Lipid Profile Changes in Rheumatoid Arthritis Patients: Investigation of Different Affecting Factors

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Abstract- It has been proved that rheumatoid arthritis (RA) is linked to dyslipidemia and the risk of cardiovascular complications is higher in these patients. The aim of this study was to evaluate dyslipidemia in RA patients. In this study, RA patients were enrolled regarding the inclusion and exclusion criteria. Their demographic information and medication profiles were evaluated. Clinical assessments were performed by evaluation of disease activity score (DAS28) and visual analogue scale. Moreover, laboratory investigations of lipid profile including triglycerides (TG), total cholesterol (Chol), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were performed. From a total of 150 patients with the mean age of 54.9±16.8 years, 65.3% were diagnosed with dyslipidemia. Females in menopausal ages had a higher prevalence of dyslipidemia as well as patients with longer disease duration. Mean serum HDL, LDL, Chol, and TG were 52.76±13.8, 96.65±21.6, 177.26±38.9, and 128.04±33.9, respectively. Considering DAS28, 100% of the patients with high disease activity were diagnosed with dyslipidemia. In the moderate and low disease activity groups and also patients in remission, the ratio was 77.02%, 66.66%, and 43.75%, respectively. According to the results, patients under treatment with prednisolone and methotrexate were more affected by dyslipidemia than those with prednisolone, methotrexate, and hydroxychloroquine. Moreover, in the patients under prednisolone, methotrexate, and leflunomide treatment, the prevalence of dyslipidemia was significantly lower than those used only prednisolone and methotrexate. Altogether, it is necessary to have more clinical suspicion towards dyslipidemia and its complications in the patients with a greater number of affecting factors.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease diagnosed mostly by presenting articular manifestations. This pathology with a prevalence of 0.5-1% in general population is more common in females (1). So far, the main pathogenesis of RA is unknown, but it seems that both genetic and environmental factors are involved (2). Similar to other chronic diseases, RA is accompanied by inflammation which has made the main target for therapeutic agents (3). Although RA is mostly known for its particular presentations, skin, ocular, and cardiac manifestations are also expectable (4).

Nowadays, cardiovascular diseases (CVD) are known as the leading cause of death worldwide (5). The most common type of CVD is atherosclerosis which is a chronic inflammatory condition (6). Interestingly, it has been showed that both CVD and RA have similar pathways of inflammation (7). Furthermore, mortality caused by CVD is more common (up to 50% higher) in RA patients compared to a normal population which makes it the most common cause of death among these patients. This increase in mortality rate is caused by the higher risk of myocardial infarction (MI) and stroke in RA population which is attributed to CVD and mainly atherosclerosis (8). Furthermore, it has been shown that

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MI risk due to CVD in RA patients is 200% (2 folds) higher compared to age and sex-matched controls (9). Taken together, it seems that CVD is a serious issue in patients diagnosed with RA since it increases the risk factors involved (7-9). Remarkable risk factors for atherosclerosis are male gender, high serum total cholesterol (Chol), low-density lipoprotein (LDL), low serum high-density lipoprotein (HDL), aging, diabetes, high blood pressure, and smoking. According to the data, some of these risk factors are more prevalent in RA patients than the normal population which makes them more prone to CVD (8). It seems that higher prevalence of CVD in RA patients also results from different associating factors with RA such as type II diabetes mellitus, positive family history of CVD, smoking, low physical activity, and impaired lipid profile. To sum up, it seems that impaired lipid profile is one of the most important causes of CVD in RA patients (10).

The aim of this study was to investigate the prevalence of dyslipidemia in RA patients and to evaluate any possible relation between types of medication and dyslipidemia.

Materials and Methods

Patient selection

This cross-sectional study was conducted between September 2014 and September 2015 in Vali-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran. Medical Ethics Committee of the hospital approved this study. RA patients diagnosed based on criteria from American College of Rheumatology (ACR) (11), aged more than 18-year-old were enrolled in this study using simple random sampling. The exclusion criteria were defined as any other metabolic diseases that affect lipid profile such as diabetes mellitus, hyperlipidemia and thyroid dysfunction as well as smoking, previous history of smoking, using lipid-lowering medications, and low medication adherence. All the patients signed a consent form freely after being explained about the aim and methods of the study according to their level of knowledge.

Clinical assessments

Patients' demographic information, disease duration, drug history, and disease activity score (DAS28) were evaluated. For calculation of DAS28 score, we considered swollen and tender joints, erythrocytes sedimentation rate (ESR) and visual analogue score (12). In this evaluation any score ≤ 2.6, $2.6 <$ score ≤ 3.2, $3.2 <$ score ≤ 5.1, and <5.1 were considered as remission, low disease activity (DA), moderate DA and high DA, respectively.

Para-clinical assessments

Laboratory makers such as serum total Chol, triglyceride (TG), LDL and HDL were evaluated after 12-hour fasting. Normal values considered as follows: LDL <100 mg/dl, TG <150 mg/dl, total cholesterol <200 mg/dl, and HDL >50 mg/dl. Also, both ESR and C-reactive protein (CRP) serum levels were evaluated. All the laboratory tests were done by the same laboratory expert using the same kits and methods for each parameter. All the kits were provided from Merck Chemi Co™.

Statistical analysis

All the statistical analyses were performed using Statistical Package for Social Sciences version 22.0 (SPSS, Inc., Chicago, IL, USA). For all parameters, mean and standard deviation were calculated. A $P<0.05$ was considered statistically significant.

Results

In this study, 150 patients who met both inclusion and exclusion criteria were enrolled, from which, 131 (87.3%) and 19 (12.7%) cases were female and male, respectively. According to the results, RA affected women by 6.8 folds more than men. Considering the previously mentioned dyslipidemia criteria, 98 patients (65.3% of total cases) were diagnosed with dyslipidemia among whom 85 (86.7%) and 13 (13.3%) were women and men, respectively. The incidence of dyslipidemia among the gender groups were 64.9% and 68.4% of all females and males with RA. Mean serum levels for HDL, LDL, total Chol and TG were 52.76±13.8, 96.65±21.6, 177.26±38.9, and 128.04±33.9, respectively. Prevalence of these items in men and women are collected in table 1.

The patients aged between 28 and 81 with the mean of 54.9±16.8 years. The most prevalent ratio of affected patients with dyslipidemia was detected in the range of 66-75 years (100% of patients were in this age group). Prevalence of dyslipidemia in the other age groups is shown in table 2. Duration of disease among patients was between 1 and 20 years with the mean of 7.74±4.9. Prevalence of dyslipidemia in a different period of disease duration is shown in table 2.

Table 1. Mean of lipid profile according to the gender

	Female	Male	Both gender
HDL	53.77±13.95	45.78±12.73	52.76±13.87
LDL	96.96±21.72	94.97±21.65	96.65±21.68
TG	128.16±33.94	127.21±33.96	128.04±33.94
Total Cholesterol	177.99±38.97	177.21±38.97	177.26±38.79

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride

Table 2. Prevalence of dyslipidemia in different ages and disease duration

Age (year)	Prevalence of dyslipidemia	Duration of disease (years)	Prevalence of dyslipidemia
25-35 (N=23, 15%)	34.78% (N=8)	1-5 (N=70, 47%)	55.71% (N=39)
36-45 (N=39, 26%)	71.79% (N=28)	6-10 (N=46, 30%)	65.21% (N=30)
46-55 (N=49, 33%)	53.06% (N=26)	11-15 (N=21, 14%)	85.71% (N=18)
56-65 (N=25, 17%)	92% (N=23)	16-20 (N=13,9%)	84.61% (N=11)
66-75 (N=11, 7%)	100% (N=11)	--	--
76-85 (N=3, 2%)	66% (N=2)	--	--

As mentioned before, the disease activity was evaluated by DAS 28. Prevalence of patients in remission phase, low, moderate, and high disease activity were 48 (32%), 24 (16%), 74 (49.3%), and 4 (2.7%), respectively. According to this classification, in the high disease activity group, 100% of cases were diagnosed with dyslipidemia, but in the moderate and low disease activity groups and patients in remission, the ratios were calculated 77.02%, 66.66%, and 43.75%, respectively.

As mentioned before, the effects of different medications on RA patients' lipid profile were analyzed in this study. The most prevalent type of treatment was the combination of prednisolone, methotrexate, and hydroxychloroquine (N=96, 64%) and 63.54% of patients under this combination therapy were diagnosed with dyslipidemia (Table 3). According to the results, the patients under treatment of prednisolone and methotrexate were more affected by dyslipidemia than those receiving prednisolone, methotrexate, and hydroxychloroquine (P<0.05). Moreover, in patients using prednisolone, methotrexate, and leflunomide, the prevalence of dyslipidemia was significantly lower than patients consumed only prednisolone and methotrexate (P<0.05).

Table 3. Prevalence of dyslipidemia in different groups of medications

Medication(s)	Number of patients	Prevalence of dyslipidemia
Prednisolone, methotrexate, and hydroxyl-chloroquine	96	63.54% (N=61)
Prednisolone and methotrexate	31	74.19% (N=23)
Prednisolone, methotrexate, and leflunomide	9	55.55% (N=5)
Prednisolone and hydroxyl-chloroquine	2	0%
Prednisolone and sulfasalazine	1	100% (N=1)
Prednisolone, methotrexate, and sulfasalazine	4	50% (N= 2)
Prednisolone, hydroxyl-chloroquine, and sulfasalazine	2	50% (N=1)
Prednisolone, methotrexate, hydroxyl-chloroquine, and Sulfasalazine	1	100% (N=1)
Prednisolone	1	100% (N=1)
No medication	3	100% (N=3)

Discussion

According to the literature, patients with RA are more susceptible to dyslipidemia and atherosclerosis (and its complications such as CVD) due to the impaired lipid profile in comparison to the normal population (13). Thus, it is very important to investigate any possible mechanism that may affect lipid profile in them. In this study, we intended to assess dyslipidemia in RA patients by categorizing them into the different groups according to the different variables such as age, sex, disease duration, and types of medications consumed. It is important to consider all the variables such as age in this study since it has been proved to significantly increase CVD(14). As the results showed, the patients' mean age in the current study was 54.9±16.8 which was the same as the other studies (15,16). Also, 87.33% and 12.66% of patients were female and male, respectively. This clearly

affirms that RA is more common in women than men as expected. Moreover, according to the epidemiological investigations, females, especially those in menopausal status, are more susceptible to impaired lipid profile which strongly increases the risk of atherosclerotic events (17). In this study, it was shown that 92% and 100% of females with the age ranges of 56-65 and 66-75, respectively (menopausal ages) were diagnosed with dyslipidemia (Table 2). In a general aspect, the prevalence of dyslipidemia in our patients was 65.3% which was similar to Nisar *et al.*,'s study (18). Also, the serum levels of HDL, LDL, TG, and total cholesterol almost were similar to another study by Vijaykumar *et al.*, (19). The cause of changes in lipid profile is still unclear, but there are some hypotheses proposed to describe this phenomenon. It seems that different polymorphisms such as REL (c-Rel) polymorphism have been shown to affect LDL levels. Also, interleukin 6 (IL-6) which is an inflammatory cytokine is able to induce lipoproteins abnormalities. This interleukin has been shown higher in RA patients with lower HDL levels (20). However, other mechanisms such as endothelial injury and accelerated inflammation of endothelial cells due to systemic inflammation (21) could be considered critical in these patients,

Considering the provided results in table 2, it looks like as disease duration increased in RA patients, so did the prevalence of dyslipidemia. This result is also stated in the other studies (22). Furthermore, as it is shown in table 2, in older age groups, the prevalence of dyslipidemia has been increased. As our results demonstrate, this increase may be caused by aging which is considered a risk factor for lipid profile disorders (23) as well as prolonged disease duration (prolonged inflammation) (24). Thus, it could be hypothesized that both aging and disease duration are possible risk factors of dyslipidemia in RA patients. However, due to the decrease in the age range of 76-85 years, this hypothesis may be confounded, although this age group only consisted of only three patients.

In the current study, the prevalence of dyslipidemia was evaluated in different disease activities measured by DAS 28. As mentioned in the results, patients with higher disease activity score had more lipid abnormalities. A higher ratio of dyslipidemia in RA patients with higher disease activity is proved by other studies as well (25,26). It seems that in patients with higher disease activity, inflammation is more bolded than other cases and exposure to higher amounts of inflammatory cytokines in this situation is responsible for the higher prevalence of dyslipidemia in RA cases.

Also as mentioned in the results, patients consuming hydroxychloroquine had less prevalence of dyslipidemia in comparison to others. Thus, it could be concluded that hydroxychloroquine is a protective agent in these patients which is also proved by Morris *et al.*,'s study (27). In their study, it was showed that hydroxychloroquine is able to reduce LDL, TC, TG and it also increases HDL levels (27). Generally, disease-modifying antirheumatic drugs (DMARDs) are introduced to improve the lipid profile, or at least, not to affect lipid profile (20).

It has been demonstrated in patients with systemic lupus erythematosus that women consuming prednisolone had impaired lipid profile in comparison to the same patients who did not receive this medication (28). Moreover, methotrexate alone has been determined to impair lipid profile of patients with RA (29). On the other hand, hydroxychloroquine is affirmed to improve lipid profile in different metabolic and inflammatory diseases (30,31).

In conclusion, we found that the prevalence of dyslipidemia is notably higher in RA patients. Impairment of lipid profile in this survey was shown by decreased HDL and increased LDL, TG and total cholesterol levels. Taken together these findings, authors strongly recommend controlling lipid profile in RA patients. Also, according to the results, in RA patients with higher disease activity index, lipid profile impairment was more frequent. Therefore, it seems only reasonable to treat RA patients to decrease the risk of hyperlipidemia as a cardiovascular risk factor. Somehow, more case-control studies with a higher number of patients should be done to confirm our results. Also, we found out that the patients using hydroxychloroquine or leflunomide had lower rates of dyslipidemia compared to others. Accordingly, we suggest using or adding these medications to control both lipid profile and disease activity as a "one stone two birds" method for the treatment of RA patients. All suggested treatment opinions in this paper, of course, need clinical trials which authors strongly recommend.

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