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Correlation between lipid profile and lipoprotein (a) with inflammatory activity of rheumatoid arthritis

Zahra Rezaieyazdi[1], Marziyeh Maghrebi[1], Kamila Hashemzadeh[1], Mohammad-Reza Hatef[1], Habibollah Esmaily[1], Mandana Khodashahi[1*]

[1]Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

The current study aimed to assess the correlation between lipoproteins, in particular lipoprotein a [Lp (a)], and inflammatory activity in rheumatoid arthritis (RA).

This retrospective case control study was conducted over a period of 6 months and studied two groups, RA patients (n = 70) and healthy control subjects (n = 52), who were matched by age and gender (*P* value < 0.005). The modified Health Assessment Questionnaire (MHAQ) was employed by self-administration. Fasting lipid profiles including LDL, HDL, total cholesterol, triglycerides, and Lp (a) were assayed, and the findings for the two studied groups were compared using the Student t test.

Thirty-two patients in the RA group (45.71%) and 27 subjects in the control group (51.92%) had abnormally high Lp (a) levels (*P* value = 0.57). Mean serum Lp (a) values between the RA and control groups were significantly different (*P* value = 0.79). Serum Lp (a) had no significant correlation with ESR (r = 0.27, *P* value = 0.028). No significant correlation was found between Lp (a) level and MHAQ (r = 0.11, *P* value = 0.37). Serum Lp (a) was also found to have no significant relationship with other laboratory parameters (CRP and RF) or clinical indices of RA activity (functional class and morning stiffness duration).

No correlation was observed between serum Lp (a) and clinical/laboratory indices of RA activity other than a weak one with ESR. It is not recommended to use routine serum Lp (a) measurements to assess RA severity.

Keywords: Arthritis, Inflammatory Activity, Lipids, Lipoproteins, Lipoprotein (A), Rheumatoid Arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disorder of unknown etiology manifested by symmetric, erosive synovitis, and usually multi-organ involvement [1, 2]. Epidemiologic studies have shown an increased premature mortality and loss of life expectancy in patients diagnosed with RA when compared with the general population. Chronic inflammation and development of pro-atherogenic agents such as lipids are the main underlying mechanisms of the observed higher mortality. Several experts have noted increased cardiovascular disease-related morbidity and mortality in active RA patients [3, 4]. In support of these observations, adding statins to standard routine agents used for RA patients can decrease RA activity [5].

There is evidence in the literature that inflammation in RA might cause an altered lipid metabolism. This adverse consequence can potentially accelerate atherosclerosis [6]. Lipoprotein (a) (Lp (a)) is a plasma lipoprotein consisting of an LDL-like particle. Lp (a) is linked to apoB-100 through disulphide bonds. Because of its structure, Lp (a) is postulated to perhaps have both pro-atherosclerotic and pro-thrombotic actions. Although Lp (a) is also suggested to act as an acute-phase reactant in certain situations, such as surgical interventions or after acute myocardial infarction (MI), this remains to be clarified [7].

The goal of this clinical study was to assess the pattern of lipoproteins in RA patients and investigate the relationship between Lp (a) and inflammatory activity. We also intended to explore whether Lp (a) acts as an acute-phase reactant in RA.

Materials and Methods

Study design and setting

This retrospective case control study was performed on RA patients referring to the Internal Ward (Academic Rheumatology Center) of Ghaem Hospital and private clinics of Mashhad, Iran.

*Corresponding Author: Mandana Khodashahi, MD, Assistant Professor of Rheumatology, Rheumatic Diseases Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Email: khodashahimn@mums.ac.ir, Tel/Fax: (+98)051-38012753, 38401036 Po Box: 9176699199.

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Study population

All RA patients who referred to our academic rheumatology clinic during the study period were eligible for inclusion in the study. RA was diagnosed using the revised criteria for RA proposed by the American College of Rheumatology [8]. Exclusion criteria were ischemic heart disease (IHD), stroke, thrombotic events, familial hyperlipidemia, diabetes mellitus, and malignancy or any sign of kidney, liver, thyroid or other inflammatory diseases. In addition, those who were receiving prednisolone > 12.5mg/day, statins, estrogenic drugs, or other medications with known effects on lipoprotein metabolism were not included.

Sample

The sample size was determined to be 44 cases in each group based on previous reports on the levels of serum lipoprotein and lipids in patients with RA (p1 = 0.39) and healthy controls (p2 = 0.140) [8] using a power of 80% and a confidence level of 95%.

A total of 70 RA patients were entered into the case group through purposive sampling. The number of patients included was higher than the estimated sample size to ensure the validity of the outcome. Of these patients, 62 were female. The mean (SD) age of the patients was 51 (±11) years (range, 17-80 years). The mean (SD) BMI was 27 (±4) kg/m2. Most patients (91.1%) were receiving corticosteroids (prednisolone, < 12.5mg daily), 75% were receiving remission-inducing drugs (methotrexate and hydroxychloroquine), and 88.9% were receiving both corticosteroid and remission-inducing drugs. About 33.3% of the patients were taking NSAIDs.

Control subjects were recruited from among patients presenting at our clinic during the study period with non-specific musculoskeletal complaints for whom RA as well as other autoimmune connective tissue diseases had been excluded. Two patients were removed at the end stage of this study due to their dissatisfaction with continuing the study. The control group consisted of 52 non-obese subjects (11 men and 41 women) who were matched to the RA group by age, gender, weight, and height. Mean (±SD) values of age and BMI in the control group were, respectively, 55 (±10) years and 26 (±3) kg/m2. Exclusion criteria for the control group were familial hyperlipidemia and cigarette smoking.

Data collection

Morning stiffness, visual analogue scale for pain (VAS) for pain, the modified Health Assessment Questionnaire (MHAQ), and functional status were examined in RA patients.

Laboratory assays

Venous blood samples were taken in the early morning to measure fasting lipid profiles. Blood was allowed to clot 45 min at room temperature; serum was obtained immediately by centrifugation and stored at -70 ºC until analysis. Total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglyceride levels were determined with the enzymatic colorimetric method (Randox Technologies reagent kits, UK). Lp (a) was measured using the enzyme-linked immunosorbent assay (ELISA) method. The normal range of Lp (a) was 1.8-3.0 mg/dl. A level higher than 30 mg/dl was considered abnormal according to the manufacturer's instructions. Erythrocyte sedimentation rate (ESR) was measured by the Westergrin method, and C-reactive protein (CRP), rheumatoid factor, white blood cells, platelets and hemoglobin were measured by routine methods.

Statistical analyses

Descriptive indices including frequency, percentage, mean, and standard deviation (SD) were used to express the data. Normal or non-normal distribution of quantitative variables was assessed with a combination of the statistical test (the Kolmogorov-Smirnov test) and histograms. The lipid profile findings of the two studied groups were compared using the Student t test when the distribution of data was normal or the Mann Whitney U test when it was abnormal. Correlations between the continuous variables were analyzed using the Pearson's correlation test. Spearman correlation coefficients were calculated to assess the relationships between variables if the variables were non-parametric. A level of P value < 0.05 was considered statistically significant. Analyses were done using SPSS software (ver. 20.0, IBM, US).

Ethics

First, the study objectives were explained to the subjects. Then, informed consent to participate was obtained from each subject prior to enrollment. Participation was on a voluntary basis. The study proposal was approved by the Ethics Committee of the Research Deputy of our university. The study protocol details were in agreement with the Declaration of Helsinki.

Results

Lipid profile

Table 1 presents the comparison of lipoproteins between the studied groups. A significant difference was observed between the two groups in terms of TC/HDL-C (P value < 0.001). Moreover, LDL-C/HDL-C was significantly different between RA patients and the control group (P value = 0.001). Mean LDL-C was considerably higher in the RA group than in the control group (P value < 0.001). There was no statistically significant difference in the mean values of serum Lp (a) between the two groups (P value = 0.64).

Table 1. Comparison of lipid profile in rheumatoid arthritis (RA) patients and control group

Variables	RA (N = 70)	Control (N = 52)	*P* value
TC, mg/dl	198.5 (±44.2)	223.2 (±44.7)	0.003
LDL-C, mg/dl	118.9 (±38.4)	136.8 (±44.9)	0.019
HDL-C, mg/dl	50.51 (±11.0)	46.69 (±15.9)	0.004
TC/HDL-C	4.06 (±1.06)	5.14 (±1.72)	< 0.001
LDL-C/HDL-C	2.45 (±0.89)	3.20 (±1.40)	0.001
Triglyceride, mg/dl	142.8 (±70.5)	188.7 (±96.7)	0.007
Lp(a),mg/dl	19.2 (±30.0)	18.9 (±31.41)	0.64

Data are presented as mean (±standard deviation); Abbreviations: TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; Lp (a) = lipoprotein a

Correlation of serum Lp (a) with inflammatory markers

Serum Lp (a) had no significant correlation with ESR (r = 0.27, *P* value = 0.028). It was noted that serum Lp (a) had no associations with other laboratory parameters or clinical indices of RA activity (Table 2). ESR correlated negatively with HDL-C (r = -0.28, *P* value = 0.019). There were no significant correlations between ESR and other lipid profiles such as TC, triglycerides, LDL, TC/HDL, or LDL/HDL. No significant correlation was found between serum CRP levels and any lipid profile. Duration of morning stiffness correlated negatively with HDL-C (r = -0.315, *P* value = 0.039).

Table 2. Correlations between lipid profile and clinic-laboratory parameters in rheumatoid arthritis patients

Variables		TC	TG	LDL	HDL	Lp(a)	TC/HDL	LDL/HDL
ESR, mm/h	r	-0.14	-0.12	-0.12	0.14	0.12	-0.14	-0.14
	P value	0.17	0.23	0.23	0.18	0.26	0.16	0.17
CRP, mg/dl	r	0.09	0.15	0.09	0.03	-0.22	0.12	0.144
	P value	0.54	0.34	0.56	0.83	0.15	0.43	0.36
Morning stiffness(min)	r	-0.106	0.22	-0.06	-0.31	-0.11	0.29	0.18
	P value	0.497	0.14	0.68	*0.03	0.49	*0.05	0.24
RF,U/L	r	-0.16	-0.32	-0.09	0.23	-0.07	-0.25	-0.2
	P value	0.109	*0.002	0.37	*0.02	0.47	*0.01	0.058
MHAQ(0-3)	r	-0.03	0.29	-0.12	-0.23	0.11	0.26	-0.01
	P value	0.75	*0.01	0.29	0.058	0.37	*0.03	0.909
Functional class(I-IV)	r	-0.03	0.25	-0.08	-0.23	0.16	0.2	0.08
	P value	0.75	*0.03	0.47	0.058	0.2	0.101	0.49

MHAQ = modified Health Assessment Questionnaire; RF = rheumatoid factor

Discussion

The increased mortality rate in RA patients is largely associated with CVD, particularly coronary atherosclerosis. The risk of CVD is 3 times more in RA patients than in the general population [4, 9]. Dyslipidemia, diabetes mellitus, hypertension, and obesity might increase the risk of CVD [10, 11]. A former study showed that untreated hypertension and hypercholesterolemia are the main predisposing factors for the risk of CVD in RA patients [12]. As chronic inflammation is a prominent component in RA, it has been supposed that RA itself could independently be a risk factor for CVD [13, 14].

To assess alterations in the lipoproteins among RA patients, the correlation between the inflammatory activity of RA and lipid profiles. The results suggested that patients with active RA had altered lipid profiles in comparison with healthy subjects. There is a theory about the association between changes in lipid profiles and acute phase reactants with accelerated atherosclerosis in RA patients.

Lp (a) is a predictive index for ischemic heart diseases in patients with hypercholesterolemia. There is controversy in the literature regarding serum Lp (a) levels in RA patients and its role in the pathophysiology of CVD in RA [15]. It has been reported that serum Lp (a) levels were significantly higher in RA patients and were significantly correlated with acute phase response, including ESR and platelet count, but not with CRP level [16]. However, another study did not find any meaningful serum Lp (a) rise in RA patients [17]. Moreover, the latter study also did not suggest an association between Lp (a) and acute phase response. Another study [18] showed that serum Lp (a) was higher in 30 RA patients (an average of 21.6 mg/dL) than in 30 participants in the control group with an average Lp (a) level of 17.2 mg/dL.

The existing data on lipid profiles in patients with RA is contradictory with some studies reporting no significant difference in TC, LDL-C, and HDL-C in RA patients compared with the control group [19-21]. In contrast, some reports have indicated lower TC, LDL, and HDL levels in active untreated RA patients [22, 23]. It seems that most studies agree on lower HDL in RA patients compared with controls, but this has not been suggested for TC and LDL [24]. In the current study, lower levels of TC, HDL, LDL, and triglycerides were observed in RA patients compared with the control group. This discrepancy can be attributed to different factors such as the age and gender of the studied patients in these studies. Active inflammation [25] and received treatments [26] are also important in this regard. In addition, socioeconomic factors, namely female gender, smoking, and alcohol consumption, have been shown to be associated with dyslipidemia [27].

Only a limited number of studies have investigated lipid levels and their association with disease activity among RA patients. An opposite association between elevated HDL-C-levels and CRP was found in a study on 204 RA cases [28]. An important aspect is the effect that treatment can have on the improvement of lipid profiles. Robust evidence exists regarding abnormal lipoproteins in untreated RA patients with active disease [24].

TNFα and other pro-inflammatory enzymes are responsible for rheumatoid cachexia and are also related to lowered TC and HDL-C levels [24]. As RA activity aggravates, a relation to higher TNF levels is observed. This might explain the converse relationship between disease activity and lipid levels. The evidence indicates that inflammation in RA has a crucial effect on HDL-C and Lp (a) metabolisms. It has been noted that the lipid profile in RA patients can influence the response to treatment [29]. The biological disease-modifying anti-rheumatic drugs (DMARD) and vitamin K level have been suggested to be correlated with lipoproteins [30, 31].

Hydroxychloroquine has a favorable effect on lipid metabolism. In addition to lipoproteins, glucose control is also better achieved among RA patients who are under treatment with hydroxychloroquine [32]. In a recent systematic review, the meta-analysis showed lower mean differences in TC, LDL, HDL, and triglycerides among RA patients who were taking hydroxychloroquine compared with those who were not receiving this agent [33]. A period of three months has been suggested as the minimum required time to observe the beneficial effects of hydroxychloroquine on the lipid profiles of RA patients [34].

Study Limitations

Among the main limitations of the current study, its retrospective nature can be noted. Because of this, it was impossible to control the confounding variables during the study. Moreover, because convenience sampling was used in this study, the data cannot be generalized to the general population.

Conclusion

Serum Lp (a) was not significantly different between the RA and control groups. No correlation between serum Lp (a) and acute phase reactants was seen other than a weak one with ESR. Routine serum Lp (a) measurement in clinical practice to assess RA activity and severity is not recommended.

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Conflict of Interest

The authors declare no conflicts of interest.

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