15-18].

In our study, we have confirmed the positive effects of atorvastatin in respect of the lipid spectrum of blood. So under the influence of the drug was able to achieve a significant decrease of values of total cholesterol, triglycerides, and LDL-C when reliable increase in HDL-C. The drug has implemented its pleiotropic anti-inflammatory effects: in comparison with a control group, patients treated with atorvastatin had significantly lower values of ESR, CRP, and TNF-α. It was also realized pleiotropic effects of the drug and in relation to the articular status: the positive effect of the drug against pain syndrome in patients both at rest and during movement. On a background of atorvastatin at a dose of 10 mg per day for 12 months, adverse reactions requiring discontinuation of the drug were noted. Significantly more effective was the treatment in the patients taking atorvastatin, compared to patients in the control group after 6 and 12 months on VAS index at rest and during movement, the Lequesne index and the WOMAC, i.e. in all major indicators of articular status. The data obtained prove the positive influence of statins not only on lipid spectrum of blood but also against the articular status and inflammatory activity in osteoarthritis, which opens up new horizons in the use of this group of drugs.

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