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RESEARCH ARTICLE

Influence of Abdominal Obesity on the Relationship of Low-Density Lipoprotein Cholesterol with Atherosclerosis and Cardiovascular Risk in Rheumatoid Arthritis

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ABSTRACT

Objective. Patients with rheumatoid arthritis (RA) and low body weight may incur higher all-cause and cardiovascular mortality than obese patients. Likewise, RA patients with low serum levels of low-density lipoprotein cholesterol (LDLc<70 mg/dl) may experience greater cardiovascular risk. We explored whether abdominal obesity (waist-to-height ratio >0.58 in females and >0.62 in males) associated with coronary atherosclerosis and influenced the relationship between low LDLc, coronary atherosclerosis and cardiovascular risk in RA.

Methods. Coronary artery calcium, number of coronary plaques, and extensive (≥5 plaques) or obstructive (>50% stenosis) disease was evaluated with computed tomography angiography in 150 patients at baseline and 101 patients 6.9±0.4 years later. Cardiovascular events were recorded. Oxidized LDL was measured with monoclonal antibody E06. Serum cholesterol loading capacity on macrophages was measured as intracellular cholesterol content with a fluorometric assay.

Results. Abdominal obesity was not associated with per-patient number of coronary plaques or coronary artery calcium score at baseline. Low LDLc positively associated with number of plaques (b 2.13 [95% confidence interval 1.03 to 3.22]), likelihood of extensive or obstructive plaque (odds ratio 6.58, 95% confidence interval [1.63 to 26.46]), and log-transformed CAC (b 1.90 [0.89 to 2.91]) exclusively in nonobese patients (p-for-interaction <0.001, 0.061, and 0.001 respectively). Low LDLc associated with increased likelihood of >median oxidized LDL and higher ratio of cholesterol loading capacity to LDLc in nonobese patients (p-for-interaction 0.041 and 0.001 respectively). Abdominal obesity negatively associated with likelihood of plaque stenosis progression (odds ratio 0.19 [0.07 to 0.54]). Low LDLc associated with greater likelihood of per-segment plaque formation (OR 4.68 [2.26 to 9.66]) and increased stenotic severity (odds ratio 5.35 [1.62 to 17.67]) only in nonobese patients (p-for-interaction 0.002 and 0.040 respectively). Abdominal obesity was not linked to cardiovascular risk (Hazard Ratio 1.57, 95% confidence interval [0.66-3.73]). Low LDLc associated with higher cardiovascular risk in nonobese (Hazard Ratio 7.94 [1.52 to 41.36]) but not obese patients (p-for-interaction=0.017).

Conclusion. Abdominal obesity was not linked to plaque progression or cardiovascular risk in RA. Only in nonobese patients, low LDLc associated with higher atherosclerosis burden, plaque progression and cardiovascular risk. This may reflect higher oxidation and macrophage cholesterol loading capacity of LDL when LDLc is <70mg/dl.

Keywords: Rheumatoid arthritis, abdominal obesity, oxidized LDL, cholesterol loading capacity, coronary atherosclerosis, cardiovascular risk

Introduction

The relationship between traditional risk factors and cardiovascular risk in rheumatoid arthritis (RA) is more complex than in the general population[1,2]. While in general patients higher cholesterol is linked to a continuous rise in risk[1], reports in RA have suggested that total cholesterol and low-density lipoprotein cholesterol (LDLc) levels may be positively[3], unrelated[4], or even negatively[5] associated with cardiovascular risk. Specifically, in the Rochester epidemiology project, lower total cholesterol and LDLc were linked to greater cardiovascular risk in patients with RA[5]. Additionally, RA patients with low LDL cholesterol (LDLc<70 mg/dl) had four times higher coronary artery calcium (CAC) score compared to controls from the MultiEthnic Study of Atherosclerosis[6]. We further reported that RA patients with low LDLc had greater coronary plaque burden, severity and vulnerability compared to RA patients with LDLc>70 mg/dL[7]. This was associated with higher LDL oxidation, enhanced production of antibodies against oxidized LDL and of proprotein convertase subtilisin kexin type-9 (PCSK9) upregulating scavenger receptors, all promoting LDL uptake in the vessel wall and plaque formation[7].

Similarly, there are conflicting reports on the role of obesity—measured as body mass index (BMI) ≥30kg/m^2—on cardiovascular risk, mortality, and all-cause mortality in RA. Some indicate increased risk[8,9] or no association[10], while others suggest a protective effect[11–14]. This benefit of obesity on all-cause mortality was independent of sex, smoking, RA age onset, RA duration, and methotrexate use but was significantly attenuated or abrogated by increasing inflammation and comorbidities[13]. BMI, however, does not account for fat distribution or body composition[15]; in contrast, waist circumference or waist-to-height ratio (WHtR) consider fat distribution, better reflect abdominal obesity (AO) and visceral adiposity on imaging[16,17] and are linked to cardiometabolic risk in RA[15,18].

LDL oxidation and excess cholesterol loading on arterial wall macrophages underly foam cell formation and atherosclerosis initiation and progression[19]. Oxidized LDL (oxLDL) may directly promote cholesterol loading on vascular macrophages, independently of inflammation in rheumatoid factor and anticitrullinated peptide antibody positive patients[7]. Moreover, oxLDL fosters cholesterol loading via increased production of specific IgG autoantibodies and through upregulation of PCSK9, depending on level of inflammation and seropositivity status[7,20].

The associations of AO with coronary atherosclerosis and cardiovascular risk in RA are unknown. Also unclear is whether AO influences the relationship between LDLc and coronary atherosclerosis or cardiovascular risk. Since RA patients exhibit greater coronary atherosclerosis burden, vulnerable plaque characteristics and cardiovascular risk compared to individuals without[21,22] understanding the contributions of obesity, dyslipidemia and their interaction would be pivotal to the implementation of targeted interventions. Our study had two aims: (i) to evaluate the association of AO with coronary atherosclerosis burden, progression, and cardiovascular risk in RA; and (ii) to examine whether AO may influence the relationship between LDLc and coronary atherosclerosis or cardiovascular risk in this disease.

Materials and Methods

PATIENT RECRUITMENT

One hundred fifty patients enrolled in our previously described *PRO*spec*T*ive *E*valuation of Latent Coronary A*T*herosclerosis in *R*heumatoid *A*rthritis (PROTECT RA) cohort—recruited on a first-come, first-served basis between March 2010 and March 2011—were included in the study[21]. All underwent atherosclerosis assessments with computed tomography angiography (CCTA) at baseline and 101 of those had follow-up evaluation 6.9±0.4 years later. Patients were 18 to 75 years old, satisfied 2010 classification criteria for RA and had no diagnosis or suspicion of cardiovascular disease including stable angina, acute coronary syndrome, transient ischemic attack, stroke, peripheral arterial disease with or without revascularization, or heart failure. Patients with concurrent autoimmune syndromes (except Sjogren's), weight >147.7 kg (scanner bed capacity), chronic or active infections, malignancy within five years, glomerular filtration rate <60 mL/min or iodine allergy were excluded. Patients provided written informed consent and the study was approved by the local institutional review board.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

Screening atherosclerosis evaluations were performed in a 64-multidetector row scanner upon enrollment between March 2010 and March 2011. Surveillance assessments were carried out in a 256-multidetector row scanner between March 2017 and March 2018. Details on image acquisition and processing protocols as well as grading reproducibility for our center were previously outlined[23]. Coronary artery calcium score according

to Agatston was measured in noncontrast scans[24]. Atherosclerotic lesion presence and burden was quantified on contrast-enhanced scans according to a standardized 17-segment American Heart Association model[25]. Both baseline and follow-up studies for each participant were reviewed concurrently and in random order by an experienced, blinded reader (MJB). Longitudinal comparisons of change in atherosclerosis burden were performed after coalignment of coronary segments utilizing fixed anatomic landmarks as fiducial points. Numbers of coronary segments with plaque (0-17) per patient were quantified. Stenotic plaque severity per segment was quantified as previously reported[21]. Five or more coronary plaques in a patient and lesions yielding greater than 50% luminal stenosis were considered extensive and obstructive disease respectively; both associated with very high cardiovascular risk[26,27].

LABORATORY EVALUATIONS

Rheumatoid factor (RF) and anticitrullinated peptide antibody (ACPA) status was obtained from the electronic medical record. Blood samples for metabolic panel, complete blood counts, c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were collected during screening and surveillance coronary atherosclerosis assessments as well as every scheduled clinic visit in-between. Fasting serum lipids were quantified on the day of baseline and follow-up scans and according to EULAR recommendations in between[28]. Serum collected for additional biomarker studies was stored at -80^{0}C as previously described[21].

Oxidized LDL (OxLDL) was measured as circulating oxidized phospholipids associated with apoB100-containing particles using the monoclonal antibody E06 as previously described[29]. In brief, apoB-specific capture antibody MB47 coated on microtiter plates was used to capture a saturating amount of apoB100 particles from patients' serum. A detection monoclonal antibody E06 was subsequently added, which binds to the phosphocholine (PC) headgroup of oxidized phospholipids—but not native phospholipids—on apoB100-containing lipoproteins. Results were reported in nanomoles (nmol/L).

Cholesterol loading capacity (CLC) was measured on human THP-1 monocyte-derived macrophages using a fluorometric assay as previously reported[30]. Briefly, THP-1 cells were differentiated into macrophages upon culture with 100ng/ml PMA for 72 hours. The cells were subsequently incubated with individual sera from RA patients at 5% dilution for 24 hours. Cells were subsequently washed and lysed, intracellular cholesterol content was measured fluorometrically in cell lysates and reported as micrograms of cholesterol per milligram of protein.

COVARIATES AND OUTCOMES

All participants had a 10-year atherosclerotic cardiovascular disease (ASCVD) risk score computed at baseline based on pooled cohort equations. Obesity was defined as a WHtR >0.58 in females and >0.62 in males[16]. Disease activity was calculated based on a 28-joint count examination for tenderness and swelling and C-reactive protein (DAS28-CRP). Medications including prednisone, Methotrexate, other conventional synthetic disease modifying anti-rheumatic drug (csDMARDs), bDMARD, and statin use and doses were documented on every clinic visit and confirmed against pharmacy records. For each patient, time-averaged CRP was calculated by adding the mean CRP values between consecutive measurements multiplied by the time interval between sequential measurements and then dividing by the patient's total follow-up time[31].

Baseline RA disease activity outcomes were DAS28-CRP, swollen joint count, tender joint count, CRP, and ESR, and cholesterol outcomes were oxLDL>median (9.75 nmol/L) and corrected CLC (ratio of CLC to LDLc). Baseline coronary plaque outcomes were the number of segments with any plaque per-patient (0-17), presence of extensive or obstructive disease, natural log (ln) transformed CAC score, and CAC>100. Per-segment plaque progression outcomes were new plaque formation in segments without plaque at baseline and increased stenosis severity in segments with baseline plaque. The cardiovascular event outcome was the prespecified composite end point of cardiac death, non-fatal myocardial infarction, unstable angina, stroke, transient ischemic attack, peripheral arterial disease with or without revascularization and heart failure.

STATISTICAL ANALYSIS

Continuous variables were presented as means with standard deviations (SD) or 95% confidence intervals (95% CIs) and categorical variables as numbers with percentages, unless otherwise specified. Non-normally distributed variables were ln transformed.

ANOVA tested differences in DAS28-CRP, swollen joint count, tender joint count, CRP, and ESR between LDLc<70 mg/dL vs >70 mg/dL groups stratified by obesity after adjusting for RA duration, prednisone use, number of csDMARDs, and bDMARD use. The effect of obesity and obesity x low LDLc interaction was assessed with logistic regression for

oxLDL>median and linear regression for corrected CLC. For baseline plaque, robust linear regression models evaluated the association of obesity and its interaction with low LDLc on number of coronary plaques and CAC (ln). Robust logistic regression examined the association of obesity and its interaction with low LDLc on presence of extensive or obstructive disease and of CAC>100. Baseline models adjusted for age, sex, diabetes, hypertension, and statin use.

For plaque progression, robust logistic regression examined the association of obesity and its interaction with low LDLc on new plaque formation in segments without plaque and with increasing stenotic severity of prevalent plaques. Plaque progression models adjusted for age, time-averaged CRP, duration of statin exposure, cumulative prednisone dose, time between scans, proximal segment location, and covariates associated with the outcome at $P < 0.10$ in the multivariable model. Per-segment models used a robust variance estimator (Huber-White Sandwich) to account for clustering of coronary segments within individual patients. Cox regression models evaluated the effect of obesity and the obesity x LDLc interaction on cardiovascular event risk Analyses were conducted using Stata 15 and SPSS 27, with $P < 0.05$ as the threshold of significance.

Results

Participants were mostly middle-aged females with established, seropositive, erosive, and well controlled disease (Table 1). Cardiovascular risk scores, RA duration, disease activity and treatments were in general evenly distributed across obesity groups and LDLc groups stratified by obesity. All patients received conventional synthetic DMARDs (80% methotrexate) and 90/150 (60%) additionally received tumor necrosis factor-alpha (TNFα) inhibitors. Coronary atherosclerosis presence and burden across groups are summarized in Table 1.

EFFECT OF OBESITY AND ITS INTERACTION WITH LDLC ON BASELINE ATHEROSCLEROSIS

In models adjusting for age, gender, hypertension, diabetes, and statin use, AO was not associated with baseline number of coronary plaques, CAC(ln), likelihood of extensive or obstructive plaque, or likelihood of CAC>100 (Figure 1A and 1B). However, there was a significant interaction between obesity and LDLc on baseline plaque: Low LDLc (<70 mg/dl) associated with more coronary plaques, higher CAC(ln), greater likelihood of extensive or obstructive plaque, and greater likelihood of CAC>100 in nonobese but not obese patients (p-for-interaction <0.001, 0.061, 0.001, and 0.034 respectively, Figure 1A and B).

No differences in disease activity or systemic inflammation were observed between LDLc groups stratified by obesity after adjusting for RA duration, prednisone use, number of csDMARDs, and bDMARD use (Figure 2). However, obesity modified the effect of low LDLc on oxLDL such that low LDLc associated with likelihood of oxLDL>median in nonobese patients (p=0.011) but not obese ones (p-for-interaction=0.041, Figure 3) after adjustments for age, gender, diabetes, hypertension, and statin use. Likewise, nonobese patients with low LDLc exhibited higher corrected CLC compared to those with LDL>70 mg/dl (p-for-interaction=0.025, Figure 3).

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EFFECT OF OBESITY AND ITS INTERACTION WITH LDLC ON ATHEROSCLEROSIS PROGRESSION

One hundred one patients underwent surveillance coronary atherosclerosis evaluation 6.9±0.4 years after the baseline assessment. The 45 patients without a follow-up scan were on average older, with higher cardiovascular risk scores, numbers of tender joints, and greater number of concurrent csDMARDs; however, differences were no longer significant after adjusting for age (Supplementary Table S1). In models adjusting for age, sex, time between scans, segment location, time-averaged CRP, statin treatment duration, and cumulative prednisone dose, AO did not associate with per-segment plaque formation (OR 1.41, 95% CI 0.71 to 2.80, p=0.327). AO inversely associated with increased stenotic severity of prevalent plaques (OR 0.19, 95% CI 0.07 to 0.54, p=0.002). AO also influenced the effect of LDLc on plaque progression such that low LDLc associated with a higher likelihood of new plaque formation and increased stenosis of prevalent plaques in nonobese but not obese patients (p-for-interaction 0.002 and 0.040 respectively) after adjusting for age, time between scans, segment location, time-averaged CRP, cumulative prednisone dose, and statin duration (Figure 4).

Table 1 Baseline characteristics (N=150)

	Nonobese n=74	Obese n=76	Nonobese		Obese	
			LDL<70 n=15	LDL≥70 n=59	LDL<70 n=16	LDL≥70 n=60
Age (years)	52.09 ±10.92	54.18 ±10.06	50.97 ±15.77	52.38 ±9.46	58.63 ±7.84	52.99 ±10.31
Female, no. (%)	59 (79.73)	72 (94.74)	11 (73.33)	48 (81.36)	16 (100.00)	56 (93.33)
RA duration (years)	10.35 ±7.98	10.93 ±7.42	11.23 ±7.08	10.13 ±8.23	12.89 ±9.49	10.41 ±6.77
RF positive, no. (%)	61 (82.43)	68 (89.47)	10 (66.67)	51 (86.44)	14 (87.50)	54 (90.00)
ACPA positive, no. (%)	62 (83.78)	65 (85.53)	12 (80.00)	50 (84.75)	15 (93.75)	50 (83.33)
Erosions, no. (%)	55 (74.32)	44 (57.89)	12 (80.00)	43 (72.88)	12 (75.00)	32 (53.33)
DAS28-CRP	2.33 ±0.88	2.81 ±1.11	2.28 ±1.05	2.35 ±0.84	2.92 ±0.99	2.78 ±1.15
Swollen joint count	1.41 ±2.11	1.97 ±2.93	1.27 ±2.34	1.44 ±2.07	2.06 ±2.35	1.95 ±3.09
Tender joint count	0.99 ±2.08	2.17 ±4.26	1.13 ±2.17	0.95 ±2.08	1.75 ±2.24	2.28 ±4.66
CRP (ln) (mg/dL)	1.2 ±1.13	1.82 ±1.08	0.97 ±1.29	1.26 ±1.09	1.99 ±1.01	1.77 ±1.10
ESR (mm/hr)	24.99 ±15.63	30.09 ±20.05	29.73 ±17.86	23.78 ±14.94	30.13 ±21.95	30.08 ±19.71
Total cholesterol (mg/dL)	168.15 ±35.53	170.53 ±34.20	124.93 ±19.39	179.14 ±29.87	125.5 ±14.54	182.53 ±27.15
LDL-c (mg/dL)	94.59 ±27.78	97.01 ±28.38	59.4 ±7.79	103.54 ±23.55	57.63 ±7.15	107.52 ±21.86
HDL-c (mg/dL)	52.08 ±15.05	49.88 ±13.40	46.07 ±16.46	53.61 ±14.42	47.5 ±11.17	50.52 ±13.95
Triglycerides (mg/dL)	129.59 ±73.57	161.07 ±97.25	127 ±94.19	130.25 ±68.32	182.38 ±142.87	155.38 ±81.72
Hypertension	32 (43.24)	40 (52.63)	8 (53.33)	24 (40.68)	10 (62.50)	30 (50.00)
Systolic blood pressure (mmHg)	126.27 ±15.98	130.95 ±14.49	131 ±15.86	125.07 ±15.92	128.63 ±10.56	131.57 ±15.39
Diabetes, no. (%)	8 (10.81)	18 (23.68)	4 (26.67)	4 (6.78)	7 (43.75)	11 (18.33)
Current smoking, no. (%)	7 (9.46)	6 (7.89)	1 (6.67)	6 (10.17)	1 (6.25)	5 (8.33)
Body mass index (kg/m^2)	25.92 ±3.62	32.24 ±5.33	25.38 ±3.90	26.06 ±3.57	31.88 ±5.70	32.33 ±5.28
Waist circumference (inches)	33.72 ±3.24	40.2 ±4.02	33.13 ±3.02	33.87 ±3.30	39.25 ±4.90	40.45 ±3.76
ASCVD risk score	4.9 ±7.66	5.54 ±6.33	8.92 ±13.29	3.88 ±5.09	5.3 ±3.52	5.61 ±6.92
Prednisone use, no. (%)	24 (32.43)	28 (36.84)	4 (26.67)	20 (33.90)	9 (56.25)	19 (31.67)
Methotrexate use, no. (%)	58 (78.38)	64 (84.21)	8 (53.33)	50 (84.75)	14 (87.50)	50 (83.33)
No. concurrent csDMARDs	1.92 ±0.75	2.07 ±0.87	1.6 ±0.74	2 ±0.74	1.94 ±0.77	2.1 ±0.90
bDMARD use, no. (%)	41 (55.41)	49 (64.47)	10 (66.67)	31 (52.54)	11 (68.75)	38 (63.33)
Segment involvement score	1.81 ±2.52	2.22 ±2.01	3.67 ±4.17	1.34 ±1.64	2.19 ±1.68	2.23 ±2.10
CAC score (ln)	1.26 ±2.37	1.59 ±1.97	2.91 ±3.46	0.84 ±1.81	1.79±2.09	1.54±1.95
CAC>100, no. (%)	12 (16.22)	7 (9.21)	6 (40.00)	6 (10.17)	1(6.25)	6(10.00)
Extensive/obstructive plaque, no. (%)	12 (16.22)	15 (19.74)	6 (40.00)	6 (10.17)	4(25.00)	11(18.33)

Values are mean ± standard deviation unless otherwise indicated. RA: rheumatoid arthritis, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibodies, DAS28-CRP: disease activity score based on 28 joint counts and C-reactive protein, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDL-c: low-density lipoprotein, HDL-c: high density lipoprotein, ASCVD: atherosclerotic cardiovascular disease score, cs-DMARDs: conventional synthetic disease modifying anti-rheumatic drugs, bDMARD: biologic disease modifying anti-rheumatic drugs, CAC: coronary artery calcium.

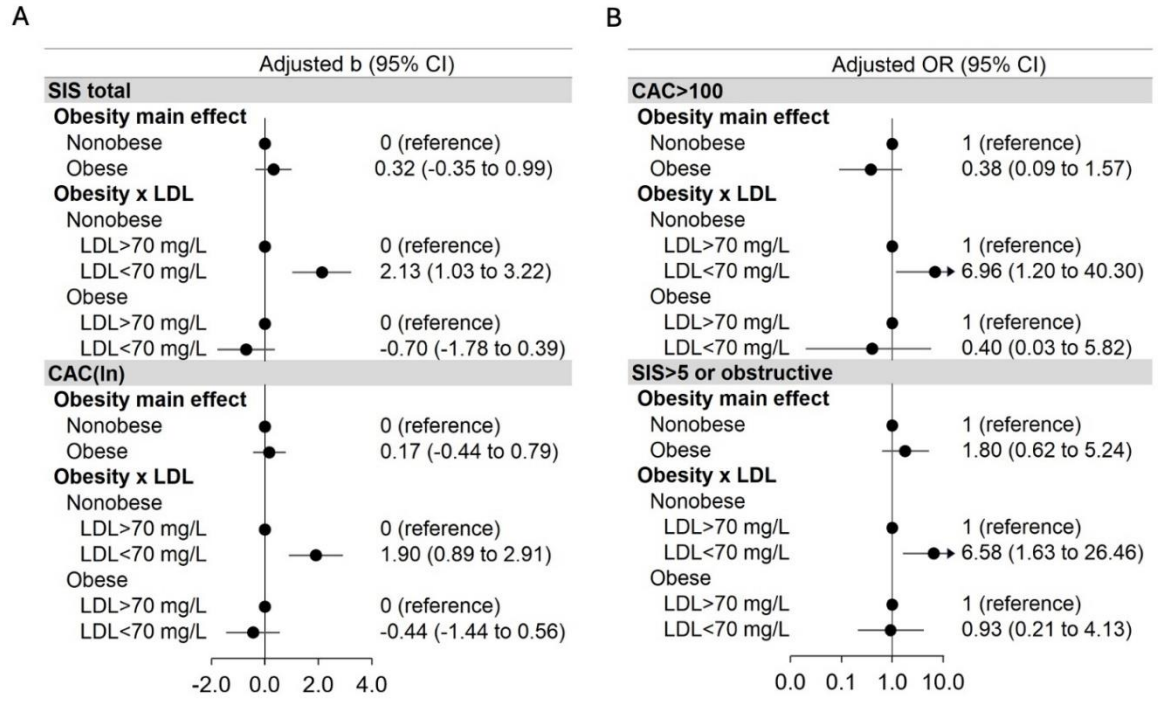

Figure 1. Associations of abdominal obesity and its interaction with LDLc on baseline atherosclerosis burden. **A** Adjusted coefficients (b) for total number of coronary atherosclerotic lesions and natural log transformed CAC score **B** Adjusted odds ratios for presence of high-risk plaque burden defined as CAC>100 and extensive (≥5 segments with plaque per patient) or obstructive disease (>50% luminal stenosis). Models adjusted for age, gender, hypertension, diabetes, and statin use.
SIS: segment involvement score, numbers of coronary segments with any plaque, CAC: coronary artery calcium score.

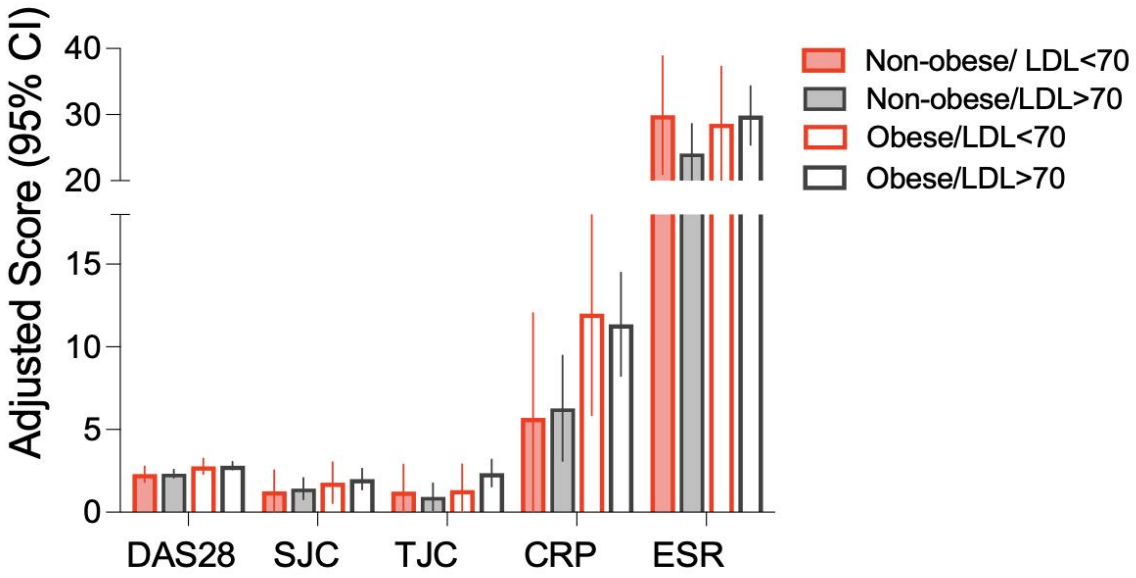

Figure 2. Differences in measures of disease activity and systemic inflammation between low LDLc (<70 mg/dl) and high LDLc (>70 mg/dl) groups stratified by abdominal obesity. All models adjusted for RA duration, prednisone use, number of csDMARDs and bDMARD use.
DAS28: Disease activity score based on a 28 joint count, SJC: swollen joint count, TJC: tender joint count, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

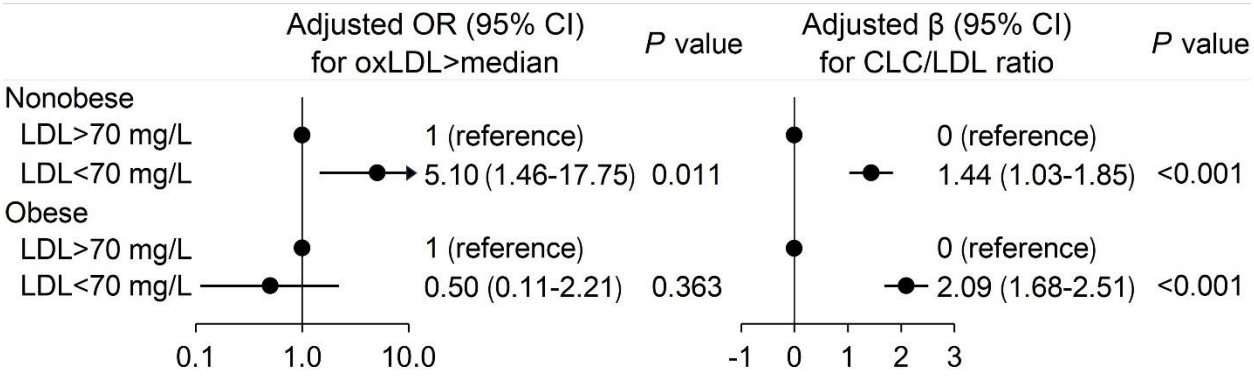

Figure 3. Likelihood of high serum levels (>median) of oxidized LDL and adjusted coefficients for higher serum corrected cholesterol loading capacity (CLC) on macrophages in low (<70 mg/dl) and high LDLc (>70 mg/dl) groups stratified by abdominal obesity. Models adjusted for age, gender, diabetes, hypertension, and statin use.
oxLDL: oxidized LDL, CLC: cholesterol loading capacity of serum, OR: odds ratio.

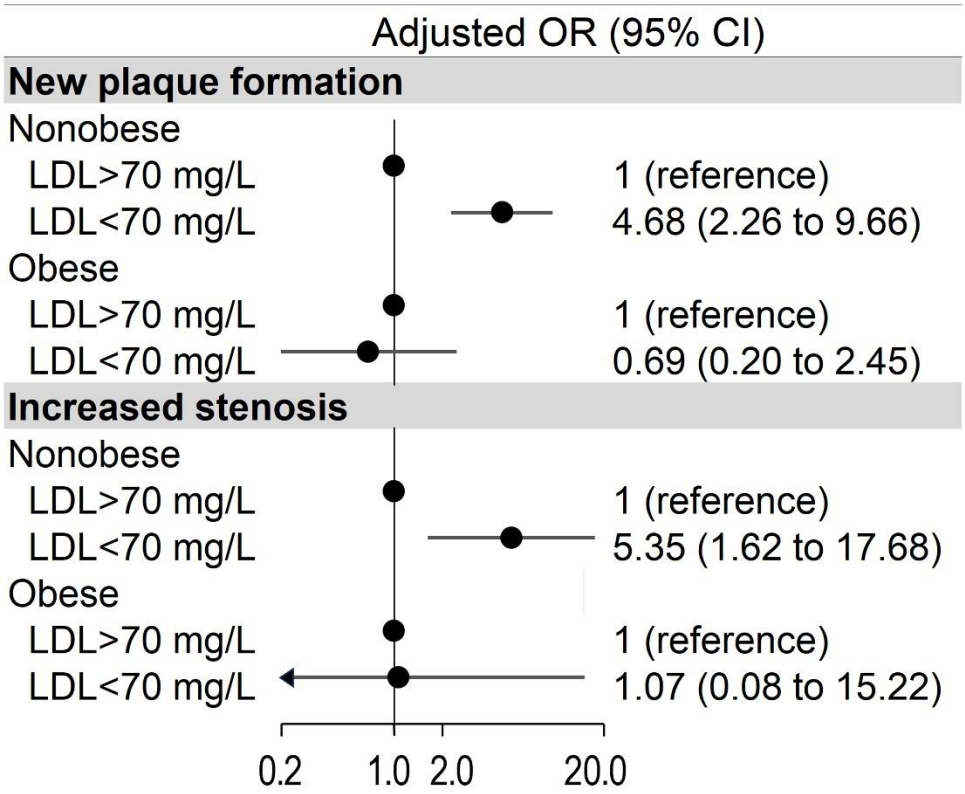

Figure 4. Likelihood of coronary atherosclerosis progression in low LDLc (<70 mg/dl) vs. high LDLc (>70 mg/dl) groups stratified by abdominal obesity. Models adjusted for age, time between scans, segment location, cumulative prednisone dose and statin duration. OR: odds ratio.

Impact of obesity and its interaction with LDLc on cardiovascular risk

Sixteen patients suffered 19 cardiovascular events, 16 first and three second (2.1, 95% CI 1.3-3.3 events/100 patient-years, Supplementary Table S2). AO was not linked to cardiovascular risk (hazard ratio [HR] 1.41, 95% CI 0.53-3.77). It did however influence the association of LDLc with cardiovascular risk (p-for-interaction= 0.017, Figure 5). Specifically, low LDLc associated with higher cardiovascular risk in nonobese (HR 7.94, 95% CI 1.45-43.37, p=0.017) but not in obese patients (HR 0.32, 95% CI 0.04-2.52, p=0.278).

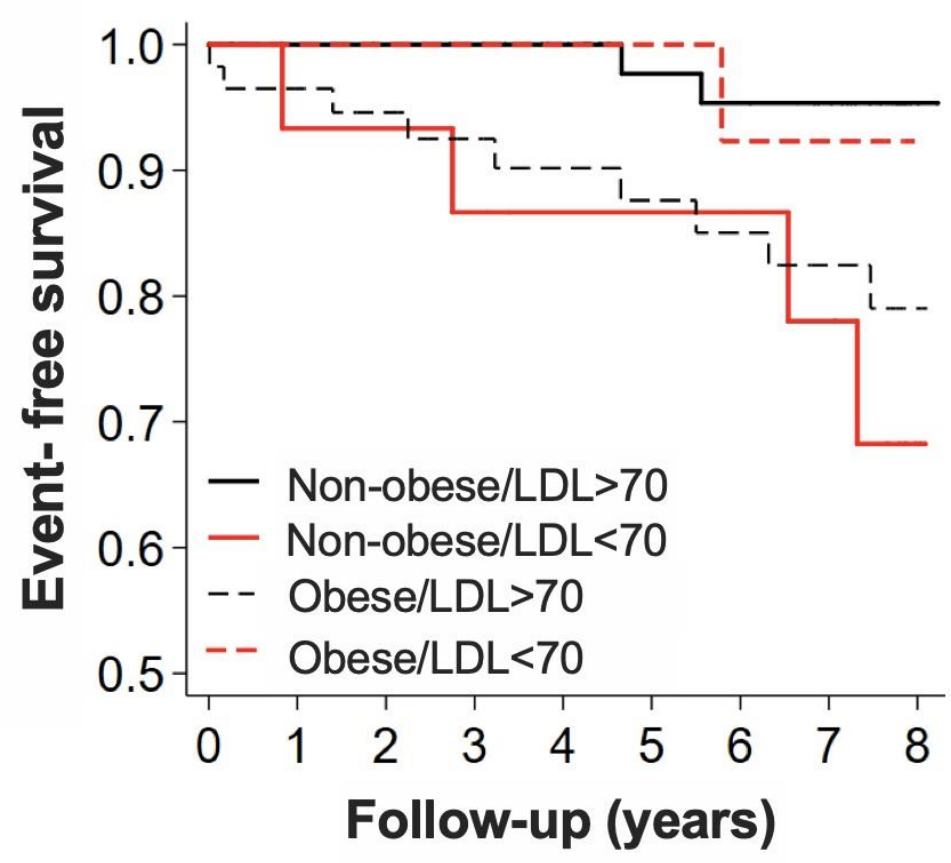

Figure 5. Event-free survival from cardiovascular events in low LDLc (<70 mg/dl) vs. high LDLc (>70 mg/dl) groups stratified by abdominal obesity.

Discussion

While obesity and high LDLc are accepted as cardiovascular risk factors with incremental contributions in the general population[32–34] their association with such risk in RA appears more nuanced. This is the first study to formally interrogate the influence of AO on coronary atherosclerosis burden, progression, and cardiovascular risk, and to examine whether AO modifies the association of serum LDLc with those outcomes in patients with RA. We made several novel observations. First, we showed no difference in coronary atherosclerosis burden in obese compared to nonobese RA patients at screening. Our findings are consistent with two prior reports describing no association of obesity with carotid atherosclerosis, one using WtHR[35] and the other BMI[36] as measures of obesity in RA. Notably, our patients were mostly classified as mildly (Grade 1) obese and it is therefore possible that their overweight/ obese status may reflect the absence of an RA-related hypercatabolic state rather than a proatherogenic condition[7,37]. Indeed, total cholesterol and LDLc were within the normal range. Moreover, we found no difference in ASCVD risk scores, disease duration, seropositivity profile, RA-specific treatments, or LDL oxidation between obese and nonobese patients. There were fewer males in the obese group, but our analyses were adjusted for gender among other covariates. Although disease activity and CRP were higher in obese patients at baseline, absolute values were overall low, and we have no information on cumulative inflammation across the two groups prior to that.

We further showed no association of AO with likelihood of new plaque formation at follow-up after adjustments for age, sex, time between scans, segment location, time-averaged CRP, duration of statin therapy and cumulative prednisone dose. This was not surprising as we saw no differences in weight change, time-averaged disease activity measures (DAS28-CRP, CRP, tender joints), time-averaged lipid levels (LDLc, HDLc), biologic or statin use during follow-up between obese and nonobese groups (not shown). This is in line with our recent report on the independent association of baseline plaque burden, cumulative inflammation, ongoing biologic and statin use with plaque progression[23,38,39]. These findings are also consistent with a prior report[40] indicating no association of

BMI-defined obesity with rapid intima-media thickness progression over three years in patients with RA. It is also congruent with the much larger population-based Norwegian Tromsø study showing that none of the obesity measures considered were linked to new carotid plaque formation or total plaque area increase over seven years after adjusting for cardiometabolic factors[41]. Several other reports in general patients similarly confirmed no association between general obesity and carotid plaque progression[42–44].

More importantly, we found no link between AO and cardiovascular risk in RA. This is consistent with some studies[10], especially after adjusting for comorbidities or inflammation[8,13] but not others that showed either greater risk[9] or instead benefit[11,12] . Nevertheless, in all these studies, BMI was again used as a measure of obesity. We recently demonstrated that baseline coronary atherosclerosis burden, cumulative inflammation, ongoing bDMARD use and ASCVD risk score independently predicted cardiovascular risk in RA[23,45]; although abdominal obesity significantly confounded clinical risk estimates[46]. Moreover, coronary plaque progression amplified cardiovascular risk independently of baseline plaque burden in general patients[47,48]. Lack of difference across all these predictors, including plaque progression, between obese and nonobese patients may therefore explain the similar long-term cardiovascular risk observed across the two groups.

We previously reported that RA patients with low LDLc (<70 mg/dl) exhibited greater coronary atherosclerosis burden compared to those with higher LDLc, providing anatomic plausibility for the "lipid paradox" concept. Mechanistically, this was attributed to higher LDL oxidation leading to greater anti-oxLDL IgG and PCSK9 production, greater cholesterol loading onto macrophages through FcgRI and scavenger receptors respectively, and greater proatherogenic TNFa and IL-6 elaboration from activated proinflammatory macrophages in the vessel wall exclusively in patients with low LDLc[7,49]. We now show that AO modified the effect of LDLc on both coronary atherosclerosis and cardiovascular risk. Specifically, low LDLc associated with greater atherosclerotic burden at baseline, compared to LDLc>70mg/dl, exclusively in nonobese RA patients. Indeed, 40% of nonobese patients in the low LDLc group had extensive or obstructive disease, CAC>100 and ≥3 coronary vessels involved at baseline compared to <10% in those with LDLc>70 mg/dl and 13-16% in those with AO alone. We previously showed that 37-45% of RA patients with either CAC>100 or extensive or obstructive disease respectively experienced cardiovascular events within five years as opposed to none without coronary atherosclerosis[50]. This observation is consistent with a recent report that the association of low LDLc with CAC was stronger in nonobese RA patients compared to controls[6].

We also observed that low LDLc associated with greater likelihood of new plaque formation and increase in stenotic severity of prevalent plaques exclusively in nonobese patients. More importantly, nonobese patients with low LDLc had almost eight times greater likelihood of a cardiovascular event compared to those with high LDLc, and this was not the case in obese patients. There were no differences in baseline or time-averaged measures of disease activity, systemic inflammation, standard lipid levels (LDLc and HDLc), or in the duration of exposure to bDMARD or statin therapies during follow-up that could explain the variations in plaque burden or progression in the low vs. higher LDLc specifically in nonobese groups.

Overall, it seems that the association of normal-low body weight and low LDLc characterizes a subgroup of RA patients with a combination of highly impactful atherosclerosis risk factors. Among these, we identified higher LDL oxidation and greater corrected CLC, both of which have been shown by our group to associate with greater plaque burden in RA[7,51]. Higher LDL oxidation maybe attributed to differences in LDL particle composition and size. Indeed, nonobese patients with low LDLc had significantly higher cholesterol content on small LDL4 particles that can readily enter the subendothelial space and promptly oxidize and lower cholesterol content on large LDL2 particles that do not (not shown).

Our findings have significant clinical implications. A nonobese, low LDLc state considered desirable in the general population in terms of cardiovascular risk, appears to represent a strong coronary risk factor in the context of RA; 40% of nonobese patients with low LDLc had extensive or obstructive disease, CAC>100 and ≥3 coronary vessels involved, all associated with extremely high risk. Yet only 12% of those were classified as such according to their ASCVD risk score. Therefore RA-specific primary prevention strategies should contemplate the high risk associated with a nonobese/ low LDLc state—even in the context of low systemic inflammation—and include prompt and strict targeting of auxiliary risk factors and perhaps consideration of noninvasive coronary atherosclerosis imaging.

An obvious question is whether it is better for an RA patient to be obese vs. non-obese, or whether RA patients should gain or lose weight. Our study did not address this issue however, as we did not manipulate patient weight during it. Limited literature however suggests that BMI reduction of >1kg/m^2 or weight loss of >30 pounds around the early RA period associated with increased all-cause mortality; in contrast, weight gain of >30 pounds did not[52,53]. In another recent study, RA weight fluctuations in both directions were associated with increased cardiovascular risk, particularly in thin patients[54]. As aforementioned, weight status likely reflects very different situations in RA, and adipose tissue— besides being an active metabolic regulator— may also represent a target and a marker of pathologic processes. Further studies are needed to clarify possible different conditions in patient subgroups.

Certain limitations of our study should be acknowledged. First, the assessment of the influence of abdominal obesity, low LDLc and their interactions on coronary atherosclerosis and cardiovascular risk in RA were not prespecified analyses in our original study design and should therefore be considered exploratory. Second, our results represent the experience of a single center with a homogeneous demographic; the vast majority of patients self-identified as white Hispanic, which may limit the generalizability of our findings. Third, we did not collect information on comorbidities and were therefore unable to assess whether the effect of nonobese/ low LDLc state on atherosclerosis was mediated by comorbidities[13]. However, our models were adjusted for time-averaged CRP and therefore the effect of nonobese/ low LDLc state on atherosclerosis progression was independent of cumulative inflammation.

Conclusion

Abdominal obesity was not associated with coronary atherosclerosis or cardiovascular risk in this cohort of RA patients without history or symptoms of cardiovascular disease. However, abdominal obesity modified the effect of low LDLc (<70 mg/dl) on both of those outcomes: low LDLc was linked to greater coronary atherosclerosis burden, progression, and cardiovascular risk in nonobese but not in obese patients with RA. Although no differences in disease activity or systemic inflammation were found, greater LDL oxidation and capacity to load arterial wall macrophages with cholesterol may explain the variance in outcomes. Consideration of the enhanced risk incurred by this group, detailed characterization and subsequent adaptation of primary prevention strategies maybe critical and necessary for effective cardiovascular risk mitigation.

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Conflict of Interest Statement

This study was supported by grants from American Heart Association and Pfizer to GAK. The authors have no conflict of interest to declare.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplementary Material

Supplementary Table S1. Baseline characteristics by follow-up CCTA status

	Follow-up CCTA (n=101)	No follow-up CCTA (n=45)
Age (years)*	51.49 ± 10.30	57.13 ± 10.14
Female, no. (%)	87 (86.14)	40 (88.89)
RA-related parameters		
RA duration (years)	10.22 ± 7.19	12.01 ± 8.77
RF positive, no. (%)	91 (90.10)	34 (75.56)
ACPA positive, no. (%)	87 (86.14)	37 (82.22)
Erosions, no. (%)	64 (63.37)	33 (73.33)
CRP (mg/dL)	0.83 ± 1.27	0.78 ± 1.10
Tender joint count*	1.12 ± 2.49	2.51 ± 4.80
Swollen joint count	1.55 ± 2.54	1.84 ± 2.68
DAS28-CRP	2.44 ± 0.92	2.75 ± 1.18
Baseline Cardiac risk factors		
Hypertension, no. (%)	45 (44.55)	24 (53.33)
Cholesterol (mg/dL)	165.87 ± 34.75	172.44 ± 33.35
LDL-c (mg/dL)	94.53 ± 31.70	97.22 ± 27.01
HDL-c (mg/dL)	50.77 ± 12.95	50.87 ± 16.33
Diabetes, no. (%)	14 (13.86)	10 (22.22)
Current smoking, no. (%)	8 (7.92)	4 (8.89)
Body mass index (kg/m^2)	28.88 ± 5.45	29.39 ± 5.75
Framingham-D'Agostino risk score*	7.28 ± 6.44	12.12 ± 10.44
Medications at baseline		
Prednisone, no. (%)	33 (32.67)	17 (37.78)
Methotrexate, no. (%)	80 (79.21)	38 (84.44)
No. concurrent csDMARDs*	1.90 ± 1.78	2.20 ± 0.87
bDMARDs, no. (%)	64 (63.37)	24 (53.33)
Statins, no. (%)	41 (40.59)	17 (37.78)
Baseline plaque burden		
Any plaque, no. (%)	70 (69.31)	33 (73.33)
Segment stenosis score	2.69 ± 4.06	3.82 ± 5.29
Any mixed/calcified plaque*, no. (%)	32 (31.68)	22 (48.89)

Except where indicated otherwise, values are the mean ± SD. CCTA = coronary computed tomography angiography; RA = rheumatoid arthritis; RF = rheumatoid factor; ACPA = anti-cyclic citrullinated peptide antibodies; CRP = C-reactive protein; DAS28-CRP = disease activity score based on 28 joint counts and CRP; LDL-c = low-density lipoprotein; HDL-c = high density lipoprotein; cs-DMARDs = conventional synthetic disease modifying anti-rheumatic drugs; bDMARD = biologic disease modifying anti-rheumatic drugs. Normal values: cholesterol, 125-199 mg/dL; LDL-c, 57-100 mg/dL; HDL-c, ≥ 40 mg/dL.

*$P < 0.05$, overall comparison of variables between the groups, by independent samples t-test for continuous variables, and chi-square test and Fisher's exact test for categorical variables.

Table 2. Incident cardiovascular events throughout the study

ID	Age	Gender	10-year risk	First CVE (months)		Second CVE (months)	
				Time	Type	Time	Type
1	45.3	Female	4.9	2.0	ACS-STEMI-PCI	95.5	ACS-UA
2	47.6	Female	2.7	69.5	HFrEF		
3	49.3	Female	4.3	66.0	Ischemic stroke		
4	52.9	Female	20	26.9	Embolic stroke/ HFrEF		
5	54.3	Female	4.8	0.0	HFrEF		
6	59.0	Female	7.9	55.8	HFpEF		
7	59.1	Male	18	66.7	HFrEF		
8	59.4	Female	9.9	16.8	ACS-UA-PCI		
9	60.5	Male	33.4	87.8	ACS-UA-CABG		
10	63.9	Male	24.7	89.7	ACS-NSTEMI		
11	66.6	Male	24.1	78.5	ACS-UA		
12	68.4	Male	24.6	6.0	ACS-NSTEMI		
13	69.8	Female	15.6	55.9	PAD-revascularization	94.6	ACS-NSTEMI
14	70.2	Female	43.6	33.0	PAD-revascularization	68.5	CV-Death
15	70.7	Female	45.1	26.3	CV-Death		
16	72.1	Female	15.6	75.9	Ischemic Stroke		

ACS: acute coronary syndrome, STEMI: ST-segment elevation myocardial infarction, PCI: percutaneous intervention, HFrEF: Heart failure with reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, UA: Unstable angina, CABG: coronary artery bypass grafting, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, PAD: peripheral arterial disease.