Title

Insulin Resistance in Rheumatoid Arthritis: Disease-Related Indicators and Associations With the Presence and Progression of Subclinical Atherosclerosis

Journal

Arthritis & Rheumatology, 67(3)

ISSN

2326-5191

Authors

Giles, Jon T
Danielides, Stamatina
Szklo, Moyses
et al.

Publication Date

2015-03-01

DOI

10.1002/art.38986

Peer reviewed

HHS Public Access

Author manuscript

Arthritis Rheumatol. Author manuscript; available in PMC 2018 July 25.

Published in final edited form as:

Arthritis Rheumatol. 2015 March ; 67(3): 626–636. doi:10.1002/art.38986.

Insulin Resistance in Rheumatoid Arthritis:

Disease-Related Indicators and Associations With the Presence and Progression of Subclinical Atherosclerosis

Jon T. Giles[1], **Stamatina Danielides**[1], **Moyses Szklo**[2], **Wendy S. Post**[2], **Roger S. Blumenthal**[2], **Michelle Petri**[2], **Pamela J. Schreiner**[3], **Matthew Budoff**[4], **Robert Detrano**[5], and **Joan M. Bathon**[1]

[1]Jon T. Giles, MD, MPH, Stamatina Danielides, MD, Joan M. Bathon, MD: Columbia University, New York, New York [2]Moyses Szklo, MD, MPH, DrPH, Wendy S. Post, MD, Roger S. Blumenthal, MD, Michelle Petri, MD, MPH: Johns Hopkins University, Baltimore, Maryland [3]Pamela J. Schreiner, PhD: University of Minnesota, Minneapolis [4]Matthew Budoff, MD: Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance, California [5]Robert Detrano, MD: University of California, Irvine

Abstract

Objective—Systemic inflammation and insulin resistance (IR) are linked, yet the determinants of IR and its impact on atherosclerosis in rheumatoid arthritis (RA) are incompletely understood. The aim of this study was to explore the prevalence of IR in RA and non-RA populations and investigate whether the associations of IR with measures of atherosclerosis differ between these groups.

Methods—IR was quantified using the homeostatic model assessment of IR (HOMA-IR), and was compared between RA patients and demographically matched non-RA controls. Differences in the associations between the HOMA-IR index and the Agatston coronary artery calcium (CAC) score, ultrasound-determined intima-media thickness (IMT) of the common carotid artery (CCA) and internal carotid artery (ICA), and focal plaque in the ICA/carotid bulb were compared according to RA status.

Results—Among the 195 RA patients and 198 controls studied, average HOMA-IR levels were higher in the RA group by 31%, and were consistently higher in the RA group regardless of stratification by demographic or cardiometabolic risk factors. While the HOMA-IR index was strongly and significantly associated with C-reactive protein (CRP) and interleukin-6 (IL-6) levels

Address correspondence to Jon T. Giles, MD, MPH, Division of Rheumatology, Columbia University, College of Physicians and Surgeons, 630 West 168th Street, Physicians & Surgeons Building, Suite 10-445, New York, NY 10032. jtg2122@columbia.edu.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Giles had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Giles, Szklo, Post, Petri, Bathon.

Acquisition of data. Giles, Szklo, Post, Blumenthal, Budoff, Detrano, Bathon.

Analysis and interpretation of data. Giles, Danielides, Szklo, Blumenthal, Schreiner, Detrano, Bathon.

in the control group, the association was weaker in the RA group. Among RA patients, higher HOMA-IR levels were associated with rheumatoid factor (RF) seropositivity in men and women, and prednisone use in women only. Before adjustment, higher HOMA-IR levels were associated with all assessed measures of subclinical atherosclerosis in the control group only; associations were diminished and lost statistical significance after adjustment for cardiovascular risk factors. Among the RA patients, neither baseline nor average HOMA-IR levels were significantly associated with change in any of the atherosclerosis measures over an average of 3.2 years of followup.

Conclusion—Although IR was higher in RA patients than in non-RA controls, higher levels may not independently impart additional risk of atherosclerosis.

Although effective treatment strategies for rheumatoid arthritis (RA) have become increasingly available over the past decades, affected individuals still have a lower life expectancy (1), manifested by a 50% higher rate of fatal cardiovascular events than the general population, regardless of sex (2). Values of subclinical measures of atherosclerosis are also increased in RA patients relative to controls, with greater coronary calcification, greater intima-media thickness (IMT) of the carotid artery, and more arterial plaque observed in RA patients compared with controls of similar age and with similar risk factors (3–5).

Determinants of increased subclinical coronary and carotid atherosclerosis in RA have not been fully elucidated. In general, traditional cardiovascular risk factors implicated in atherogenesis (e.g., diabetes, hypertension, and hyperlipidemia) do not fully account for the increase in atherosclerosis (6). Among nontraditional cardiovascular risk factors, several studies have indicated an increased prevalence of insulin resistance (IR) in patients with RA (7–10), a finding potentially correlated with the degree of RA disease activity (8,9). However, to date there is a paucity of published data defining the degree of IR in RA patients compared with matched controls (7), and only a few studies have sought to determine the relationship of IR with other cardiometabolic risk factors in the context of RA-related factors (11–13). Moreover, studies of the effect of RA therapies, including glucocorticoids and tumor necrosis factor (TNF) inhibitors, on IR have yielded divergent results (10,11,14–16). The few studies that have explored the relationship between IR and measures of atherosclerosis in RA have involved relatively small sample sizes, were restricted in the ability to control for traditional cardiovascular risk factors, and many lacked a non-RA comparator group (12,17–19). Moreover, no study has explored the relationship between IR and measures of atherosclerosis in multiple vascular beds.

Therefore, we sought to compare levels and indicators of IR in RA patients and non-RA controls, using the homeostatic model assessment of IR (HOMA-IR). We hypothesized that IR would be higher among RA patients than controls, even among those with low levels of traditional cardiometabolic risk factors. Further, we speculated that the degree of IR among RA patients would correlate with RA disease characteristics and treatments and would be associated with the degree of subclinical coronary and carotid atherosclerosis.

PATIENTS AND METHODS

Study participants and timing of visits

Participants were enrolled in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis (ESCAPE RA) study, a prospective cohort study investigating subclinical cardiovascular disease (CVD) in RA, which has been previously described in detail (3,5). Participants met the American College of Rheumatology 1987 RA classification criteria (20), had an RA duration of >6 months from the time of diagnosis, were 45–84 years of age, and were without known prior cardiovascular events.

Among the 197 RA patients completing the baseline visit, 186 (94%) returned for the second visit (at a mean ± SD of 21 ± 3 months postbaseline), and 158 (80%) returned for the third visit (at a mean ± SD of 39 ± 4 months postbaseline). Imaging assessments of coronary and carotid atherosclerosis occurred at visits 1 and 3, with 195 participants completing all assessments at visit 1 and 155 at visit 3. Clinical data and biologic specimens were collected at all visits (after a morning fast). Controls were participants in the Multi-Ethnic Study of Atherosclerosis (MESA) from the Baltimore Field Center; they did not have RA (exclusions were based on the use of disease-modifying antirheumatic drugs [DMARDs] typical in the treatment of RA). RA patients and controls were similarly assessed by MESA-trained staff using identical procedures and protocols, as previously described (5). The control group for the current study was a subgroup from the Baltimore MESA cohort, frequency matched by demographic characteristics to the RA group, as previously described (3). Frequency matching was performed such that balance in age and ethnicity distributions between RA cases and non-RA controls was maintained when the cohorts were stratified by sex. The study was approved by the Institutional Review Board of the Johns Hopkins Hospital. Control enrollment occurred between 2000 and 2002, and RA enrollment occurred between 2004 and 2006. The final followup visit for the RA cohort occurred in April 2009.

Imaging of subclinical atherosclerosis

Coronary artery calcium (CAC) was measured using multidetector row computed tomography, as previously described (5). Scans were transmitted electronically to the MESA Computed Tomography Reading Center, where calcium scores were quantified using the method described by Agatston et al (21). MESA personnel scoring the scans were blinded with regard to group allocation and clinical characteristics. Carotid imaging was performed as previously described (3) and involved measures in the common carotid artery (CCA), internal carotid artery (ICA), and the carotid blub. Videotaped scans were analyzed at the MESA Ultrasound Reading Center. Carotid plaques were localized to the ICA and carotid bulb and were defined as maximal focal protrusion into the lumen with reduction in the lumen diameter of >25%. Baseline and followup scans were reanalyzed concurrently by a single MESA reader who was aware of the temporal ordering but unaware of clinical characteristics.

Sociodemographic and lifestyle covariates

Demographic characteristics and smoking history were assessed based on self-reported information. Physical activity was assessed with the Seven-Day Physical Activity Recall

Questionnaire (22). Current use and dosage of medications were ascertained by review of prescription bottles. Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in meters.

CVD risk factors

The HOMA-IR index (HOMA2 model) was used to quantify IR. This index is a validated estimate of glucose handling based on fasting assessments of glucose and insulin (23). Hypertension was defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or antihypertensive medication use. Diabetes was defined as a fasting serum glucose level of ≥126 mg/dl or use of anti-diabetic medications. Impaired fasting glucose was defined as a fasting glucose level of 101–125 mg/dl. Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel III criteria (24), with those meeting 3 or more of the 5 criteria classified as having metabolic syndrome.

RA disease characteristics

Forty-four joints were examined by a single trained assessor. RA disease duration was assessed as of the self-reported date of diagnosis. RA disease activity was calculated based on the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP) (25). Current and past use of glucocorticoids and DMARDs was queried by detailed examiner-administered questionnaires. The Stanford Health Assessment Questionnaire (HAQ) (26) was used to assess disability related to common activities. Single-view, anteroposterior radiographs of the hands and feet were scored by a single trained rheumatologist, using the Sharp/van der Heijde (SHS) method (27).

Laboratory covariates

Levels of high-sensitivity CRP and interleukin-6 (IL-6) were measured as previously described (28). None of the participants had an IL-6 level below the detectable threshold. Plasma lipid and glucose levels were measured using standard assays; low-density lipoprotein (LDL) cholesterol levels were estimated using the Friedewald equation. Rheumatoid factor (RF) was assessed by enzyme-linked immunosorbent assay (ELISA), with seropositivity defined as ≥40 units. Anti–cyclic citrullinated peptide (anti-CCP) antibody levels were assessed by ELISA, with seropositivity defined as ≥60 units. HLA alleles bearing the shared epitope were investigated by DRB1 gene sequencing as previously described (3).

Statistical analysis

Differences in participant characteristics between the RA and control groups were compared using *t*-tests for normally distributed continuous variables, the Kruskal-Wallis test for non-normally distributed continuous variables, and the chi-square goodness-of-fit test or Fisher's exact test, as appropriate, for categorical variables. Differences in the associations between characteristics of the participants and the HOMA-IR according to RA status were explored in linear regression models using RA status and the given characteristic as interaction terms, with the outcome of HOMA-IR log transformed to meet modeling requirements. For ease of

interpretation, transformed HOMA-IR index levels were back-transformed from regression modeling and expressed as mean HOMA-IR index levels. Interactions were tested using analysis of covariance. Adjusted models included characteristics associated with the outcome in univariate analyses at the level of $P < 0.20$. Within the RA group, the associations between RA characteristics and the log HOMA-IR index were explored using linear regression, adjusting for non-RA covariates associated with the outcome as above. Noncontributory RA characteristics were excluded from the model using Akaike's information criterion for nested models. Multivariable models were constructed with each significant RA characteristic modeled in separate linear regression models adjusted for demographic, lifestyle, and CVD risk factors associated with HOMA-IR. Next, extended and reduced multivariable models were constructed by co-modeling all of the RA characteristics that were significant at $P < 0.20$ from prior models. Differences in the association of the log HOMA-IR index with cardiovascular outcomes according to RA status were explored in general linear models using RA status and the log HOMA-IR as interaction terms.

Linear regression was utilized for continuous outcomes (Agatston CAC score, IMT, and yearly averaged progression rate for CAC and IMT) and ordinary logistic regression was used for dichotomous outcomes (carotid plaque, strata of change in CAC, etc.), with covariate adjustment as described above. The average HOMA-IR level was calculated from the area under the curve for the 3 repeated measures divided by the total number of days between repeated measures. All statistical calculations were performed using Intercooled Stata 12 (StataCorp). A 2-tailed alpha level of 0.05 was used throughout.

RESULTS

Baseline characteristics

Baseline characteristics of the 195 RA patients and 198 controls are summarized in Table 1. Demographic and anthropometric characteristics and reported exercise were balanced between groups, but duration of TV watching was statistically significantly higher in the RA group. Among cardiovascular risk factors, the prevalence of hypertension was higher in the RA group (54%) than in the control group (38%) ($P = 0.002$); however, RA patients and controls had a similar prevalence of impaired fasting glucose, diabetes, smoking, and similar mean levels of high-density lipoprotein (HDL), LDL, and triglycerides, and they received similar treatment with lipid-lowering medications. Controls were slightly more likely to meet classification requirements for the metabolic syndrome (23% of RA patients versus 31% of controls; $P = 0.051$). As expected, median levels of CRP and IL-6 were significantly higher in RA patients than in controls.

Prevalence rates of CAC and ICA/bulb plaque and the average IMT in this cohort have been reported previously (3,5). Briefly, the prevalence of moderate-to-severe CAC (defined as an Agatston score of >100), the median ICA-IMT (but not median CCA-IMT), and the prevalence of ICA/bulb plaque were higher in the RA group than in the control group.

Among RA patients, median disease duration was 9 years, and 78% of patients were seropositive for either RF or anti-CCP. Shared epitope alleles were observed in 70% of

patients. The median DAS28 was in the moderate range (3.6 units), and baseline HAQ scores indicated mild-to-moderate reported disability for the majority of enrollees. Glucocorticoids were prescribed in 38% of patients at the time of data collection, but 74% of patients had received glucocorticoids at some point in their clinical course. Current treatment with biologic and nonbiologic DMARDs was recorded in 46% and 85% of patients, respectively.

Insulin resistance according to RA status

Average HOMA-IR levels, according to RA status and stratified by selected participant characteristics, are shown in Table 2. Mean HOMA-IR levels were significantly higher (by 31%) in the total RA group than in the control group, a relative increase that was evident in both men and women with RA, although only among white patients. As expected, increasing BMI was associated with higher HOMA-IR levels in both groups; however, the RA group demonstrated higher mean HOMA-IR levels than controls at all BMI categories. Importantly, the largest relative difference in HOMA-IR between RA patients and controls was observed in RA patients in the “normal” BMI group (i.e., BMI <25), in which mean HOMA-IR levels were 61% higher in the RA group than in the control group.

In both the RA and control groups, mean HOMA-IR levels were higher among those with metabolic syndrome versus those without metabolic syndrome or any of its components. Additionally, mean HOMA-IR levels were significantly higher in the RA group compared with the control group for all strata of metabolic syndrome and its components. In fact, the relative difference in the mean HOMA-IR level between the RA and control groups was similar for those meeting and those not meeting classification criteria for metabolic syndrome (+39% versus +37%, respectively), and was not meaningfully different for those with no metabolic syndrome components compared with those with 3 or more components of metabolic syndrome (+35% versus +44%, respectively). Adjustment, where appropriate, for relevant characteristics associated with HOMA-IR in the combined RA and control groups (ethnicity, educational attainment, waist circumference, exercise, TV watching, hypertension, diabetes, HDL cholesterol levels, triglyceride levels, and use of lipid-lowering medication) did not meaningfully alter the relative differences in mean HOMA-IR levels between the RA and control groups from those observed in the crude comparisons.

Association of IL-6 and CRP levels with IR according to RA status

Comparisons (between the RA and control groups) of the associations of IL-6 and CRP levels with the HOMA-IR index are depicted in Figure 1. The linear association of the log IL-6 level with the log HOMA-IR index (Figure 1A) was strong and significant in the control group ($\beta = 0.38$, $P < 0.001$) but weaker and not statistically significant in the RA group ($\beta = 0.06$, $P = 0.18$). The linear association differed between the RA and control groups ($P < 0.001$ for the interaction between RA status and IL-6 level). The linear association of log CRP level with the log HOMA-IR index (Figure 1B) was significant in both the control and RA groups ($\beta = 0.17$ [$P < 0.001$] and $\beta = 0.09$ [$P = 0.007$], respectively). Although the association of log CRP level with log HOMA-IR index was weaker in the RA group, the difference in linear slope was not significantly different from that in the control group ($P = 0.15$ for the interaction). For both associations, RA patients

with the lowest IL-6 and CRP levels had significantly higher HOMA-IR levels than control subjects.

Associations of RA characteristics with IR

Crude and adjusted associations of RA characteristics with the log HOMA-IR index are shown in Table 3. Before any adjustment, higher log HOMA-IR levels were associated with RF and anti-CCP seropositivity, higher HAQ and SHS scores, the presence of rheumatoid nodules, and higher cumulative prednisone dose in women. After adjustment for relevant demographic, lifestyle, CVD risk factor, and RA characteristics (model 3), RF seropositivity, current prednisone use, and higher cumulative prednisone dose were the only RA characteristics significantly associated with the log HOMA-IR in women. In men, only RF seropositivity was significantly associated with higher log HOMA-IR levels after adjustment. These data translate to average adjusted HOMA-IR levels 48% higher among those with versus those without RF (0.92 versus 0.62 units, respectively; $P < 0.001$) for men and women combined, and average adjusted HOMA-IR levels 40% higher among female prednisone users versus nonusers (0.99 versus 0.70, respectively; $P = 0.013$).

Association of IR with measures of subclinical atherosclerosis according to RA status

Associations of the log HOMA-IR index with measures of coronary and carotid atherosclerosis are depicted in Figure 2. In the control group, higher HOMA-IR levels were significantly associated, on average, with higher CAC scores (r = 0.227, $P = 0.0013$) (Figure 2A) before adjustment. In contrast, higher HOMA-IR levels did not correlate with higher CAC scores in the RA group, a difference in associations as compared with controls that was statistically significant ($P = 0.024$ for the interaction). The association of the log HOMA-IR index with log CAC + 1 remained significant in the control group after adjusting for demographic characteristics and physical activity, but was no longer significant after additional adjustment for waist circumference or traditional CVD risk factors. Similarly, before adjustment, higher HOMA-IR levels were associated, on average, with significantly higher CCA-IMT (Figure 2B) and ICA-IMT (Figure 2C) levels in the control group, but not in the RA group. Adjustment for demographic characteristics, physical activity, waist circumference, and traditional CVD risk factors further reduced the magnitude of the associations of HOMA-IR with IMT in both groups, and narrowed the difference in association between the groups. Similar relationships were observed for the association of HOMA-IR with the frequency of carotid plaque (data not shown). Within the RA group, adjustment dose for RF and cumulative prednisone did not alter the association between HOMA-IR and atherosclerosis measures (data not shown).

Association of baseline and average HOMA-IR with change in measures of subclinical atherosclerosis among the RA group

A total of 155 RA patients had repeated CAC and carotid ultrasonographic measures of atherosclerosis, which occurred a mean ± SD of 39 ± 4 months postbaseline. Rates of change in these outcomes have been reported previously (29,30). Although there was intrasubject variation in HOMA-IR for the 3 repeated measures over the study interval, the correlation between baseline and time-weighted average HOMA-IR was high (Spearman's rho = 0.869; $P < 0.001$). However, neither baseline nor average HOMA-IR levels were

significantly associated with the change in CAC, CCA-IMT, ICA-IMT, or carotid plaque, either in crude analyses or in models adjusted for pertinent demographic, lifestyle, or RA characteristics or cardiovascular risk factors (data not shown).

DISCUSSION

Among our cohort of RA patients and demographically similar controls without overt CVD, we detected significantly higher levels of IR, estimated using the HOMA-IR index, among white patients in the RA group compared with controls regardless of demographic characteristics, lifestyle characteristics, and levels of cardiometabolic risk factors. Among RA patients, RF seropositivity and glucocorticoids (both current use and cumulative exposure) (in women only) were associated with higher IR levels. However, we did not detect an association of IR, either at baseline or averaged over the study interval, with baseline or change in measures of coronary or carotid atherosclerosis, either in crude analyses or after adjustment for relevant cardiometabolic correlates.

A few prior smaller studies (7,9,10,31) have reported higher levels of IR among RA patients compared with non-RA controls. Differing from previous studies, we compared levels of IR between RA and non-RA groups according to strata of relevant characteristics. Of interest, RA patients with characteristics atypical for IR (i.e., those with lower BMI and those with no risk factors for metabolic syndrome) had higher levels of IR compared with controls with similar characteristics. In fact, compared with other strata, relative differences in IR between RA and non-RA were highest within these low-risk strata. The etiology of higher IR among this low-risk RA group is unclear, but is likely multifactorial. A major determinant of IR is fat mass, in particular visceral fat. With increasing visceral fat mass, adipose and skeletal muscle uptake and utilization of glucose and free fatty acid is impaired, hepatic glycogen storage is reduced, and synthesis of triglyceride-rich lipoproteins is increased concomitant with a reduction in their clearance—common features of the metabolic syndrome that accompanies IR (32). In prior studies (33,34), we demonstrated higher levels of total and truncal fat as well as visceral fat among RA patients as compared with controls. Notably, the largest relative difference in fat mass between RA patients and controls was among those in the “normal weight” BMI group, suggesting that RA patients classified as being of normal weight may actually have a higher fat mass than would be implied from their BMI classification. This may account, at least in part, for the higher IR among RA patients with lower BMI. In the present study, we did not have body composition assessments for the non-RA controls other than basic anthropometrics. Thus, we could not confirm the possibility of higher truncal or visceral fat levels among the RA patients with IR in the lower BMI categories as compared with controls.

In addition to fat mass, inflammatory cytokines have been recognized as key regulators of metabolism. In particular, TNFα and other proinflammatory cytokines have been shown to have pleiotropic effects on metabolism in multiple tissues. Specifically, TNFα inhibits signaling through insulin receptors via inhibition of tyrosine phosphorylation (35). In light of this, we were somewhat surprised to see a weaker association of measures of systemic inflammation with IR among the RA group as compared with the control group. There are several possible explanations. For one, we observed that RA patients with lower levels of

IL-6 had higher levels of IR compared with controls with similar levels of IL-6, while those with higher levels of IL-6 had similar levels of IR as compared with controls. This could indicate other noninflammatory processes accounting for higher IR at lower IL-6 levels. Another possibility is a ceiling effect in tissue IR response to higher levels of inflammatory cytokines, as indicated by prior in vitro studies (35). Finally, since levels of inflammatory cytokines are known to fluctuate in RA, a single measurement of IL-6 at baseline may not account for variability in levels in the preceding period that may be relevant to current insulin sensitivity. This effect may be more limited among controls, in which levels of inflammatory cytokines, even higher levels, are presumably more stable over time.

Although we did not detect a strong association between levels of systemic inflammation and IR among RA patients, we did note several RA characteristics that had strong associations. For one, IR levels among RF-seropositive patients were nearly 50% higher than among those who were seronegative, an effect roughly equivalent to the difference in HOMA-IR between an RA patient meeting 2 metabolic syndrome criteria versus one meeting no criteria. Although RF seropositivity could be a surrogate for RA severity or higher cumulative levels of systemic inflammation, we did not observe the same association with other measures of RA severity (i.e., SHS scores, HAQ), other autoantibodies (i.e., anti-CCP), or genetic markers of disease (i.e., shared epitope), raising the possibility of a specific causal effect of RF on IR that remains to be elucidated. In confirmation of our findings, higher HOMA-IR levels were observed among patients with seropositive early inflammatory polyarthritis in a recent study (36).

The biologic plausibility behind higher IR levels among prednisone users is not surprising, as in vitro the insulin-resistant state (i.e., reduced insulin-stimulated glucose and free fatty acid uptake in muscle and adipose tissue) is recreated with glucocorticoid exposure (37). Although recent studies (38) reporting modest effects of short-term glucocorticoid exposure on IR in RA patients are reassuring, our data support the potential for adverse effects related to long-term exposure that may be underestimated in the shorter time frame of an interventional trial. In our study, glucocorticoid use was primarily associated with IR among women only, perhaps due to an interaction with estrogens and/or other sex-specific physiologic processes (39). This finding requires further study into the mechanisms of disease.

Perhaps most surprisingly, despite higher IR levels among nearly every subgroup of RA patients studied as compared with controls (consistent with the well-established increase in CVD in RA), we did not observe any apparent association between IR and multiple measures of subclinical atherosclerosis within our RA cohort. In several prior studies of the general population, higher HOMA-IR levels were associated with CVD events (40), CAC (41), and extra-coronary vascular calcification (42), in some even after adjustment for CVD risk factors (40,41); however, not all studies have demonstrated an independent association (42). Because higher HOMA-IR levels are so strongly associated with multiple components of metabolic syndrome that themselves may be proatherogenic, it is not surprising that HOMA-IR has been shown to be a predictive index of CVD risk. In our study, HOMA-IR was associated with measures of atherosclerosis in the control group, and was diminished only upon adjustment for the elements of metabolic syndrome to which it is linked.

However, we did not observe the same associations within the RA group. This could suggest an unlinking of the mechanisms mediating higher HOMA-IR levels and those mediating atherosclerosis in RA, perhaps reducing the predictive ability of HOMA-IR for CVD. Our findings are broadly compatible with other reports in RA demonstrating an unlinking between adipokine indicators of insulin resistance (i.e., adiponectin and leptin) and atherosclerosis (43). At present, our cohort is being followed up longitudinally for CVD events, which will provide information as to whether HOMA-IR is better at predicting events than is subclinical atherosclerosis (44).

There are notable strengths and limitations to our study. Among strengths, this is, to our knowledge the largest study of the relationship between IR and atherosclerosis to date in RA and the only one to explore longitudinal associations in multiple vascular beds in the same cohort. An additional strength is the comparability of the RA cases and controls, who were not only geographically compatible (with all atherosclerosis assessments performed on the same equipment), but were also carefully balanced with regard to demographic characteristics, even within subgroups. Among study limitations, there are well-recognized limitations of HOMA as an estimate of IR compared with the more accurate timed oral glucose tolerance test or hyperinsulinemic euglycemic clamp (23). However, since measurements in cases and controls were performed in the same way, there is little reason to believe that between-group comparisons in HOMA-IR are impugned. Moreover, the cumbersome methodology of the hyperinsulinemic clamp makes it largely unsuitable for a study of our size. Finally, our comparisons of associations according to RA status were cross-sectional and are thus subject to uncertainties in causality.

In summary, we found higher levels of whole-body IR among RA patients of all strata compared with controls. However, we found little indication that these higher levels impart a higher risk of subclinical atherosclerosis progression in either the coronary or the carotid arteries among a population with increased cardiovascular risk.

Acknowledgments

We thank the Johns Hopkins Bayview Medical Center General Clinical Research Center and staff, the field center of the Baltimore MESA cohort, and the MESA Coordinating Center at the University of Washington, Seattle. We gratefully acknowledge the dedication and hard work of the ESCAPE RA staff (Marilyn Towns, Michelle Jones, Patricia Jones, Marissa Hildebrandt, Shawn Franckowiak, and Brandy Miles) and the participants in the ESCAPE RA study who graciously agreed to take part in this research. We also thank Drs. Uzma Haque, Clifton Bingham III, Carol Ziminski, Jill Ratain, Ira Fine, Joyce Kopicky-Burd, David McGinnis, Andrea Marx, Howard Hauptman, Achini Perera, Peter Holt, Alan Matsumoto, Megan Clowse, Gordon Lam, and others for generously recommending their patients for this study. We thank Dr. William Scott Jr. for interpreting all baseline radiographs.

Supported by the NIH (National Institute of Arthritis and Musculoskeletal and Skin Diseases grants 1K23-AR-054112-01 to Dr. Giles and AR-050026-01 to Dr. Bathon) and the Rheumatology Research Foundation (Clinical Investigator Fellowship to Dr. Giles and Within Our Reach grant to Dr. Bathon). Dr. Blumenthal holds the Kenneth Jay Pollin Professorship in Cardiology at Johns Hopkins University. The Johns Hopkins Bayview Medical Center General Clinical Research Center is supported by the NIH (grant M01-RR-02719). The Multi-Ethnic Study of Atherosclerosis (MESA) is funded by the NIH (National Heart, Lung, and Blood Institute contracts N01-HC-95159 through N01-HC-95169).

References

1. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2005; 52:722–32. [PubMed: 15751097]
2. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008; 59:1690–7. [PubMed: 19035419]
3. Kobayashi H, Giles JT, Polak JF, Blumenthal RS, Leffell MS, Szklo M, et al. Increased prevalence of carotid artery atherosclerosis in rheumatoid arthritis is artery-specific. J Rheumatol. 2010; 37:730–9. [PubMed: 20110515]
4. Kumeda Y, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis Rheum. 2002; 46:1489–97. [PubMed: 12115178]
5. Giles JT, Szklo M, Post W, Petri M, Blumenthal RS, Lam G, et al. Coronary arterial calcification in rheumatoid arthritis: comparison to the Multi-Ethnic Study of Atherosclerosis. Arthritis Res Ther. 2009; 11:R36. [PubMed: 19284547]
6. Del Rincon I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum. 2001; 44:2737–45. [PubMed: 11762933]
7. Svenson KL, Pollare T, Lithell H, Hallgren R. Impaired glucose handling in active rheumatoid arthritis: relationship to peripheral insulin resistance. Metabolism. 1988; 37:125–30. [PubMed: 2893241]
8. Dessein PH, Stanwix AE, Joffe BI. Cardiovascular risk in rheumatoid arthritis versus osteoarthritis: acute phase response related decreased insulin sensitivity and high-density lipoprotein cholesterol as well as clustering of metabolic syndrome features in rheumatoid arthritis. Arthritis Res. 2002; 4:R5. [PubMed: 12223108]
9. Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis Rheum. 2006; 54:2765–75. [PubMed: 16947779]
10. Rosenvinge A, Krogh-Madsen R, Baslund B, Pedersen BK. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNF therapy. Scand J Rheumatol. 2007; 36:91–6. [PubMed: 17476613]
11. Dessein PH, Joffe BI, Stanwix AE. Effects of disease modifying agents and dietary intervention on insulin resistance and dyslipidemia in inflammatory arthritis: a pilot study. Arthritis Res. 2002; 4:R12. [PubMed: 12453315]
12. Rho YH, Chung CP, Solus JF, Raggi P, Oeser A, Gebretsadik T, et al. Adipocytokines, insulin resistance, and coronary atherosclerosis in rheumatoid arthritis. Arthritis Rheum. 2010; 62:1259–64. [PubMed: 20213808]
13. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis. 2008; 196:756–63. [PubMed: 17266963]
14. Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis. 2005; 64:765–6. [PubMed: 15458960]
15. Tam LS, Tomlinson B, Chu TT, Li TK, Li EK. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin Rheumatol. 2007; 26:1495–8. [PubMed: 17237906]
16. Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. Arch Intern Med. 2006; 166:902–8. [PubMed: 16636217]
17. Dessein PH, Tobias M, Veller MG. Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. J Rheumatol. 2006; 33:2425–32. [PubMed: 17080519]
18. La Montagna G, Cacciapuoti F, Buono R, Manzella D, Mennillo GA, Arciello A, et al. Insulin resistance is an independent risk factor for atherosclerosis in rheumatoid arthritis. Diab Vasc Dis Res. 2007; 4:130–5. [PubMed: 17654447]

19. Pamuk ON, Unlu E, Cakir N. Role of insulin resistance in increased frequency of atherosclerosis detected by carotid ultrasonography in rheumatoid arthritis. J Rheumatol. 2006; 33:2447–52. [PubMed: 17143979]
20. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31:315–24. [PubMed: 3358796]
21. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990; 15:827–32. [PubMed: 2407762]
22. Blair SN, Haskell WL, Ho P, Paffenbarger RS Jr, Vranizan KM, Farquhar JW, et al. Assessment of habitual physical activity by a seven-day recall in a community survey and controlled experiments. Am J Epidemiol. 1985; 122:794–804. [PubMed: 3876763]
23. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004; 27:1487–95. [PubMed: 15161807]
24. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C, for the Conference Partcipants. 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. [PubMed: 14744958]
25. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995; 38:44–8. [PubMed: 7818570]
26. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980; 23:137–45. [PubMed: 7362664]
27. Van der Heijde DM. How to read radiographs according to the Sharp/van der Heijde method [corrected and republished in J Rheumatol 2000;27:261–3]. J Rheumatol. 1999; 26:743–5. [PubMed: 10090194]
28. Nettleton JA, Steffen LM, Mayer-Davis EJ, Jenny NS, Jiang R, Herrington DM, et al. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Clin Nutr. 2006; 83:1369–79. [PubMed: 16762949]
29. Giles JT, Post WS, Blumenthal RS, Polak J, Petri M, Gelber AC, et al. Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis. Arthritis Rheum. 2011; 63:3216–25. [PubMed: 21965129]
30. Chung CP, Giles JT, Kronmal RA, Post WS, Gelber AC, Petri M, et al. Progression of coronary artery atherosclerosis in rheumatoid arthritis: comparison with participants from the Multi-Ethnic Study of Atherosclerosis. Arthritis Res Ther. 2013; 15:R134. [PubMed: 24286380]
31. Hoes JN, van der Goes MC, van Raalte DH, van der Zijl NJ, den Uyl D, Lems WF, et al. Glucose tolerance, insulin sensitivity and -cell function in patients with rheumatoid arthritis treated with or without low-to-medium dose glucocorticoids. Ann Rheum Dis. 2011; 70:1887–94. [PubMed: 21908880]
32. Bush NC, Basu R, Rizza RA, Nair KS, Khosla S, Jensen MD. Insulin-mediated FFA suppression is associated with triglyceridemia and insulin sensitivity independent of adiposity. J Clin Endocrinol Metab. 2012; 97:4130–48. [PubMed: 22933539]
33. Giles JT, Allison M, Blumenthal RS, Post W, Gelber AC, Petri M, et al. Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. Arthritis Rheum. 2010; 62:3173–82. [PubMed: 20589684]
34. Giles JT, Ling SM, Ferrucci L, Bartlett SJ, Andersen RE, Towns M, et al. Abnormal body composition phenotypes in older rheumatoid arthritis patients: association with disease characteristics and pharmacotherapies. Arthritis Rheum. 2008; 59:807–15. [PubMed: 18512711]
35. Hotamisligil GS, Murray DL, Choy LN, Spiegelman BM. Tumor necrosis factor α inhibits signaling from the insulin receptor. Proc Natl Acad Sci U S A. 1994; 91:4854–8. [PubMed: 8197147]

36. Mirjafari H, Farragher TM, Verstappen SM, Yates A, Bunn D, Marshall T, et al. Seropositivity is associated with insulin resistance in patients with early inflammatory polyarthritis: results from the Norfolk Arthritis Register (NOAR): an observational study. Arthritis Res Ther. 2011; 13:R159. [PubMed: 21959060]

37. Lundgren M, Buren J, Ruge T, Myrnas T, Eriksson JW. Gluco-corticoids down-regulate glucose uptake capacity and insulin-signaling proteins in omental but not subcutaneous human adipocytes. J Clin Endocrinol Metab. 2004; 89:2989–97. [PubMed: 15181089]

38. Den Uyl D, van Raalte DH, Nurmohamed MT, Lems WF, Bijlsma JW, Hoes JN, et al. Metabolic effects of high-dose prednisolone treatment in early rheumatoid arthritis: balance between diabetogenic effects and inflammation reduction. Arthritis Rheum. 2012; 64:639–46. [PubMed: 21953589]

39. Alemany M. Do the interactions between glucocorticoids and sex hormones regulate the development of the metabolic syndrome? Front Endocrinol (Lausanne). 2012; 3:27. [PubMed: 22649414]

40. Tenenbaum A, Adler Y, Boyko V, Tenenbaum H, Fisman EZ, Tanne D, et al. Insulin resistance is associated with increased risk of major cardiovascular events in patients with preexisting coronary artery disease. Am Heart J. 2007; 153:559–65. [PubMed: 17383294]

41. Lee KK, Fortmann SP, Fair JM, Iribarren C, Rubin GD, Varady A, et al. Insulin resistance independently predicts the progression of coronary artery calcification. Am Heart J. 2009; 157:939–45. [PubMed: 19376325]

42. Tison GH, Blaha MJ, Budoff MJ, Katz R, Rivera JJ, Bertoni AG, et al. The relationship of insulin resistance and extracoronary calcification in the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2011; 218:507–10. [PubMed: 21798541]

43. Dessein PH, Norton GR, Badenhorst M, Woodiwiss AJ, Solomon A. Rheumatoid arthritis impacts on the independent relationships between circulating adiponectin concentrations and cardiovascular metabolic risk. Mediators Inflamm. 2013; 2013:461849. [PubMed: 23690663]

44. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2013; 61:1231–9. [PubMed: 23500326]

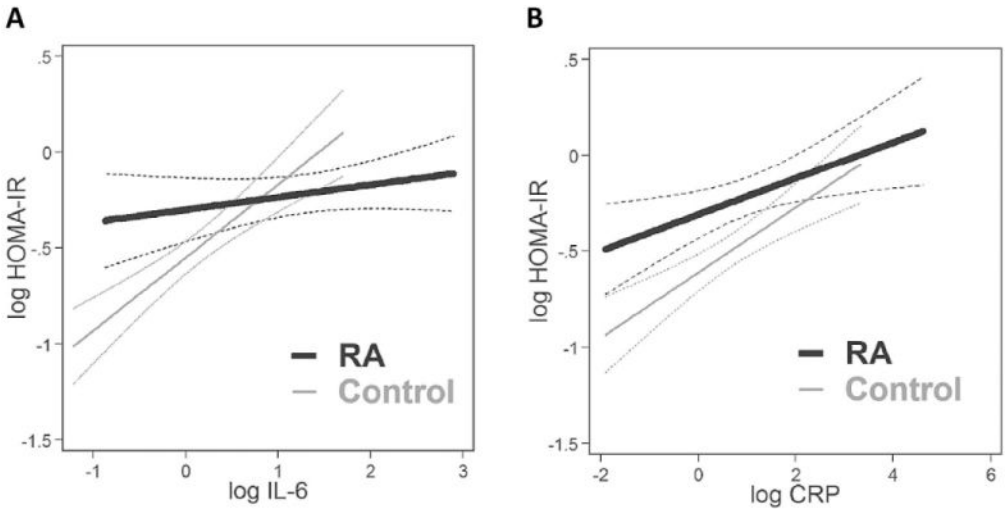

Figure 1.

Associations of log-transformed interleukin-6 (IL-6) and C-reactive protein (CRP) levels with the log-transformed homeostatic model assessment of insulin resistance (HOMA-IR) index in the rheumatoid arthritis (RA) group and the non-RA control group. Shown are the least squares estimators for the average association and the 95% confidence intervals (dotted lines). **A**, A strong linear association between the IL-6 level and the HOMA-IR index was found in the control group ($\beta = 0.381$, $P = 0.001$), although the association was weaker, and not significant, in the RA group ($\beta = 0.064$, $P = 0.18$) ($P < 0.001$ for the interaction between RA status and IL-6 level). **B**, The linear association between the CRP level and the HOMA-IR index was significant in both the RA group ($\beta = 0.094$, $P = 0.007$) and the control group ($\beta = 0.169$, $P < 0.001$) ($P = 0.15$ for the interaction between RA status and CRP level).

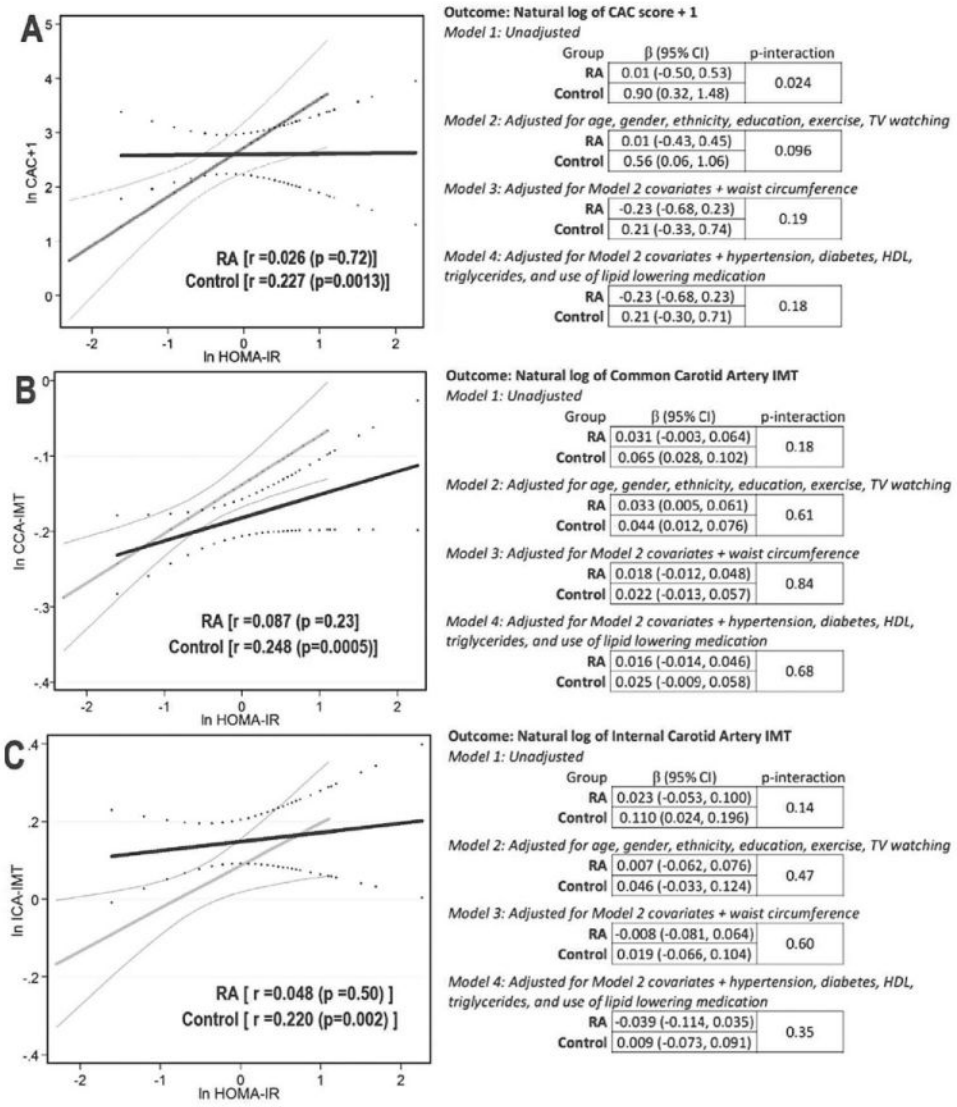

Figure 2.

Associations of the natural log–transformed homeostatic model assessment of insulin resistance (HOMA-IR) index with coronary artery calcium (CAC) (**A**), the intima-media thickness (IMT) of the common carotid artery (CCA) (**B**), and the IMT of the internal carotid artery (ICA) (**C**). Shown at left are least squares estimators for the average association in the rheumatoid arthritis (RA) group (solid lines) and the non-RA control group (shaded lines) and corresponding 95% confidence intervals (95% CIs) (dotted lines), as well as Spearman's correlation coefficients for each group. Shown at right are crude and adjusted β coefficients following linear regression with associated 95% CIs for the average association between IR and measures of coronary and carotid atherosclerosis. *P* values are for the interaction between RA status and the measures of coronary and carotid atherosclerosis. HDL = high-density lipoprotein.

Table 1

Characteristics of the study participants*

	RA patients (n 195)	Controls (n 198)	*P*
Age, years	59 ± 9	60 ± 9	0.55
Male, no. (%)	77 (39)	71 (36)	0.46
White, no. (%)	169 (87)	177 (89)	0.40
Any college education, no. (%)	147 (75)	153 (78)	0.59
Body mass index, kg/m^2	28.4 ± 5.3	28.8 ± 5.7	0.48
Waist circumference, cm	96 ± 16	97 ± 15	0.40
Exercise, minutes/day	32 (0–77)	32 (11–77)	0.55
TV watching, minutes/day	120 (60–180)	103 (45–180)	0.036
Hypertension, no. (%)	104 (54)	75 (38)	0.002
Fasting glucose, no. (%)			
Normal	151 (77)	139 (70)	0.10
Impaired	33 (17)	42 (21)	0.28
Diabetes	11 (6)	17 (9)	0.26
Ever smoking, no. (%)	115 (59)	107 (54)	0.35
Current smoking, no. (%)	23 (12)	19 (10)	0.49
HDL cholesterol, mg/dl	55 ± 19	52 ± 15	0.13
LDL cholesterol, mg/dl	116 ± 31	118 ± 30	0.46
Triglycerides, mg/dl	107 (68–151)	114 (76–161)	0.25
Taking lipid-lowering medications, no. (%)	34 (17.4)	46 (23.2)	0.15
Metabolic syndrome, no. (%)	44 (23)	62 (31)	0.051
CRP, mg/liter	2.5 (1.1–7.2)	2.3 (0.9–4.7)	0.041
IL-6, pg/ml	3.9 (1.8–7.8)	1.1 (0.7–1.9)	<0.001
CAC score >0, no. (%)	107 (55)	107 (54)	0.87
CAC score ≥100, no. (%)	69 (35)	48 (24)	0.016
Carotid plaque, no. (%)	42 (22)	23 (12)	0.009
ICA-IMT, mm	1.09 (0.84–1.54)	0.92 (0.80–1.23)	0.002
CCA-IMT, mm	0.82 (0.75–0.92)	0.84 (0.75–0.94)	0.31
RA duration, years	9 (4–17)	–	–
RF or anti-CCP seropositivity	152 (78)	–	–
Any HLA–DRB1 shared epitope, no. (%)	135 (70)	–	–
DAS28-CRP, units	3.6 (2.9–4.4)	–	–
HAQ, units	0.63 (0.13–1.25)	–	–
Total SHS, units	44 (15–119)	–	–
Current prednisone, no. (%)	75 (38)	–	–
Current oral prednisone dose, mg/day	5 (5–10)	–	–
Ever prednisone, no. (%)	145 (74)	–	–
Cumulative prednisone, gm	5.5 (2.5–11.4)	–	–
Current nonbiologic DMARD, no. (%)	164 (85)	–	–

	RA patients (n 195)	Controls (n 198)	*P*
Methotrexate	124 (64)	–	–
Hydroxychloroquine	47 (24)	–	–
Current biologic DMARD, no. (%)	89 (46)	–	–
TNF inhibitor	85 (44)	–	–

*Except where indicated otherwise, values are the mean ± SD or median (interquartile range). RA = rheumatoid arthritis; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CRP = C-reactive protein; IL-6 = interleukin-6; CAC = coronary artery calcium; ICA-IMT = internal carotid artery intima-media thickness; CCA-IMT = common carotid artery IMT; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; DAS28-CRP = Disease Activity Score in 28 joints using the CRP level; HAQ = Health Assessment Questionnaire; SHS = Sharp/van der Heijde score; DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.

Table 2

Crude and adjusted mean HOMA-IR levels, stratified by selected characteristics of the participants *

	Crude				Adjusted†			
	Mean HOMA-IR (95% CI)				Mean HOMA-IR (95% CI)			
	RA patients	Controls	*P*	% difference	RA patients	Controls	*P*	% difference
Total (n 393)	0.80 (0.73–0.88)	0.61 (0.55–0.67)	<0.001	+31	0.80 (0.73–0.88)	0.61 (0.55–0.67)	<0.001	+31
Sex								
Women (n = 245)	0.77 (0.68–0.87)	0.59 (0.52–0.66)	0.002	+31	0.80 (0.72–0.89)	0.57 (0.51–0.63)	<0.001	+40
Men (n = 148)	0.86 (0.74–1.00)	0.64 (0.55–0.75)	0.008	+34	0.82 (0.72–0.93)	0.68 (0.59–0.78)	0.040	+21
Ethnicity								
Nonwhite (n = 47)	0.85 (0.65–1.09)	0.95 (0.71–1.28)	0.56	−11	0.86 (0.68–1.07)	0.93 (0.72–1.21)	0.63	−8
White (n = 346)	0.80 (0.72–0.88)	0.58 (0.52–0.64)	<0.001	+38	0.80 (0.73–0.87)	0.58 (0.53–0.63)	<0.001	+38
BMI, kg/m^2								
<25.0 (n = 108)	0.61 (0.52–0.71)	0.38 (0.33–0.45)	<0.001	+61	0.62 (0.53–0.71)	0.38 (0.32–0.44)	<0.001	+63
25–29.9 (n = 147)	0.72 (0.63–0.83)	0.58 (0.50–0.66)	0.026	+24	0.72 (0.64–0.82)	0.57 (0.50–0.65)	0.012	+26
≥30.0 (n = 138)	1.15 (0.99–1.32)	0.91 (0.79–1.05)	0.026	+26	1.13 (0.99–1.29)	0.94 (0.82–1.07)	0.051	+20
No. of metabolic syndrome components								
0 (n = 74)	0.54 (0.45–0.66)	0.40 (0.33–0.48)	0.026	+35	0.55 (0.45–0.66)	0.40 (0.33–0.48)	0.017	+35
1–2 (n = 209)	0.73 (0.65–0.82)	0.55 (0.49–0.62)	0.001	+33	0.72 (0.65–0.81)	0.56 (0.50–0.63)	0.002	+33
≥3 (n = 110)	1.34 (1.13–1.58)	0.93 (0.80–1.08)	0.002	+44	1.33 (1.13–1.56)	0.94 (0.81–1.09)	0.003	+44

*95% CI 95% confidence interval; RA rheumatoid arthritis; BMI body mass index.

†Adjusted for ethnicity, education, waist circumference, exercise, sedentary activity, hypertension, diabetes, high-density lipoprotein cholesterol, log-transformed triglyceride levels, and use of lipid-lowering medication. The adjusted homeostatic model assessment of insulin resistance (HOMA-IR) index was obtained from linear regression of the log HOMA-IR index with back-transformation.

Table 3

Associations of RA characteristics with the log HOMA-IR index*

	Model 1		Model 2		Model 3	
	β	*P*	*β*	*P*	*β*	*P*
Women						
RA duration, per year	0.005	0.42				
RF seropositive	0.517	<0.001	0.441	0.002	0.441	<0.001
Anti-CCP seropositive	0.260	0.047	−0.080	0.58		
Any shared epitope alleles	0.177	0.16	−0.011	0.93		
DAS28, per unit	0.002	0.97				
HAQ, per unit	0.077	0.39				
SHS, per log unit	0.078	0.080	0.020	0.64		
Current rheumatoid nodules	0.185	0.13	0.147	0.21		
Any current prednisone	0.328	0.010	0.272	0.023	0.285	0.013
Current prednisone, per gm/day	0.034	0.037				
Cumulative prednisone, per gm	0.015	0.030	0.011	0.093	0.014	0.023
Any nonbiologic DMARD	0.059	0.72				
Current methotrexate	−0.015	0.91				
Current hydroxychloroquine	−0.014	0.31				
Any current biologic DMARD	0.140	0.22				
Current TNF inhibitor	0.126	0.29				
Men						
RA duration, per year	−0.010	0.13	−0.005	0.35		
RF seropositive	0.315	0.015	0.265	0.057	0.322	0.009
Anti-CCP seropositive	0.237	0.11	0.130	0.40		
Any shared epitope alleles	0.068	0.64				
DAS28, per unit	−0.033	0.53				
HAQ, per unit	−0.102	0.33				
SHS, per log unit	−0.033	0.51				
Current rheumatoid nodules	0.082	0.58				
Any current prednisone	0.011	0.94				

	Model 1		Model 2		Model 3	
	β	*P*	*β*	*P*	*β*	*P*
Current prednisone, per gm/day	0.005	0.67				
Cumulative prednisone, per gm	0.010	0.098	−0.009	0.11	−0.010	0.074
Any nonbiologic DMARD	−0.119	0.53				
Current methotrexate	0.001	0.99				
Current hydroxychloroquine	0.143	0.33				
Any current biologic DMARD	0.051	0.70				
Current TNF inhibitor	0.090	0.50				

*Beta coefficients represent the average change in the log homeostatic model assessment of insulin resistance (HOMA-IR) index per 1-unit higher value of the independent continuous variable of interest or for those with versus those without the independent dichotomous variable of interest. Covariates in model 1 include the covariate of interest and the non–rheumatoid arthritis (non-RA)–related covariates of education, waist circumference, exercise, TV watching, hypertension, diabetes, high-density lipoprotein, triglycerides, and use of lipid-lowering medications. The complex model 2 includes all of the RA covariates listed and the non-RA–related covariates from model 1. The reduced model 3 includes all of the RA covariates listed and the non-RA–related covariates from model 1. RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire; SHS = Sharp/van der Heijde score; DMARD = disease-modifying antirheumatic drug; TNF = tumor necrosis factor.