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Increased Prevalence of Metabolic Syndrome Associated with Rheumatoid Arthritis in Patients Without Clinical Cardiovascular Disease

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Abstract

Objective—The purpose of our study was to examine whether rheumatoid arthritis (RA) patients with no overt cardiovascular disease (CVD) have a higher prevalence of metabolic syndrome (MetS) than subjects without RA or CVD. We also examined whether RA disease characteristics are associated with the presence of MetS in RA patients without CVD.

Methods—Subjects from a population-based cohort of patients who fulfilled 1987 ACR criteria for RA between 1/1/1980 and 12/31/2007 were compared to non-RA subjects from the same population. All subjects with any history of CVD were excluded. Waist circumference, body mass index (BMI), and blood pressure were measured during the study visit. Data on CVD, lipids and glucose measures were ascertained from medical records. MetS was defined using NCEP/ATP III criteria. Differences between the 2 cohorts were examined using logistic regression models adjusted for age and sex.

Results—The study included 232 RA subjects without CVD and 1241 non-RA subjects without CVD. RA patients were significantly more likely to have an elevated waist circumference and elevated blood pressure than non-RA subjects, even though BMI was similar in both groups. Significantly more RA patients were classified as having MetS. In RA patients, MetS was associated with Health Assessment Questionnaire disability index, large joint swelling and uric acid levels, but not with C-reactive protein or RA therapies.

Conclusion—Among subjects without a history of CVD, RA patients are more likely to have MetS than non-RA subjects. MetS in RA patients was associated some measures of disease activity.

INTRODUCTION

Persons with rheumatoid arthritis (RA) suffer from an excess burden of cardiovascular disease (CVD) and the mechanisms of this increased risk are not yet fully understood.(1–3)

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In addition to other traditional cardiovascular risk factors, metabolic syndrome (MetS) is considered to be a significant and independent determinant of increased risk of CVD, although its definition and utility are controversial.(4,5) The main difference in the various definitions involves the measure of central obesity and a report on the efforts to reach a consensus definition was published recently.(6) MetS is a cluster of 3 or more of the following abnormalities: elevated waist circumference, elevated triglycerides, reduced high density lipoprotein, elevated blood pressure and elevated fasting glucose. Several studies have examined the prevalence of MetS in RA subjects and whether it is increased compared to subjects without RA, but the results have been inconsistent, perhaps due to differences in MetS definitions and in study populations.(7–10) Given the increased prevalence of CVD in RA subjects, an increased prevalence of MetS in these subjects would not be surprising. A more clinically relevant question is whether the prevalence of MetS is increased in RA subjects without overt CVD, as knowledge of such a relationship would present an opportunity for risk reduction interventions. The purpose of our study was to examine whether RA subjects with no history of CVD have a higher prevalence of MetS than subjects without RA and no history of CVD, and to examine whether RA disease characteristics are associated with the presence of MetS in RA subjects without CVD.

METHODS

Study Subjects and Design

This community population-based study of residents of Olmsted County, Minnesota was conducted using the resources of the Rochester Epidemiology Project (REP), a population-based medical records linkage system that allows ready access to the complete medical records from all community medical providers.(11) An incidence cohort of all residents of Olmsted County, Minnesota aged ≥18 years who first fulfilled 1987 American College of Rheumatology (ACR) classification criteria for RA between 1/1/1980 and 12/31/2007 was identified. (12,13) From among this incident RA cohort, we identified eligible RA subjects, namely those alive and living in Olmsted County. For this study, we recruited 232 (58%) of the 401 eligible RA subjects without CVD.

A cross-sectional study comparing these RA subjects to subjects from a community population-based cohort of subjects without RA was performed.(14) The institutional review boards of the Mayo Foundation and the Olmsted Medical Center approved this study. All subjects provided written informed consent prior to participation.

Data Collection

Study participation for subjects in both the RA and non-RA cohorts was identical except that RA subjects were asked additional questions pertaining to their RA disease. Subjects in both cohorts completed a cardiovascular risk factor and medication usage questionnaire, underwent a physical exam (including measurement of blood pressure, waist circumference, body mass index [BMI]) and provided a blood sample. Medical records were reviewed to ascertain diagnoses of CVD and to obtain recent measures of lipids and glucose. For each patient, the available laboratory measurements were performed after fasting and the measurements closest to the study visit within the period from 5 years prior to 1 year after the study visit (median: 2.3 years prior, interquartile range: 0.9 years to 3.6 years prior to study visit) were obtained. Lipid measures were not available in 21 RA and 324 non-RA subjects, and glucose measures were not available in 35 RA and 284 non-RA subjects. History of CVD was defined as physician diagnosis prior to the study visit of any of the following: angina pectoris, coronary artery disease, myocardial infarction or coronary revascularization procedures (i.e. bypass grafting, percutaneous coronary intervention). MetS was defined using the National Cholesterol Education Program (NCEP) Adult

Treatment Panel III (ATP III) criteria as affirmed and slightly modified by the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI)(15). The MetS definition requires any 3 of these 5 criteria: elevated waist circumference (≥102 cm in non-Asian men, ≥88 cm in non-Asian women, ≥90 cm in Asian men, ≥80 cm in Asian women), elevated triglycerides (TG ≥150 mg/dL or treatment with fibrates or nicotinic acid), reduced high-density cholesterol (HDL<40 mg/dL in men or <50 mg/dL in women or treatment with fibrates or nicotinic acid), elevated BP (≥130 mmHg systolic or ≥85 mmHg diastolic or treatment for hypertension) or elevated fasting glucose (FG ≥ 100 mg/dL or treatment for elevated glucose). In addition, these criteria are identical to those recently published in a joint interim statement for MetS.(6) However, the statement suggested another set of waist circumference thresholds for Europeans (≥94 cm in men, ≥80 cm in women) and recommended evaluation of both sets of thresholds in U.S. populations until a consensus is reached. Therefore, additional analyses using these lower thresholds were performed.

For individuals in the RA cohort, rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), C-reactive protein (CRP), interleukin 6 (IL-6) and uric acid levels were measured using the sample obtained at the study visit. RF testing was performed by nephelometry (latex enhanced assay; Behring Nephelometer II, Dade Behring, Inc., Newark, DE). ACPA and IL-6 testing were performed by enzyme immunoassay (INOVA Diagnostics, San Diego, CA and R & D Systems, Minneapolis, MN, respectively). CRP testing was performed by immunoturbidimetric assay (Roche CRPLX reagent, Indianapolis, IN). Uric acid testing was performed by Photometric, Uricase/Quinone-Imine Dye Formation (Roche Diagnostics, Indianapolis, IN). Medical records were reviewed to obtain RA disease duration and the presence of radiographic erosions based on radiographs obtained during clinical care. The questionnaire included the health assessment questionnaire (HAQ) disability score and RA medication usage at the time of the study visit, including systemic glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), biologic agents, and nonsteroidal anti-inflammatory drugs (NSAIDs). Systemic glucocorticoid use included either oral or intravenous forms (e.g., prednisone, methylprednisolone, hydrocortisone, and/or dexamethasone); DMARDs included methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, and/or azathioprine; and biologic agents included tumor necrosis factor inhibitors, anakinra, abatacept, and/or rituximab. RA medication usage at the study visit was verified with subjects' pill bottles and by reviewing the most recent medication list in the medical record for discrepancies.

Statistical Methods

Descriptive statistics were used to summarize the demographics and the criteria for MetS for both cohorts, as well as the RA disease characteristics for the RA cohort. Descriptive statistics in the non-RA cohort were adjusted to the age and sex distribution of the RA cohort to allow comparison. Differences between the two cohorts were tested using linear and logistic regression models adjusted for age and sex. Two-way interactions between cohort and age and sex were examined. Logistic regression models were also used to examine the association between MetS and RA disease characteristics adjusting for age, sex and RA disease duration. Chi-square and t-tests were used to examine differences between characteristics of patients with RA who participated in the study and those who did not participate.

RESULTS

The study included 232 RA subjects (mean age [SD] 58.8 [12.8] years, 75% women) and 1241 subjects without RA (mean age [SD] 63.9 [9.2] years, 55% women). Subjects with any history of CVD were excluded from both cohorts. Baseline characteristics for both cohorts

are reported in Table 1. Both cohorts were predominantly white (93% in RA vs. 92% in non-RA). The difference in racial distribution ($p<0.001$) was due to the higher percentage of Asians in the RA cohort (3% in RA vs. 0.4% in non-RA) and the higher percentage of persons of unknown race in the non-RA cohort. BMI, smoking and the use of statins were similar in both cohorts.

The criteria for MetS are reported in Table 2. RA subjects were significantly more likely to have an elevated waist circumference than non-RA subjects (age and sex adjusted odds ratio [OR]: 2.3; 95% confidence interval [CI]: 1.7, 3.1; $p<0.001$). This difference was even more pronounced after additional adjustment for BMI (OR: 4.7; 95% CI: 3.0, 7.5; $p<0.001$). RA subjects were also more likely to have elevated blood pressure (OR: 1.5; 95% CI: 1.1, 2.1; $p=0.02$). The proportion of subjects with elevated triglycerides, reduced HDL and elevated fasting glucose was similar in both groups ($p>0.25$).

The prevalence of MetS was higher in RA subjects (33%) compared to non-RA subjects (25%; Table 2). This difference was more pronounced after adjustment for age and sex (OR: 1.6; 95% CI: 1.2, 2.2; $p=0.004$) and was similar for both genders (interaction $p=0.87$). Among women, the prevalence of MetS was 32% in RA subjects compared to 25% in non-RA subjects. Among men, the prevalence of MetS was 36% in RA subjects compared to 26% in non-RA subjects. While the prevalence of MetS in both groups increased with age, the difference in prevalence between the RA and non-RA cohorts did not change significantly with age (interaction $p=0.18$). When subjects without laboratory measures were removed from both groups, results were similar with a higher prevalence of MetS among the 183 RA subjects (38%) compared to the 889 non-RA (34%; age and sex adjusted to the RA cohort, 21%) with complete data. However, this difference no longer achieved statistical significance (OR 1.3; 95% CI: 0.94, 1.9; $p=0.11$). Of note, comparisons of subjects with and without laboratory measures in both groups indicated subjects without laboratory measures were younger and less likely to be hypertensive ($p<0.001$ for both). Due to differences in the racial distribution of the 2 cohorts, analyses were performed excluding non-White subjects from each group and revealed identical results to those for the full dataset.

Using the lower waist circumference thresholds for Europeans, a higher percentage of each cohort met criteria for elevated waist circumference (71% of RA and 62% of non-RA), but the significant difference in the prevalence of elevated waist circumference among RA subjects compared to non-RA subjects persisted (OR=1.8; 95% CI: 1.3, 2.4; $p<0.001$). In addition, the prevalence of MetS increased minimally in each cohort (35% in RA and 31% in non-RA compared to the original values of 33% in RA and 25% in non-RA) and the significant difference in prevalence of MetS in RA subjects compared to non-RA subjects persisted (OR= 1.5; 95% CI: 1.1, 2.0; $p=0.013$).

In a secondary analysis, each RA subject was matched to 3 non-RA subjects with similar age and sex. Conditional logistic regression analyses revealed the prevalence of MetS was significantly increased in RA compared to non-RA subjects (OR=2.2; 95% CI: 1.5, 3.1; $p<0.001$).

Characteristics of RA subjects are summarized in Table 3. The median duration of RA was 7.0 years (interquartile range: 4.1 – 12.8 years), 69% were RF positive and 40% were ACPA positive. About one half of RA subjects had erosive disease on radiography with 97% having at least one radiographic assessment. The median HAQ score was 0.4 (interquartile range: 0 – 0.8). Current medications for RA subjects at the time of the study visit included methotrexate (56%), hydroxychloroquine (32%), other DMARDs (11%), biologic agents (16%), glucocorticoids (25%) and non-steroidal anti-inflammatory drugs (NSAIDs; 60%).

Age was significantly associated with MetS (OR: 1.5 per 10 year increase; 95% CI: 1.2, 1.9), but no significant association between RA disease duration and MetS was apparent (p=0.18; Table 3). HAQ score and history of large joint swelling were significantly associated with MetS (OR: 3.2 per 1 unit of HAQ, 95% CI: 1.9, 5.7 and OR 2.5, 95% CI: 1.2, 5.3, respectively). There were no significant associations with MetS for inflammatory markers (i.e. CRP, IL-6), RF positivity, ACPA positivity, presence of erosions or medication use. Cumulative steroid dose was also examined and was not found to be associated with MetS (p=0.73). However, the use of glucocorticoids was significantly associated with elevated waist circumference (OR: 2.1; 95% CI: 1.1, 3.9). Finally, there was a strong association between MetS and uric acid (OR: 1.6 per 1 mg/dL; 95% CI: 1.3, 2.1).

Additional analyses were performed to examine the differences between patients with RA who chose to participate in the study and those who declined to participate in order to determine whether participation bias may influence the results (Table 4). No differences were found in age, sex, duration of RA, RF positivity or marital status. Participants were significantly less likely to have smoked and achieved a higher level of education compared to non-participants. No differences were found for other cardiovascular risk factors (obesity, hypertension, diabetes mellitus and dyslipidemia).

DISCUSSION

RA patients without CVD are more likely to have MetS than non-RA subjects without CVD. Of MetS related characteristics, RA patients particularly have a higher prevalence of abdominal obesity and elevated blood pressure compared to non-RA subjects. After adjusting for age, sex and BMI, RA patients were more than 4 times as likely to have elevated waist circumference compared to non-RA subjects. The presence of MetS in RA patients was associated with higher HAQ scores and large joint swelling, but no significant associations with RA therapies were found.

Due to exclusion of patients with CVD, our estimates of the prevalence of MetS in RA were lower than other studies of RA patients, which reported prevalences of 40–50%. (9,10) Similarly, our estimated 25% prevalence of MetS in non-RA subjects was lower than the 34% reported by the National Health and Nutrition Examination Surveys (NHANES) for the general population.(16) Additional analyses including subjects with and without CVD who had available laboratory measures revealed the prevalence of MetS was 40% in RA and 35% in non-RA subjects, which are similar to the prevalences reported by others. Dessein et al reported a lower prevalence of MetS (only 19%) in RA patients, but patients taking glucose or lipid-lowering agents were excluded from their study.(8)

Results of previous studies comparing the prevalence of MetS in RA and non-RA subjects have been conflicting. Karvounaris et al reported 44% of their study cohort of Mediterranean patients with RA met NCEP/ATP III criteria for MetS, but found this to be no different than the 41% prevalence of MetS in their non-RA cohort.(9) However, their control group had an unusually high prevalence of abdominal obesity (83%) and elevated blood pressure (78%). In contrast, Chung et al reported a significant increase in prevalence of MetS in RA patients, especially those with long standing RA (30% in patients with early RA, 42% in patients with long-standing RA and 22% in non-RA subjects).(10)

Results of the association between MetS and RA disease characteristics and medications were widely varying. This variation is undoubtedly due, at least in part, to differing populations studied and study methodology. Whereas Chung et al report a strong association between MetS and RA disease duration, this association was not found by Karvounaris et al or in our study. (9,10) While we did not have Disease Activity Score (DAS) measures in our

cohort, we found MetS to be associated with higher HAQ scores and a history of large joint swelling, which are both indicators of RA disease severity related to physical disability. However, Chung et al found MetS was associated with the DAS and the erythrocyte sedimentation rate (ESR), but not with the HAQ.(10) Our findings of lack of association between MetS and other markers of inflammation (CRP and IL-6) in RA are in agreement with several studies (9,10,17), but differ from findings in patients with systemic lupus erythematosus (SLE) and in the general population.(18–21). Although the results of these studies are not consistent, an association between MetS and RA disease activity or severity seems likely and cannot be excluded.(22)

We also noted an association between MetS and elevated uric acid levels, which was not examined in previous studies of MetS in RA patients, but has been associated with MetS in patients with SLE and in the general population. (18,19,23) In addition, Panoulas et al reported uric acid is independently associated with hypertension in RA patients.(24) Evidence of a link between uric acid and cardiovascular risk is mounting, but treatment of asymptomatic hyperuricemia to reduce cardiovascular risk is not yet supported.(25)

Our study found no significant associations between MetS and medication use, although glucocorticoids were associated with elevated waist circumference. However, Chung et al reported a higher prevalence of MetS in patients taking glucocorticoids or hydroxychloroquine, but other medications such as methotrexate and biologic agents were not assessed. In contrast, several studies reported improvement of cardiovascular risk factors among patients using hydroxychloroquine.(26,27) Furthermore, Karvounaris et al reported a lower prevalence of MetS in patients taking glucocorticoids or biologic agents, but no significant association with methotrexate use.(9) Methotrexate use was associated with reduced prevalence of MetS by Toms et al, who also found no association between MetS and glucocorticoid use.(17,28) The role of glucocorticoids is complex as their use is associated with elevated waist circumference, but their use may also be confounded with disease severity. As none of these studies were randomized trials, it is likely that confounding by indication plays a role in these conflicting results.

Elevated waist circumference appears to play a bigger role in MetS in RA patients compared to non-RA subjects, since RA patients are more than 4 times as likely to have elevated waist circumference compared to non-RA subjects after adjustment for BMI. Although we did not measure body composition, this finding is consistent with Giles et al who found concomitant increased fat mass and decreased muscle mass was more common in RA patients than non-RA subjects, particularly among subjects with normal BMI.(29) Similarly, Stravropoulos-Kalinoglou et al reported increased body fat in RA patients and recommended lower BMI thresholds for defining obesity in RA patients.(30) Furthermore, concomitant increased fat mass and decreased muscle mass, also referred to as rheumatoid cachexia, is likely related to MetS in RA patients.(31)

Strengths of our study include its population-based design with a sizable RA cohort (>200 subjects) and a large population-based comparison cohort (>1000 subjects). In addition, comprehensive review of all inpatent and outpatient medical records from the community ensured accurate assessment of cardiovascular disease that was not subject to recall bias. A limitation of this study is that only 58% of eligible subjects agreed to participate in the study. However, the participation rate among RA subjects was similar to that in the non-RA cohort, as was the finding that participants were better educated than non-participants, so participation bias is unlikely to have had a substantial effect on the comparisons between the cohorts.(32) Also, some subjects in each cohort did not have available measures of lipids or glucose. However, analyses excluding subjects without these measures revealed similar results, albeit the difference in prevalence of MetS comparing RA with non-RA subjects no

longer achieved statistical significance. The use of lipids/glucose measurements up to 5 years prior to the study visit is also potentially problematic as these values may have changed during the interval. However, the current primary care guidelines recommend measurement of lipids every 5 years.(33,34) Thus the closest lipids measurement in the past 5 years is representative of the information available clinically for risk assessment in these patients. Finally, the population of Olmsted County, Minnesota is predominantly white, so the results of this study may not be generalizable to other more diverse populations.

In conclusion, among subjects without CVD, RA patients have a higher prevalence of MetS than non-RA subjects. MetS in RA patients was associated with higher disability and a history of large joint swelling, but not with RA therapy. More research is needed to understand the reasons for these metabolic changes in RA and the impact of MetS on development of CVD in RA patients. Recognition of MetS in RA patients who have not yet developed CVD could provide a valuable opportunity for preventative intervention in these patients.

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References

1. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: A population-based cohort study. Arthritis Rheum 2005;52(2):402–411. [PubMed: 15693010]
2. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: A population-based study over 46 years. Arthritis Rheum 2005;52(2):412–420. [PubMed: 15692992]
3. Crowson CS, Nicola PJ, Maradit Kremers H, O'Fallon WM, Therneau TM, Jacobsen SJ, et al. How much of the increased incidence of heart failure in Rheumatoid Arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? Arthritis Rheum 2005;52(10):3039–3044. [PubMed: 16200583]
4. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med 2006;119(10):812–9. [PubMed: 17000207]
5. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech 2009;2(5–6):231–7. [PubMed: 19407331]
6. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120(16):1640–5. [PubMed: 19805654]
7. Pereira RM, de Carvalho JF, Bonfa E. Metabolic syndrome in rheumatological diseases. Autoimmun Rev 2009;8(5):415–9. [PubMed: 19168158]
8. Dessein PH, Tobias M, Veller MG. Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. J Rheumatol 2006;33(12):2425–32. [PubMed: 17080519]
9. Karvounaris SA, Sidiropoulos PI, Papadakis JA, Spanakis EK, Bertsias GK, Kritikos HD, et al. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. Ann Rheum Dis 2007;66(1):28–33. [PubMed: 16793841]

10. 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(2):756–63. [PubMed: 17266963]
11. Maradit Kremers H, Crowson CS, Gabriel SE. Rochester Epidemiology Project: a unique resource for research in the rheumatic diseases. Rheum Dis Clin North Am 2004;30(4):819–34. vii. [PubMed: 15488695]
12. 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(3):315–24. [PubMed: 3358796]
13. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the Incidence of Rheumatoid Arthritis Rising? Results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheum 2010;62(6):1576–82. [PubMed: 20191579]
14. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of Systolic and Diastolic Ventricular Dysfunction in the Community: Appreciating the Scope of the Heart Failure Epidemic. JAMA 2003;289(2):194–202. [PubMed: 12517230]
15. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112(17):2735–52. [PubMed: 16157765]
16. Ervin RB. Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003–2006. Natl Health Stat Report 2009; (13):1–7. [PubMed: 19634296]
17. Toms TE, Panoulas VF, John H, Douglas KM, Kitas GD. Methotrexate therapy associates with reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60-more than just an anti-inflammatory effect? A cross sectional study. Arthritis Res Ther 2009;11(4):R110. [PubMed: 19607680]
18. Sabio JM, Vargas-Hitos J, Zamora-Pasadas M, Mediavilla JD, Navarrete N, Ramirez A, et al. Metabolic Syndrome Is Associated with Increased Arterial Stiffness and Biomarkers of Subclinical Atherosclerosis in Patients with Systemic Lupus Erythematosus. J Rheumatol. 2009
19. Sabio JM, Zamora-Pasadas M, Jimenez-Jaimez J, Albadalejo F, Vargas-Hitos J, Rodriguez del Aguila MD, et al. Metabolic syndrome in patients with systemic lupus erythematosus from Southern Spain. Lupus 2008;17(9):849–59. [PubMed: 18755869]
20. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107(3):391–7. [PubMed: 12551861]
21. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342(12): 836–43. [PubMed: 10733371]
22. Sidiropoulos PI, Karvounaris SA, Boumpas DT. Metabolic syndrome in rheumatic diseases: epidemiology, pathophysiology, and clinical implications. Arthritis Res Ther 2008;10(3):207. [PubMed: 18492218]
23. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. Am J Med 2007;120(5):442–7. [PubMed: 17466656]
24. Panoulas VF, Douglas KM, Milionis HJ, Nightingale P, Kita MD, Klocke R, et al. Serum uric acid is independently associated with hypertension in patients with rheumatoid arthritis. J Hum Hypertens 2008;22(3):177–82. [PubMed: 17960169]
25. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008;359(17): 1811–21. [PubMed: 18946066]
26. Wasko MC, Hubert HB, Lingala VB, Elliott JR, Luggen ME, Fries JF, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. Jama 2007;298(2):187–93. [PubMed: 17622600]
27. Rho YH, Oeser A, Chung CP, Milne GL, Stein CM. Drugs Used in the Treatment of Rheumatoid Arthritis: Relationship between Current Use and Cardiovascular Risk Factors. Arch Drug Inf 2009;2(2):34–40. [PubMed: 19684849]

28. Toms TE, Panoulas VF, Douglas KM, Griffiths HR, Kitas GD. Lack of association between glucocorticoid use and presence of the metabolic syndrome in patients with rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther 2008;10(6):R145. [PubMed: 19091101]

29. 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(6):807–15. [PubMed: 18512711]

30. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Nevill AM, Douglas KM, Jamurtas A, et al. Redefining overweight and obesity in rheumatoid arthritis patients. Ann Rheum Dis 2007;66(10):1316–21. [PubMed: 17289757]

31. Elkan AC, Hakansson N, Frostegard J, Cederholm T, Hafstrom I. Rheumatoid cachexia is associated with dyslipidemia and low levels of atheroprotective natural antibodies against phosphorylcholine but not with dietary fat in patients with rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther 2009;11(2):R37. [PubMed: 19284557]

32. Jacobsen SJ, Mahoney DW, Redfield MM, Bailey KR, Burnett JC Jr, Rodeheffer RJ. Participation bias in a population-based echocardiography study. Ann Epidemiol 2004;14(8):579–84. [PubMed: 15350958]

33. U S Preventive Services Task Force. Screening adults for lipid disorders: recommendations and rationale. American Journal of Preventive Medicine 2001;20(3 Suppl):73–6. [PubMed: 11306235]

34. US Preventive Services Task Force. Guide to Clinical Preventive Services. Washington, DC: 2009.

Table 1

Descriptive characteristics in subjects with and without rheumatoid arthritis who did not have cardiovascular disease

Characteristic	RA (n=232)	Non-RA (n=1241)	p-value
Age, years, mean ± SD	58.8 ± 12.8	63.9 ± 9.2	<0.001
Female, n (%)	174 (75)	681 (55)	<0.001
Race, n (%)			<0.001
White	218 (93)	1146 (92)	
Asian/Pacific Islander	6 (3)	5 (0.4)	
Other*	3 (1)	17 (1)	
Unknown	5 (2)	73 (6)	
Smoking (current or former), n (%)	105 (45)	547 (44)	0.74
BMI, kg/m^2, mean ± SD	28.5 ± 5.8	28.3 ± 5.4	0.52
Use of statins	42 (18)	272 (22)	0.20

* includes Native American, Black, and subjects reporting more than one race

RA = rheumatoid arthritis; BMI = body mass index; SD = standard deviation

Table 2

Criteria for Metabolic Syndrome in subjects with and without rheumatoid arthritis who did not have cardiovascular disease

Criteria†	RA (n=232) n (%)	Non-RA (n=1241) n (%*)	Odds Ratio (95% CI) Adjusted for age and sex	p-value
Elevated waist circumference	127 (54)	432 (35/40)	2.3 (1.7, 3.1)	<0.001
Elevated TG or treatment**	64 (30)	321 (35/28)	0.8 (0.6, 1.2)	0.26
Reduced HDL or treatment**	50 (24)	198 (22/16)	1.2 (0.8, 1.7)	0.43
Elevated blood pressure or treatment	135 (58)	725 (58/47)	1.5 (1.1, 2.1)	0.02
Elevated fasting glucose or treatment***	64 (32)	355 (37/28)	1.0 (0.7, 1.4)	0.96
Metabolic Syndrome (≥3 of 5 criteria)	76 (33)	316 (25/20)	1.6 (1.2, 2.2)	0.002

† MetS was defined using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria as affirmed and slightly modified by the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI) (14). The MetS definition requires any 3 of these 5 criteria: elevated waist circumference (≥102 cm in non-Asian men, ≥88 cm in non-Asian women, ≥90 cm in Asian men, ≥80 cm in Asian women), elevated triglycerides (TG ≥ 150 mg/dL or treatment with fibrates or nicotinic acid), reduced high-density cholesterol (HDL<40 mg/dL in men or <50 mg/dL in women or treatment with fibrates or nicotinic acid), elevated BP (≥130 mmHg systolic or ≥85 mmHg diastolic or treatment for hypertension) or elevated fasting glucose (FG ≥ 100 mg/dL or treatment for elevated glucose).

* non-RA percentages are presented raw and adjusted to the age and sex distribution of the RA subjects.

** lipid measures were not available in 21 RA and 324 non-RA subjects

*** glucose measures were not available in 35 RA and 284 non-RA subjects

RA = rheumatoid arthritis; TG = triglycerides; HDL = high-density cholesterol; CI = confidence interval

Table 3

Characteristics of rheumatoid arthritis subjects and association with metabolic syndrome

Characteristic	RA (n=232)	Odds ratio (95% CI) Adjusted for age, sex and RA duration	p-value
Age, years, median (IQR)	58 (50, 68)	1.5 (1.2, 1.9) per 10 years	<0.001
Female, n (%)	174 (75)	1.1 (0.6, 2.2)	0.81
RA duration, years, median (IQR)	7.0 (4.1, 12.8)	0.7 (0.5, 1.2) per 10 years	0.23
RF positive, n (%)	159 (69)	1.2 (0.6, 2.2)	0.60
ACPA positive, n (%)	92 (40)	1.0 (0.5, 1.7)	0.90
CRP, mg/L, median (IQR)	2.1 (0.8, 4.6)	1.0 (0.95, 1.04)	0.85
Interleukin 6, pg/mL, median (IQR)	2.3 (1.4, 4.4)	1.0 (0.97, 1.03)	0.95
Uric Acid, mg/dL, median (IQR)	4.8 (4.0, 5.8)	1.6 (1.3, 2.1)	<0.001
Erosions/destructive changes on radiographs, n (%)	119 (51)	0.8 (0.5, 1.5)	0.54
HAQ score, median (IQR)	0.4 (0.0, 0.8)	3.2 (1.9, 5.7)	<0.001
History of large joint swelling	177 (76)	2.5 (1.2, 5.3)	0.02
Medication usage, n (%)*			
Methotrexate	131 (56)	1.1 (0.6, 2.0)	0.69
Hydroxychloroquine	75 (32)	0.9 (0.5, 1.6)	0.69
Other DMARDs	25 (11)	1.6 (0.6, 3.7)	0.33
Biologics	38 (16)	1.2 (0.6, 2.6)	0.59
Glucocorticoids (systemic)	59 (25)	1.0 (0.6, 2.0)	0.89
NSAIDs	140 (60)	0.7 (0.4, 1.2)	0.17

*At time of study visit. Systemic glucocorticoids included either oral or intravenous forms (e.g., prednisone, methylprednisolone, hydrocortisone, dexamethasone). Other DMARDs included sulfasalazine, lleflunomide, azathioprine. Biologics included tumor necrosis factor inhibitors, anakinra, abatacept, rituximab

RA = rheumatoid arthritis; CI= confidence interval; RF = rheumatoid factor; CCP = cyclic citrullinated peptide antibody; CRP= C-reactive protein; IQR = interquartile range; HAQ = Health Assessment Questionnaire; DMARDs = disease-modifying antirheumatic drugs, NSAIDs = nonsteroidal anti-inflammatory drugs

Table 4

Descriptive characteristics in subjects with rheumatoid arthritis who participated in the study compared to non-participants

Characteristic	Participants (n=232)	Non-Participants (n=169)	p-value
Age, years, mean ± SD	58.8 ± 12.8	60.3 ± 15.2	0.27
Female, n (%)	174 (75)	132 (78)	0.47
Race, n (%)			0.51
White	218 (93)	148 (88)	
Asian/Pacific Islander	6 (3)	9 (5)	
Other*	3 (1)	5 (3)	
Unknown	5 (2)	7 (4)	
Ever Married	209 (90)	154 (91)	0.73
Education level			<0.001
< High school	4 (2)	16 (10)	
High school	65 (28)	65 (39)	
Technical school/college	145 (63)	77 (46)	
Graduate school	17 (7)	10 (6)	
Duration of RA, years, mean ± SD	8.8 ± 6.2	9.8 ± 7.5	0.13
RF positive, n (%)	151 (65)	111 (66)	0.90
Smoking (current or former), n (%)	101 (44)	99 (59)	0.003
Ever BMI >30 kg/m^2, n (%)	114 (49)	82 (49)	0.90
Hypertension, n (%)	194 (84)	145 (86)	0.55
Diabetes Mellitus, n (%)	27 (12)	28 (17)	0.16
Dyslipidemia, n (%)	163 (70)	110 (65)	0.27

*includes Native American, Black, and subjects reporting more than one race

RA = rheumatoid arthritis; BMI = body mass index; SD = standard deviation; RF = rheumatoid factor