Rheumatoid factor mediates excess serum lipoprotein(a) for independent association with type 2 diabetes in men

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ABSTRACT

Objective: The potential association of rheumatoid factor (RF) and lipoprotein (Lp)(a) levels, as well as with the likelihood of type 2 diabetes and hypertension, needs exploring.
Methods: Cross-sectional associations were sought in this unselected and population-based 1539-adult cohort (age 58.8±10.6 years). RF was assayed nephelometrically. Multiple logistic regression analyses were used for covariates of RF positivity and for the latter's association with diabetes and hypertension.
Results: RF-positive individuals were older, fewer current smokers, had significantly lower fasting triglycerides (by 13%), higher fibrinogen, and tended to higher sex hormone-binding globulin (SHBG) levels. Whereas, women had a similar risk profile irrespective of RF status, RF-positive men had significantly higher Lp(a). In contrast to Lp(a) being positively correlated with SHBG in RF-negative subjects (r=0.08; p=0.007), an inverse correlation existed in seropositive individuals (r=-0.32, p=0.011), suggesting the interplay of an immune complex. In regression analyses, RF positivity was associated with Lp(a) in men but not in women, [OR 1.53 (1.19; 1.96)], independent of age, SHBG, and C-reactive protein (CRP). RF positivity was further associated with diabetes [OR 1.98 (95% CI 1.11; 3.52)] in the whole sample, additively to waist circumference and CRP, major determinants of diabetes. RF-positive subjects were not significantly associated independently with hypertension.
Conclusion: Autoimmune activation linked to Lp(a) is mediated by the autoantibody RF in contributing to the development of type 2 diabetes.
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Keywords: autoimmune activation, diabetes type 2, lipoprotein(a), rheumatoid factor, rheumatoid arthritis

Introduction

Rheumatoid factor (RF) is an autoantibody directed against the Fc portion of immunoglobulin G and is found in every 3 of 4 patients with rheumatoid arthritis (RA) (1, 2). Being not specific for RA, RF is found in other diseases, including Sjögren's syndrome, systemic lupus erythematosus, hepatitis C, and subacute bacterial endocarditis, as well as in 5% of healthy persons, at an increasing prevalence with age (1, 2). Seropositivity in RA can be of prognostic significance inasmuch as patients with elevated titers tend to have more severe and progressive disease with extra-articular manifestations, including vasculitis, thus helping guide the physicians to more aggressive treatment (1-3).

Lipoprotein (Lp)(a) is a cardiovascular risk factor and is known to promote thrombosis, inflammation, and coronary artery disease (4, 5). Two findings-namely, the independent and inverse association with fasting triglyceride in subjects with MetS (6) and in women with serum γ-glutamyltransferase (6) led us to hypothesize that an inverse association of Lp(a) may appear in pro-inflammatory state/oxidative stress, whereby low Lp(a) levels might actually represent failure of the assayability of Lp(a) in an immune complex and result from pro-inflammatory state/oxidative stress (7). As an LDL-like particle consisting of an apoB100 molecule linked to a glycoprotein, apolipoprotein (a), Lp(a) has been recognized to be in a very weak correlation with other lipid and non-lipid parameters (4, 8, 9). This particle's function remains largely uncertain; Lp(a) binds proinflammatory-oxidized phospholipids (10) and is a preferential carrier of oxidized phospholipids (ox-PL) in human plasma. Lp(a) also contains lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$ (or PAF-

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AH)), which may cleave oxidized fatty acids to yield short-chain fatty acids and lysolecithin (11).

To our knowledge, the association between the presence of RF and Lp(a) has at best scarcely been studied, as has been RF's association with metabolic disorders, such as diabetes or hypertension. We, therefore, investigated these relationships of RF in a representative sample of middle-aged Turkish adults, with an emphasis on the relationship with markers of diabetes risk. Current findings shed light on the link of Lp(a) to RF and provide evidence for the interplay of the immune mechanism, as well as for a novel potential immune pathway in the development of type 2 diabetes that may be shared with RA (12).

Methods

The study sample of the longitudinal TARF study (13, 14), a representative sample of Turkey's middle-aged and elderly adults, is formed by all participants who attended the survey in 2011/2012 (n=1551). They were aged 40 years or over and resided in all regions of Turkey. Eight men and 4 women who had substantial renal functional impairment, as assessed by serum creatinine >227 µmol/L, were excluded. The study was approved by the Ethics Committee of the İstanbul University İstanbul Medical Faculty. Written informed consent was obtained from all participants.

Measurements of risk variables

Waist circumference was measured with the subject standing at the end of gentle expiration at the level midway between the lower rib margin and the iliac crest. Status of cigarette smoking was categorized into current, former, and never-smokers. Blood pressure (BP) was measured in the seated position on the right arm using an aneroid sphygmomanometer (Erka, Bad Tölz, Germany) after 5 minutes of rest, and the mean of two recordings was computed.

Serum concentrations of total cholesterol, fasting triglycerides, glucose, and high-density lipoprotein (HDL)-cholesterol (directly without precipitation) were determined using enzymatic kits from Roche Diagnostics. Concentrations of insulin, sex hormone-binding globulin (SHBG), and total testosterone were determined by the electrochemiluminescent immunoassay method using Roche kits and an Elecsys 1010 immunoautoanalyzer (Roche Diagnostics, Mannheim, Germany). Concentrations of serum Lp(a), apoA-I apoB, C-reactive protein (CRP), RF, and complement C3c were measured by Behring kits and Behring nephelometry (Behring Diagnostics, Marburg, Germany, or Westwood, MA). Fasting sera were assayed for concentrations of acylation-stimulating protein (ASP) with ELISA kits purchased from Biotechist Co. (Beijing, China).

Definitions

Individuals with diabetes were diagnosed with criteria of the American Diabetes Association (15), namely, when plasma fast-ing glucose was ≥7 mmol/L (or 2-h postprandial glucose >11.1 mmol/L) and/or the current use of diabetes medication. Individuals having a fasting glucose level of 5.6-6.9 mmol/L were designated as prediabetes (16). Hypertension was defined as blood pressure ≥140 mm Hg and/or ≥90 mm Hg and/or use of antihypertensive medication.

Statistical analysis

Descriptive parameters were shown as means [± standard deviation (SD)]. Due to skewed distribution, geometric means were used uniformly for triglycerides, CRP, insulin, SHBG, testosterone, ASP, and Lp(a) values. RF assays did not detect titers <10 IU/mL, which were therefore considered negative. To analyze the differences between continuous variables with normal distribution, student's t-test and between-categorical variables Pearson's chi-square test were used. Pearson's correlations served to analyze univariate correlations. Sex- and age-adjusted associations for RF positivity were assessed in multiple logistic regression analyses for diabetes and hypertension, whereby likelihood estimates (OR) and 95% confidence intervals (CIs) were obtained. A value of p<0.05 on the two-tailed test was considered statistically significant. Statistical analyses were performed using SPSS-10 for Windows (Chicago, IL, USA).

Results

The study sample consisted of 1539 men and women (n=792) at a mean age of 58.8 ±10.6 years. RF positivity was found in 75 subjects (5%, 42 men). Values considered to be positive ranged from 10.6 to 200 (median 39) IU/mL.

Subjects reacting positively for RF were 5 years older, had fewer current smokers (p=0.03), had lower fasting triglycerides by 13% (p=0.025), had higher fibrinogen (by 10%, p=0.027) and SHBG (by 11%, 44.3 vs. 40.1 nmol/L, p<0.12) concentrations, and more frequently had type 2 diabetes (32.4% vs. 20.3%, p=0.017) and hypertension (64% vs. 50.5%, p=0.022). Clinical characteristics, stratified by gender and RF status, are presented in Table 1. Men reacting positively for RF had, in addition, significantly (2.0-fold) higher Lp(a) and higher systolic and diastolic BP (by 9/4.5 mm Hg). Women positive for RF showed no further significant differences compared to those negative for RF. RF-positive (compared with RF-negative) women tended to have lower creatinine and a slightly more favorable lipid and metabolic profile.

Correlation between SHBG and Lp(a) according to RF status

In 4/5 of the sample, simultaneous Lp(a) and SHBG measures were available. In 1161 RF-negative subjects, Lp(a) was positively though weakly correlated with SHBG in each sex and combined genders (r=0.08; p=0.007) (Fig. 1). Among 61 RF-positive individuals, SHBG was inversely correlated with Lp(a) in each sex and combined genders (r=-0.32, p=0.011). Lp(a) concentrations were positively correlated with RF titers (r=0.32 in men, 0.17 in women).

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Table 1. Anthropometric and biochemical mean values of the study sample by gender and RF status

| | | Men n=747 | | | | | Women n=792 | | | | |
| | | RF-neg | | RF-pos | | | RF-neg | | RF-pos | | |
	n	Mean	SD	Mean	SD	*P*	Mean	SD	Mean	SD	*P*
Sex, n, %	1539	713		42	5.9		763		33	4.1	0.19
Age, years	1539	58.4	10.5	64.7	11.9	<0.001	58.9	10.8	63.8	10.7	0.014
Height, cm	1539	169.4	6.9	168.5	5.8	0.41	156.2	7.1	155.8	6.2	0.77
Waist circum., cm	1539	98.3	11	97	11	0.45	97.8	12.8	97.3	14.2	0.84
Systolic BP, mm Hg	1539	121	17.4	130.4	25	0.02	125.8	20	128.3	17	0.49
Diastolic BP, mm Hg	1539	75.2	10	79.7	13	0.006	77	11.7	78	9	0.63
ASP,¶ nmol/L	782	8.30	2.41	11.0	2.53	0.37	9.21	2.5	11.3	2.02	0.34
Total cholest, mmol/L	1539	5.04	1.05	5.02	1.04	0.91	5.39	1.03	5.24	1.12	0.40
LDL cholest, mmol/L	1539	3.09	0.9	3.14	0.89	0.74	3.32	0.89	3.17	0.99	0.14
HDL cholest, mmol/L	1539	1.08	0.39	1.12	0.30	0.40	1.30	0.34	1.38	0.25	0.33
F. triglyceride,¶ mmol/L	1539	1.59	1.69	1.42	1.68	0.23	1.58	1.58	1.39	1.57	0.21
Fast glucose, mmol/L	1535	5.70	2.3	5.84	1.8	0.79	5.68	2.36	5.49	1.98	0.71
Fast insulin,¶ mIU/L	1407	8.72	2.08	8.50	1.95	0.81	9.02	1.91	7.54	1.86	0.14
Apolipoprotein A-I, g/L	1478	1.356	0.23	1.385	0.14	0.41	1.51	0.25	1.523	0.20	0.76
Apolipoprotein B, g/L	1483	1.03	0.26	1.10	0.27	0.12	1.05	0.27	1.06	0.30	0.79
Lipoprot.(a),¶ mg/dl	1305	10.4	2.86	20.9	2.72	<0.001	13.3	2.9	12.35	2.6	0.72
Creatinine, µmol/L	1539	106	19	110	21.5	0.24	88	19	86	17	0.47
Fibrinogen, µmol/L	1251	103.7	32	117.3	40	0.07	115.6	33.7	126	31.6	0.18
C-react. prot.,¶ mg/L	1539	1.90	2.59	2.19	3.04	0.35	2.45	2.87	2.78	2.43	0.49
Complement C3, g/L	698	1.28	0.27	1.33	0.30	0.50	1.33	0.28	1.37	0.37	0.49
SHBG¶ nmol/L	1304	35.1	1.57	40	1.76	0.103	44.8	1.76	50.4	1.52	0.27
Total testo.,¶ nmol/L	1322	12.1	2.25	12.6	2.46	0.77	0.62	2.49	0.66	2.44	0.71
Curr. & past smok., n	1538	243	287	8	23	0.088	109	79	2	4	0.40
Prediabetes, n	1245*	60	8.4	4	9.5	0.56	77	12.3	3	12.5	0.98
Diabetes, n	1395*	133	20.4	13	34.2	0.042	139	20.3	9	30.	0.20

¶log-transformed values; ASP - acylation-stimulating protein
*total number excludes the other dysglycemic category

Table 2 shows two logistic regression analyses for RF positivity. The first model comprised sex, age, Lp(a), CRP, SHBG, and statin usage, all recognized biomarkers and variables associated with metabolic disorders. The model disclosed age and Lp(a) (OR 1.22, 95% CI 1.03; 1.45) to be significantly positively and independently associated in men. Age alone was associated in this model in women, wherein Lp(a) had an OR below unity. In the second model with fasting glucose categories, diabetes attained only borderline significance in the total sample [OR 1.63 (95% CI 0.96; 2.77)]. Individuals with prediabetes were not associated with RF positivity.

The association of RF positivity with diabetes and hypertension is seen in the logistic regression analyses in Table 3, along with age and selected markers (waist circumference and CRP) of low-grade inflammation. Diabetes was significantly associated with RF positivity (OR 1.98 in the whole sample, 95% CI 1.11;

3.52) and additively to age and waist circumference. RF positivity was not associated with hypertension in men and only tended to exhibit a non-significant 1.9-fold OR in women, independent of age, waist girth, and CRP.

Discussion

The autoantibody RF, commonly observed in patients with RA, was found in 5% in this sample of a middle-aged and elderly general population. RF positivity was significantly and independently associated with Lp(a), particularly in men. Positive RF titers were inversely associated with SHBG, though SHBG tended to have a positive independent association with RF positivity. RF positivity was further associated with prevalent type 2 diabetes and additively to age, waist circumference, and serum CRP. These findings shed light on the immunological

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Table 2. Logistic regression analysis for rheumatoid factor positivity

	Total		Men		Women	
	OR	95% CI	OR	95% CI	OR	95% CI
Model 1	60/1203†		34/573†		26/630†	
Sex, male	1.69	0.97; 2.94				
Lipoprotein(a)¶, 2.9-fold	1.22	1.03; 1:45	1.53	1.19; 1:96	0.94	0.74; 1:20
SHBG¶, 1.7-fold	1.11	0.88; 1:39	1.05	0.75; 1:48	1.17	0.86; 1:59
C-react. protein¶, 3-fold	1.06	0.87; 1:27	1.05	0.81; 1:37	1.04	0.79; 1:36
Age, 11 years	1.54	1.18; 2:02	1.61	1.10; 2:33	1.49	1.01; 2:17
Statin drug usage, y/n	1.20	0.55; 2.62	1.27	0.45; 3.59	0.98	0.28; 3.38
Model 2	75/1539†		42/747†		33/792†	
Sex, male	1.39	0.87; 2.08				
Age, 11 years	1.61	1.58; 2.02	1.71	1.26; 2:31	1.49	1.07; 2:08
Prediabetes (n=144)	0.98*	0.43; 2.25	1.06	0.35; 3.23	0.88	0.26; 3.05
Diabetes (n=294)	1.63*	0.96; 2.77	1.74	0.86; 3.53	1.49	0.67; 3.36

¶log-transformed values; †number RF pos/number at risk.
*Referent normoglycemic group (n=1113); SHBG - sex hormone-binding globulin

Table 3. Cross-sectional associations of rheumatoid factor positivity for type 2 diabetes and hypertension, adjusted for sex, age, waist circumference, and C-reactive protein

	Total		Men		Women	
	OR	95% CI	OR	95% CI	OR	95% CI
Diabetes	244/1303†		124/628†		127/675†	
Age, 11 years	1.27	1.09; 1.49	1.23	1.00; 1.49	1.28	1.06; 1.55
RF positivity	1.98	1.11; 3.52	2.29	1.07; 4.88	1.60	0.64; 4.01
Waist circumfer., 12 cm	1.80	1.53; 2.10	2.15	1.68; 2.74	1.56	1.27; 1.93
C-reactive protein, 3-fold	1.01	0.91; 1.11	0.92	0.78; 1.06	1.10	0.95; 1.27
Lipoprotein(a)¶, 2.9-fold	0.99	0.91; 1.08	1.05	0.92; 1.19	0.95	0.84; 1.06
Hypertension	785/1537†		317/748†		458/789†	
Age, 11 years	2.19	1.92; 2.49	2.08	1.75; 2.47	2.31	1.92; 2.78
RF positivity	1.43	0.83; 2.46	1.21	0.60; 2.43	1.91	0.78; 4.68
Waist circumfer., 12 cm	1.70	1.49; 1.88	1.86	1.55; 2.23	1.58	1.34; 1.86
C-reactive protein, 3-fold	1.12	1.04; 1.22	1.08	0.96; 1.21	1.17	1.04; 1.30

¶log-transformed values. Referent RF - negative. †number of cases/number at risk. Lp(a) was not measured in 16% of sample. Sex was not significant with respect to diabetes; female sex had a significant OR of 1.92 to hypertension

role of Lp(a), mediated by RF positivity, in the development of diabetes. RF positivity can be considered to reflect autoimmune activation underlying diseases, ranging from well-known RA to diabetes.
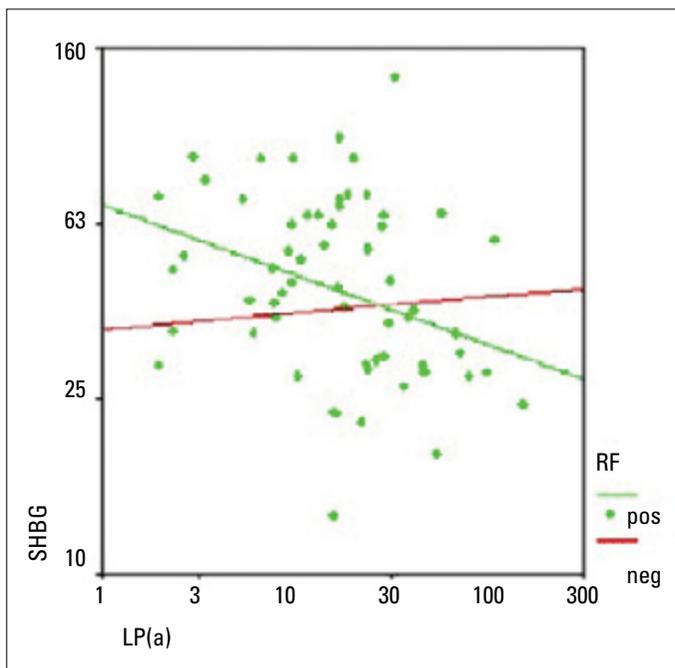
Clinical significance of RF

Detection of autoantibodies, such as RF and anti-cyclic citrullinated peptides, are valuable for early identification of patients with undifferentiated inflammatory arthritis at risk of developing RA [17]. Baseline RF positivity in patients with varying degrees of early inflammatory arthritis varied between 8% and 55% in 10 studies reviewed by Barra et al. [18], and seroconversion rates in these patients were as low as 2%-5% at follow-up.

We could find no reports on the association of RF with diabetes. Prevalence rates of diabetes in patients with and without RA were similar in the report by Gabriel et al. [19], in the NHANES III participants [20], and in the female cohort of the Nurses' Health Study [21]. In contrast, in a large patient-centric health plan database, the prevalence of type 2 diabetes was significantly though moderately higher in RA patients than in matched controls [22]. These observations leave room for the possibility that RF-positive RA patients may have a higher likelihood of diabetes.

Association of Lp(a) with RF is remarkable

It is noteworthy that Lp(a), known to be in weak correlation with other lipid and non-lipid parameters (5, 8, 9), emerged as

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Figure 1. Graph depicting the correlation between log-transformed serum lipoprotein (Lp)(a) (in mg/dL) and sex hormone-binding globulin (SHBG, in nmol/L) in 1116 RF-negative and 61 RF-positive participants. The respective regression lines cross each other at about 40 nmol/L of SHBG, above which the RF-positive group is distinct from the large RF-negative group by displaying disproportionately frequent Lp(a) values <20 mg/dL. The distinction manifests in a positive correlation coefficient (0.08) of sero-negative individuals, shifting to a negative one (-0.32) in sero-positive subjects

the most significant covariate of RF positivity in our analysis, which was, in turn, associated with diabetes. This finding is consistent with a report on circulating Lp(a) being linked to diabetes (23). In the large prospective Women's Health Study (23), Lp(a) was found to be inversely associated with the development of type 2 diabetes, with a roughly 25% higher relative risk in the bottom quintile compared with the remainder of the sample. This observation, unexpected to the authors, can be explained by a mechanism of immune complex formation involving Lp(a) and interfered assay results due to failure by capturing antibodies. The TARF study has generated numerous articles on instances of Lp(a) assayed as "reduced" and the clearly increased risk of diabetes (24), the enhanced proinflammatory state with HDL dysfunction (25), autoimmune activation involving serum creatinine (26), asymmetric dimethylarginine (27) or other serum proteins, and the autoimmune physiopathology shared between diabetes and CHD (28).

Correlation between SHBG and Lp(a) disparate by RF status

A major and novel finding was that Lp(a) declined significantly with decreasing SHBG among RF-negative individuals, whereas Lp(a) rose significantly with both declining SHBG and rising RF titers among seropositive subjects, regardless of sex, except that the titer was less weakly correlated with Lp(a) in women. Together with the finding that SHBG tended to be higher

in seropositive than in -negative subjects, these findings can be explained only by incriminating immune complex formation between Lp(a), damaged in oxidative stress, and SHBG (and/or an HDL-related protective protein) in RF positivity. At a threshold of above-average SHBG concentration, the concurrence of impaired function of HDL and excess Lp(a), both induced by a heightened pro-inflammatory state mediated by decreasing SHBG, may provide the setting for RF positivity and increasing titers. In other words, the epitope of oxidized Lp(a), interfered with by the interacting capture antibody/SHBG and no longer immunoassayable, will result in apparently "reduced" Lp(a) levels in the presence of elevated or normal SHBG. The side finding of both HDL-cholesterol and apoA-I being higher in seropositive than in RF-negative women is consistent with HDL dysfunction, shown in the TARF nondiabetic cohort (29). Serum SHBG is well recognized to be a determinant of MetS (30) or diabetes (31).

Elevated serum concentrations of β2-glycoprotein I-Lp(a) complexes have been shown in case-control studies by two different research groups to be associated with the presence of coronary artery disease (32), systemic lupus erythematosus (33), and rheumatoid arthritis (34). Immunoassay results may be interfered with due to failure by capture antibodies to recognize oxidized epitopes interacting with β2-GPI, ubiquitously present in plasma (32).

Relation to inflammatory and metabolic disorders

Periodontal disease, proposed as having an etiologic or modulating role in cardiovascular disease and diabetes, is associated with RA, on which seropositivity toward RF impacts (35). Evidence exists that autoantibodies, such as RF, can develop several years before the onset of clinical disease (36, 37), which suggests that environmental factors may influence disease susceptibility during early life.

Immunologic role of Lp(a) and gender modulation

In vitro, Lp(a) binds to extracellular matrix proteins, such as fibrin and defensins, peptides that are released by neutrophils during inflammation (38). Lp(a) may operate in two ways: a) excess plasma levels may provide a proinflammatory milieu, which in turn may induce immune activation that leads to RF positivity, concomitantly inducing inflammatory and cardiometabolic diseases (this pathway is typical in men of most ethnicities), and b) Lp(a) may initiate by antigenicity of its apo(a) moiety immune responses, with concomitant involvement of Lp(a) protein, in which case an inverse relationship between Lp(a) protein and the immune process (RF positivity) or outcome disorder may be inverse (this pathway is typical in women). Given the independent positive association of Lp(a) with RF positivity and the underestimation in this state of circulating Lp(a), the Lp(a) concentrations in seropositive subjects are likely substantially higher than our (or others') data reflect.

Overall, among male and female diabetics of a large meta-analysis (5), diabetes was associated with significantly lower Lp(a) than in non-diabetic participants, suggesting that this lipo-

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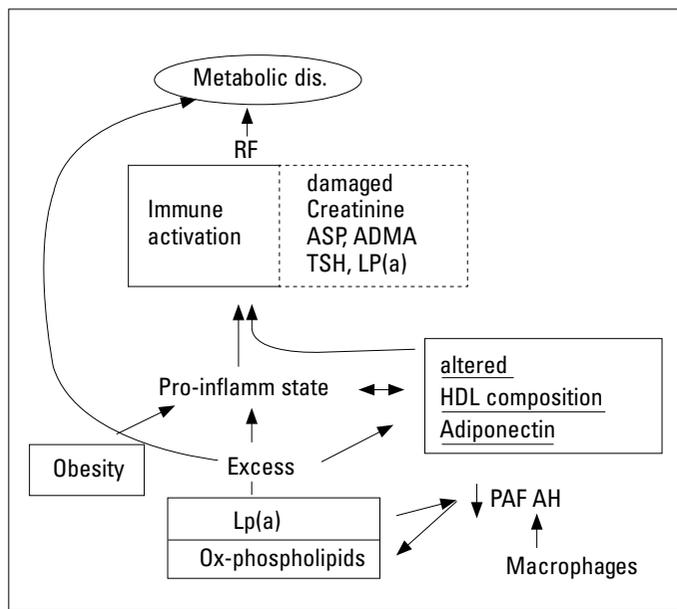
Figure 2. Schema depicts hypothesized role of lipoprotein (Lp)(a), autoimmune activation, and rheumatoid factor positivity (RF) in the development of type 2 diabetes and hypertension (metabolic disorders). Mediated by low platelet activating factor (PAF-AH) levels, derived from macrophages and Lp(a), excess Lp(a) and/or oxidized phospholipids lead to an outcome either simply as shown (usually observed in men) or by involvement of Lp(a) itself in the immune process, yielding reduced Lp(a) lipoprotein due to partial non-assayability (typically observed in women). HDL composition and apoA-I, as well as other presumably damaged serum peptides/proteins, such as creatinine, thyrotropin, acylation-stimulating protein, or asymmetric dimethylarginine, may compose the autoimmune complex

protein may be involved in immune responses in the majority of diabetic people. In the association with diabetes, the partial gender-specific mediation of RF positivity may be due to the herein documented weaker correlation between Lp(a) and RF titers in women than in men.

Hypothesis and implications

This study supports our previously proposed hypothesis (7) that inflammation is mediated-beyond central obesity-by reduced mass or activity of the PAF-AH enzyme, secreted in human macrophages (39) and found to be more concentrated on Lp(a). The low-grade inflammation induces inadequate hydrolysis of excess oxidized phospholipids in Lp(a) and alterations in the composition of HDL particles, all potentially promoting autoimmune activation (Fig. 2). One of the possible consequences is RF positivity; other consequences being inflammatory rheumatic diseases (12); periodontal disease, metabolic disorders, such as hypertension or diabetes; or cardiovascular disease. Recognition of RF positivity as a marker of autoimmune activation associated with enhanced low-grade inflammation may be useful in the early detection of a variety of chronic diseases. Much further research is obviously needed in this area.

Study limitations

The cross-sectional design of the study limits the inference of a causal relationship of the elicited RF positivity. The study sample, exhibiting a relatively high prevalence of diabetes, both forms a strength and may limit the applicability of the findings to some other ethnic populations at large. The availability of measurements of relevant variables that are uncommonly studied in subjects with RF positivity forms a further strength of the study.

Conclusion

In a general population, RF positivity is directly and independently associated with circulating Lp(a) and prevalent type 2 diabetes, additively to age, waist circumference, and serum CRP. RF positivity that marks the likelihood of diabetes is also associated with elevated serum SHBG, suggesting involvement of both in the autoimmune complex, likely induced by apo(a) of Lp(a). In women, in whom Lp(a) is not independently associated with RF, a second type of Lp(a)-associated immune mechanism likely leads to "reduced" assayability of this lipoprotein. These novel pathophysiological pathways require much further research to illuminate the autoimmune activation underlying a variety of diseases of rheumatic, renal, or cardiometabolic origin.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

References

1. Lipsky PE. Rheumatoid arthritis. Chapter 285 in: Harrison's Principles of Internal Medicine, Vol 2, 13th edit. Isselbacher KJ, Braunwald E, Wilson JD, et al (Eds). McGraw-Hill, Inc., New York, 1994.p.1648-55.
2. Farheen K, Agarwal SK. Assessment of disease activity and treatment outcomes in rheumatoid arthritis. J Manag Care Pharm 2011; 17: S9-S13.
3. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008; 59: 762-84. **[CrossRef]**
4. Boffa MB, Marcovina SM, Koschinsky ML. Lipoprotein(a) as a risk factor for atherosclerosis and thrombosis: mechanistic insights from animal models. Clin Biochem 2004; 37: 333-43. **[CrossRef]**
5. The Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke and nonvascular mortality. JAMA 2009; 302: 412-23. **[CrossRef]**
6. Onat A, Hergenç G, Özhan H, Kaya Z, Bulur S, Ayhan E, et al. Lipoprotein(a) is associated with coronary heart disease in women independent of metabolic syndrome. Coron Artery Dis 2008; 19: 125-31. **[CrossRef]**
7. Onat A, Can G. Enhanced proinflammatory state and autoimmune activation: a breakthrough to understanding chronic diseases. Curr Pharm Des 2014; 20: 575-84. **[CrossRef]**

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Anatol J Cardiol 2015; 15: 782-8

8.   Bennet A, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. Arch Intern Med 2008; 168: 598-608. **[CrossRef]**

9.   Werba JP, Safa O, Gianfranceschi G, Michelagnoli S, Sirtori CR, Franceschini G. Plasma triglycerides and lipoprotein(a): inverse relationship in a hyperlipidemic Italian population. Atherosclerosis 1993; 101: 203-11. **[CrossRef]**

10. Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. N Engl J Med 2005; 353: 46-57. **[CrossRef]**

11. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, et al. European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: current status. Eur Heart J 2010; 31: 2844-53. **[CrossRef]**

12. Onat A, Direskeneli H. Excess cardiovascular risk in inflammatory rheumatic diseases: pathophysiology and targeted therapy. Curr Pharma Des 2012; 18: 1465-77. **[CrossRef]**

13. Onat A. Risk factors and cardiovascular disease in Turkey. Atherosclerosis 2001; 156: 1-10. **[CrossRef]**

14. Onat A, Hergenç G, Can G, Uğur M, Nartop F. Dual activity of serum lipoprotein-associated phospholipase A2 yielding positive and inverse associations with cardiometabolic risk. Clin Chem Lab Med 2011; 49: 1349-57. **[CrossRef]**

15. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003; 26: 3160-7. **[CrossRef]**

16. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004; 109: 433-8. **[CrossRef]**

17. Trouw LA, Huizinga TW. Which elements of the criteria for RA are stable over time? Rheumatology 2011; 50: 248-9. **[CrossRef]**

18. Barra L, Pope J, Bassette L, Haraoui B, Bykerk V. Lack of seroconversion of rheumatoid factor and anticyclic citrullinated peptide in patients with early inflammatory arthritis: a systematic literature review. Rheumatology 2011; 50: 311-6. **[CrossRef]**

19. Gabriel SE, Crowson CS, O'Fallon WM. Comorbidity in arthritis. J Rheumatol 1999 ; 26 : 2475-9.

20. Simard JF, Mittleman MA. Prevalent rheumatoid arthritis and diabetes among NHANES III participants aged 60 and older. J Rheumatol 2007; 34: 469-73.

21. Solomon DH, Curhan GC, Rimm EB, Cannuscio CC, Karlson EW. Cardiovascular risk factors in women with and without rheumatoid arthritis. Arthritis Rheum 2004; 50: 3444-9. **[CrossRef]**

22. Han C, Robinson DW Jr, Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2006; 33: 2167-72.

23. Mora S, Kamstrup PR, Rifai N, Nordestgaard BG, Buring JE, Ridker PM. Lipoprotein(a) and risk of type 2 diabetes. Clin Chem 2010; 56: 1252-60. **[CrossRef]**

24. Onat A, Çoban N, Can G, Yüksel M, Karagöz A, Ademoğlu E, et al. Low "quotient" Lp(a) concentration mediating autoimmune activation predicts cardiometabolic risk. Exp Clin Endocr Diabetes 2014; 122: Oct 14 [Epub].

25. Onat A, Can G, Murat S, Çiçek G, Örnek E, Yüksel H. Aggregation of lipoprotein(a) to apolipoprotein A-I underlying HDL dysfunction as a major coronary risk factor. Anadolu Kardiyol Derg 2013; 13: 543-51.

26. Onat A, Can G, Ademoğlu E, Çelik E, Karagöz A, Örnek E. Coronary disease risk curve of serum creatinine is linear in Turkish men, U-shaped in women. J Investig Med 2013; 61: 27-33.

27. Onat A, Köroğlu B, Can G, Karagöz A, Yüksel M, Aydın M. Apparently "low" serum asymmetric dimethylarginine is associated with fasting glucose and tends toward association with type 2 diabetes. Anadolu Kardiyol Derg 2014; 14: 26-33.

28. Onat A, Dönmez İ, Karadeniz Y, Çakır H, Kaya A. Type-2 diabetes and coronary heart disease: Common physiopathology, viewed from autoimmunity. Expert Rev Cardiovasc Ther 2014; 12: 667-79. **[CrossRef]**

29. Onat A, Can G, Örnek E, Altay S, Yüksel M, Ademoğlu E. Elevated serum uric acid levels in nondiabetic people mark pro-inflammatory state and HDL dysfunction, and independently predicts coronary disease. Clin Rheumatol 2013; 32: 1767-75. **[CrossRef]**

30.   Brand JS, Rovers MM, Yeap BB, Schneider HJ, Tuomainen TP, Haring R, et al. Testosterone, sex hormone-binding globulin and the metabolic syndrome in men: an individual participant data meta-analysis of observational studies. PLoS One 2014; 9: e100409. **[CrossRef]**

31. Onat A, Hergenç G, Karabulut A, Albayrak S, Can G, Kaya Z. Serum sex hormone-binding globulin, a determinant of cardiometabolic disorders, independent of abdominal obesity and insulin resistance in elderly men and women. Metabolism 2007; 56: 1356-62. **[CrossRef]**

32. Lopez LR, Bruckner TR, Hurley BL, Kobayashi K, Matsuura E. Determination of oxidized low-density lipoprotein (ox-LDL) versus oxLDL/beta2-GPI complexes for the assessment of autoimmune-mediated atherosclerosis. Ann N Y Acad Sci 2007; 1109: 303-10. **[CrossRef]**

33. Zhang C, Li X, Niu D, Zi R, Wang C, Han A, et al. Increased serum levels of ss2-GPI-Lp(a) complexes and their association with premature atherosclerosis in patients with rheumatoid arthritis. Clin Chim Acta 2011; 412: 1332-6. **[CrossRef]**

34. Zhang C, Li K, Shi B, Wang X, Liu X, Qin W, et al. Detection of serum ss2-GPI-Lp(a) complexes in patients with systemic lupus erythematosus. Clin Chim Acta 2010; 411: 395-9. **[CrossRef]**

35. Detert J, Pischon N, Burmester GR, Buttgereit F. The association between rheumatoid arthritis and periodontal disease. Arthritis Res Ther 2010; 12: 218. **[CrossRef]**

36. Colebatch AN, Edwards CJ. The influence of early life factors on the risk of developing rheumatoid arthritis. Clin Exp Immunol 2010; 163: 11-6. **[CrossRef]**

37. Nielen MM, van Scaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004; 50: 380-6. **[CrossRef]**

38. Bdeir K. Defensin promotes the binding of lipoprotein(a) to vascular matrix. Blood 1999; 94: 2007-19.

39. Stafforini DM, Elstad MR, McIntyre TM, Zimmerman GA, Prescott SM. Human macrophages secrete platelet-activating factor acetylhydrolase. J Biol Chem 1990; 265: 9682-7.