European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 7, Issue 2, 2020

DYSLIPIDEMIA AND WAYS OF ITS CORRECTION IN RHEUMATOID ARTHRITIS PATIENTS WITH METHOTREXATE TREATMENT

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***Abstract:** This article aims to study lipid profile disorders and the efficacy of phenofibrate (Lipidex SR) in young rheumatoid arthritis (RA) patients with methotrexate (MT) treatment. Materials and methods: We examined 102 patients of RA. Diagnosis of RA has been verified on the basis of classification criteria proposed by the American College of Rheumatologists (ACR) in 1987 and/or criteria of ACR/European Anti-Rheumatic League (EULAR) in 2010. Among the examined, 10 (9.8%) were male, 92 (90.2%) were female and more than half (54%) were young patients under 30. The control group consisted of 110 healthy middle-aged individuals. In the surveyed population, those with 1 to 5 years of age were the largest group (38.3%), followed by those with 5 to 10 years of age (34%). In 66.3% of the patients of RA MT was used as a base preparation. The average dose (median) of MT over the study period was 10 mg per week. 80% of patients took prednisolone in an average dose of 10 mg/day. The content of lipids in venous blood was determined by photocolometry on Vitros SYSTEM Chemistry DT 60 biochemical analyzer (Austria). Results: RA patients who took MT showed a significant increase in the level of triglycerides (TG). Also, it is characterised by an increase in TG levels and a decrease in the concentration of high-density lipoprotein cholesterol (HDL) and an increase in the atherogenicity factor. A more pronounced decrease in HDL levels. Significantly high indicators of the atherogenicity coefficient, which to a lesser extent depended on the duration of MT use. Low-density lipoprotein cholesterol (LDL) and triglyceridemia are also proved to be serious risk factors for atherosclerosis and cardiovascular heart diseases (CHD). Also according to the results of the research, special attention is paid to the use of hypolipidemic drugs, which is promising in improving the prognosis and reducing cardiovascular injuries in RA patients. In the group of patients who received additional lipidex SR, there was a decrease in the level of OHS by 17.1%, an important shift was observed on the part of TG, this indicator decreased by 29.7% and practically did not differ from the control indicators. HDL cholesterol in the SR lipidex group increased significantly by 37.7%. These fibrates have a stimulating effect on all components of*

atherogenic dyslipidemia and can mitigate the risk of cardiovascular disasters in RA. Conclusion. Thus, in RA patients of young age when using MT there is a reliable increase in the level of Tg, Cholesterol VLDL, a decrease in Cholesterol HDL with an increase in the atherogenicity coefficient, which indicates the proatherogenic effect of the MT base drug against the background of a pronounced fatty hepatosis of the liver. Fibrates have a favorable effect on all components of atherogenic dyslipidemia and can reduce the risk of cardiovascular disasters in RA.

Keywords: rheumatoid arthritis, dyslipidemia, diagnostics, treatment, methotrexate, statins, fibrates.

Rheumatoid arthritis (RA) - chronic autoimmune disease with a polygenic predisposition, leading to erosive and destructive changes in the peripheral joints and accompanied by lesions of internal organs and cardiovascular complications. Until recently, many experts believed that RA, resulting in early disability, was not a cause of premature death (1). Recent clinical researches show the necessity to change the attitude of physicians to the assessment of prognosis for life in this category of patients. The analysis of the structure of mortality of RA patients has led to the understanding of the fact that the cause of premature death in half of them are diseases of the cardiovascular system associated with atherosclerotic vascular lesions, rather than with rheumatic lesions of the heart structures [1,2].

The concept of risk factors for the development of cardiovascular disasters has some peculiarities in relation to RA patients. Along with traditional factors, such as age, sex, dyslipidemia, additional risk factors in patients of this group should be taken into account [3-5]. This is a chronic inflammatory background, a side effect of glucocorticosterides leading to atherogenic changes in the lipid spectrum. The lipid spectrum in RA patients is characterized by an increase in triglyceride levels (TG) and a decrease in the concentration of high-density lipoprotein cholesterol (HDL), an increase in the atherogenicity factor. It was also proved that high levels of Cholesterol LDL and triglyceridemia are serious risk factors for atherosclerosis and CHD [6,7].

Such peculiarity of the ratio of lipoprotein fractions is typical for inflammatory diseases, the prescription of prednisolone also plays a certain role.

There is evidence that, besides the hypolipidemic effect, statins also have anti-inflammatory and immunomodulatory effects. These effects are manifested in the reduction of C-reactive protein, which plays an important role in chronic inflammatory diseases, particularly in RA. The results of several randomized studies earlier showed a modest effect of statins in reducing the activity of the inflammatory process in RA. However, large-scale trials have not confirmed the efficacy of using statins to treat this disease (8).

In addition to statins, fibroic acid derivatives (fibrates) have been used in the treatment of dyslipidemia in clinical practice for over 60 years. Fibrates activate the nuclear receptors of PPAR-a (peroxisome proliferator-activated receptor) hepatocytes, which through a number of complex mechanisms increases the activity of lipoproteinlipase. Fibrates mainly reduce the level of an empty stomach TG, moderately reduce the level of cholesterol LDL, increase the level of cholesterol HDL. They also change the composition of small atherogenic particles of LDL, as a result of which the latter are enlarged and their atherogenicity decreases. Finally, fibrates stimulate the reverse transport of cholesterol and increase bile acid synthesis in the liver.

The main indications for prescription of fibrates are dyslipoproteidemia of IIb, IV, V types in combination with low level of cholesterol LDL in patients with metabolic syndrome, diabetes mellitus of type 2, familial combined hyperlipidemia and familial endogenous hypertriglyceridemia (HTG) [8].

Against the background of intensive research and increasing use of statins in modern medicine, fibrates appeared as if "in the shadows". However, with the accumulation of epidemiological data and clinical experience, it becomes clear that the final refusal to study and use fibrates would be premature.

Numerous studies emphasize the important role of traditional risk factors in the development of atherosclerotic vascular lesions in RA. According to our data, hyperlipidemia/dyslipidemia is the most frequent risk factor for cardiovascular diseases in young RA patients.

Objective: To study lipid profile disorders and efficacy of phenofibrate (Lipidex SR) in young RA patients with methotrexate (MT) treatment.

Materials and methods of research: We examined 102 patients of RA who are inpatient in the rheumatology department of the first clinic of Tashkent Medical Academy. Diagnosis of RA has been verified on the basis of classification criteria proposed by the American College of Rheumatologists (ACR) in 1987 and/or criteria of ACR/European Anti-Rheumatic League (EULAR) in 2010. The control group consisted of 110 healthy middle-aged individuals.

Among the examined, 10 (9.8%) were male, 92 (90.2%) were female and more than half (54%) were young patients under 30. The age approach for younger patients was related to taking into account the increase in cardiovascular disease in older patients.

In the surveyed population, those with 1 to 5 years of age were the largest group (38.3%), followed by those with 5 to 10 years of age (34%).

In 66.3% of the patients of RA MT was used as a base preparation. The average dose (median) of MT over the study period was 10 mg per week. 80% of patients took prednisolone in an average dose of 10 mg/day.

The lipid spectrum indicators were analyzed in the examined patients who received MT during 3 years.

The content of lipids in venous blood was determined by photocolometry on Vitros SYSTEM Chemistry DT 60 biochemical analyzer (Austria).

The results of the research. The indices of lipid metabolism in the general population of RA patients are presented in Table 1.

Table 1.: **Lipid profile indices in patients' rheumatoid arthritis (M±m)**

Indicators	**Control (n=110)**	**RA patients (n=102)**
General Cholesterol	4,82 ± 0,331	5,87 ± 0,250*
TG	1,90 ± 0,072	2,61 ± 0,224*
Cholesterol LDL	1,24 ± 0,130	2,17 ± 0,231*
Cholesterol HDL	2,21 ± 0,141	0,92 ± 0,152*
Cholesterol VLDL	0,67 ± 0,050	1,03 ± 0,064*
Atherogenicity ratio	1,79 ± 1,048	3,41 ± 0,645

*Note: * P<0.01 valid difference with control group*

As can be seen from the table, the study of the lipid profile in the main group showed an increase in the amount of total serum cholesterol by 17.9%; triglycerides by 27%; Cholesterol LDL by 43%, with Cholesterol HDL decreasing by 58%; atherogenicity ratio in the population increased 1.9 times. It is known that reduction of Cholesterol HDL is a serious risk factor of atherosclerosis development.

We have also analyzed lipid spectrum indicators in RA patients in the age aspect (Table 2).

Table 2: **Age-related lipid profile of rheumatoid arthritis patients (M±m)**

Indicators	**Control (n=110)**	**Age (y.o.)**	
		20-30 y.o. (n=48)	**30-40 y.o. (n=47)**
General cholesterol	4,82 ± 0,331	5,11 ± 0,137	5,61 ± 0,440
TG	1,90 ± 0,072	2,14 ± 0,179	2,71 ± 0,421*
Cholesterol LDL	1,24 ± 0,130	1,56 ± 0,257	2,13 ± 0,204*
Cholesterol HDL	2,21 ± 0,141	0,97 ± 0,299*	0,89 ± 0,139*
Cholesterol VLDL	0,67 ± 0,050	0,94 ± 0,108*	1,64 ± 0,065*
Atherogenicity ratio	1,79 ± 1,348	2,63 ± 0,542*	3,62 ± 1,169*

*Note: * P<0.05 valid difference with control group*

As can be seen from the table above, lipid metabolism indices depended on the age of patients. Thus, the most reliable difference was noted for Cholesterol VLDL ($P < 0.05$). Other indicators had an upward trend: General cholesterol - by 9%, TG - by 26.6%, Cholesterol LDL - by 27%, while Cholesterol HDL, on the contrary, was low in older persons than in the age of 20-30 years (by 8.3%) and, accordingly, the atherogenicity coefficient was significantly higher in persons aged 30-40 years (27.3%). This situation in RA patients is somewhat incompatible with the data of healthy people. This is probably due to the rapid onset and rapid progression of the disease, especially with seropositive forms.

In this context, age, in the disease's debut, is also of interest, as physiological changes in the lipid profile are not observed or are minimal at younger ages.

According to the analysis of these indicators, at the age of 17-20 years (the juvenile form of RA is not included in the study) the increase of the ECS by 7.7% and the increase of the lipid-triglyceride high-atherogen fraction by 41.1% were observed in comparison with the control, although other fractions have changed insignificantly (Table 3).

Table 3: **Lipid profile indices in rheumatoid arthritis patients depending on age, debut disease (M±m)**

Indicators	**Control (n=110)**	**age, onset of illness (years)**		
		under 20 years old (n=30)	**20-30 y.o. (n=60)**	**30-40 y.o (n=12)**
General cholesterol	4,82±0,331	5,19±0,314	5,23±0,146	5,90±0,262*^
TG	1,90±0,072	3,23±0,582*	2,41±0,258	2,61±0,393
Cholesterol LDL	1,24±0,130	1,89±0,483	2,35±0,258*	3,07±0,388*
Cholesterol HDL	2,21±0,141	1,02±0,462	0,88±0,240*	0,64±0,204*
Cholesterol	0,67±0,050	1,48±0,107*	1,1±0,084	1,19±0,087*

VLDL				
Atherogenicity ratio	1,79±1,348	2,85±0,321	3,44±0,394	4,19±0,287

*Note: * P<0.05 valid difference with control group*

^ P<0.05 reliable difference between groups of onset age 20-30 and 30-40 years old

It proves the opinion of E.L. Nasonov and others that the defeat of the cardiovascular system starts from the moment of the development of the RA. From this stance, the dependence of lipid shifts on disease duration is of practical interest (Table 4).

Table 4: **Indexes of lipid fractions in patients with rheumatoid arthritis depending on the age of the disease (M±m)**

Indicators	**Control (n=110)**	**disease history (years)**			
		Up to 1 year (n=17)	**1-5 years (n=39)**	**5-10 years (n=34)**	**More than 10 years (n=12)**
General cholesterol	4,82 ± 0,331	4,80 ± 0,252	4,93 ± 0,265	5,33 ± 0,342	5,76 ± 0,471
TG	1,90 ± 0,072	2,42 ± 0,481	2,04 ± 0,347	2,79 ± 0,244*	3,75± 0,189*^•$^{+}$
Cholesterol LDL	1,24 ± 0,130	1,88 ± 0,447	2,16 ± 0,791	2,33 ± 0,264	2,49 ± 0,887
Cholesterol HDL	2,21 ± 0,141	0,81 ± 0,519	0,83±0,235*	0,73 ± 0,221*	0,54 ± 0,113*
Cholesterol VLDL	0,67 ± 0,050	1,11± ,135*	0,93±0,033*	1,27±0,068•	1,72± 0,040*•
Atherogenicity ratio	1,79 ± 1,348	3,25 ± 0,341	3,45 ± 0,126	4,08 ± 0,551	4,74 ± 0,620^•

*Note: * P<0.05 valid difference with control group*
^ P < 0.05 reliable difference with the group of prescription of disease up to 1 year
- P<0.05 reliable difference with the group of 1 to 5 years' old
+P < 0.01 reliable difference with the group of 1 to 5 years' old

According to the data presented in the table, with the limitation period up to 1 year, there was a selective increase of Tg by 15%, increasing in parallel with the increase of the disease limitation period, achieving reliable differences not only with the control, but also with the initial period of RA. Very pronounced and in most cases reliable decrease was noted in the indicators of Cholesterol HDL (P<0,05), which indicates the emergence of stable dyslipidemia against the background of relatively calm situation on the part of atherogenicity coefficient indicators. Consequently, the duration of the disease affects the lipid profile more negatively than the age of the patient.

The severity of the RA flow and the prognosis of the disease largely depend on the presence of rheumatoid factor in the blood of RA patients. Rheumatoid factor is an aggregated pathological immunoglobulin G, which carries a degree of immunoactivity. In the study of the blood lipid spectrum of RA patients, some differences in the lipidogram were also found depending on the seroprinciple belonging (Table 5).

Table 5: **Dependence of blood lipid spectrum in patients with rheumatoid arthritis depending on immunological affiliation (M±m)**

Indicators	**Control (n=110)**	**Immunological affinity**	
		seropositive (n=67)	**seronegative (n=35)**
General cholesterol	4,82 ± 0,331	5,35 ± 0,510	5,17 ± 0,445
TG	1,90 ± 0,072	2,65 ± 0,289*	2,39 ± 0,245*
Cholesterol LDL	1,24 ± 0,130	1,89 ± 0,366*	1,62 ± 0,290
Cholesterol HDL	2,21 ± 0,141	0,90 ± 0,207*	1,32 ± 0,184*^
Cholesterol VLDL	0,67 ± 0,050	1,46 ± 0,079*^	1,06 ± 0,059
Atherogenicity ratio	1,79 ± 1,348	3,87 ± 0,21*	2,76 ± 0,012*^

*Note: * P<0.05 valid difference with control group*

^ P<0,05 reliable difference between seropositive and seronegative groups

It should be noted that no reliable differences were found in the content of General cholesterols, also in Tg, Cholesterol LDL s, whereas in the content of Cholesterol HDLs there was a reliable decrease by 1.4 times (P < 0.05), and an increase in Cholesterol VLDLs by 1.4 times (P < 0.05), which indicates an imbalance towards an increase in the risk of atherogenicity and is also confirmed by a 20% increase in the atherogenicity factor.

Taking into account the fact that against the background of MT therapy in RA patients hyper- and dyslipidemia, which is a proatherogenic factor, increases, we studied the efficacy of phenofibrate (lipidex SR, 250 mg), which acts along with other fractions for atherogenic hypertriglyceridemia. IIB-IV type of dyslipidemia according to Fredrikson was performed in 68 patients who received prolonged MT more often.

Fat hepatosis was also detected in 58% of the RA patients receiving MT, during the ultrasound of the liver.

Patients receiving MT were divided into 2 groups: Group I (n=30) - patients receiving MT + phenofibrate (SR lipidex) of 250 mg 1 time in the evening after meals for 1 month, Group II (n=38) - patients receiving MT (without phenofibrate).

The study on the dynamics of lipid metabolism indices revealed the following (Table 6): the group of patients receiving lipidex SR showed a 17.1% decrease in the level of General cholesterol (P<0.05), while this index increased in the 2nd group by 18.9% compared to the control (P<0.05). An important shift was observed on the part of TG in Group I, this indicator compared to Group II has decreased by 29.7% (P<0.05) and practically did not differ from the control indicators (Table 6).

Table 6: **Impact of phenofibrate on lipid indicators rheumatoid arthritis (M±m) patients**

Indicators	**Control (n=110)**	**MT (n=38)**	**MT+ pheno-fibrate (n=30)**
General cholesterol	4,82 ± 0,331	5,94 ± 0,130*	4,92 ± 0,210^
TG	1,90 ± 0,072	2,73 ± 0,320*	1,92 ± 0,012^
Cholesterol LDL	1,23 ± 0,130	3,03 ± 0,210*	2,69 ± 0,219*
Cholesterol HDL	2,21 ± 0,141	0,75 ± 0,114*	1,18 ± 0,115*^
Cholesterol VLDL	0,67 ± 0,050	0,91 ± 0,041	0,78 ± 0,219
Atherogenicity ratio	1,79 ± 1,348	4,24 ± 0,140*	1,67 ± 0,826^

*Note: * - valid difference with control group*
^ - reliable difference between groups of MT and MT+ phenofibrate

In the I group decrease of Cholesterol LDL indexes was noted by 11%, Cholesterol HDL in the I group - by 37,7% (P<0,05). At the same time, if in Group II the atherogenicity coefficient increased by 4,6 times, then in Group I, on the contrary, reliably decreased in comparison with Group II by 60,6% (P<0,05) (Fig. 1).

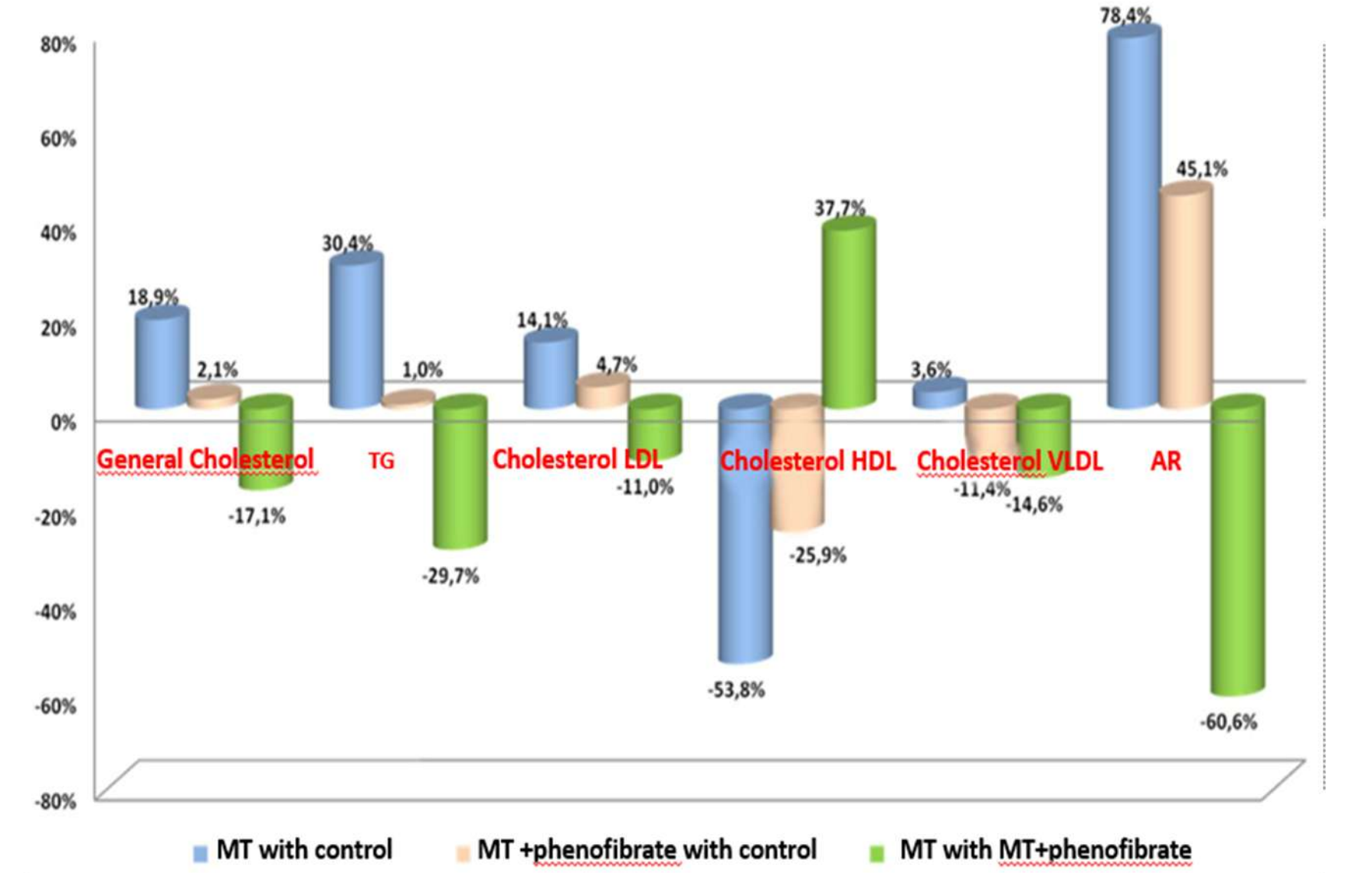

Fig. 1. Comparative efficacy of phenofibrate (SR lipidex) in rheumatoid arthritis patients with methotrexate treatment

It is worth mentioning that the main hypolipidemic effect of lipidex SR is based on a decrease in the synthesis and mobilization of free fatty acids, as well as a decrease in General cholesterol and an increase in Cholesterol HDL.

Conclusion.

Thus, in RA patients of young age when using MT there is a reliable increase in the level of Tg, Cholesterol VLDL, a decrease in Cholesterol HDL with an increase in the atherogenicity coefficient, which indicates the proatherogenic effect of the MT base drug against the background of a pronounced fatty hepatosis of the liver.

Correction of lipid disorders in RA patients against the background of MT treatment should be carried out not so much from the point of view of clinical lipidology as from the point of prevention of cardiovascular diseases.

Fibrates have a favorable effect on all components of atherogenic dyslipidemia and can reduce the risk of cardiovascular disasters in RA.

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