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Association of Cardiovascular Disease with the Metabolic Syndrome in a Predominantly Male Cohort with Rheumatoid Arthritis

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1. Introduction

Despite the therapeutic advances in RA that have led to reduced pain, joint destruction and disability, as many as 50% of patients are at risk of death from a cardiovascular event (Maradit-Kremers et al., 2005; Stevens et al., 2005). Inexplicable by the usual traditional risk factors, the accelerated atherosclerosis (Gaonzalez-Gay et al., 2005) has been postulated to result from the increased systemic inflammatory burden of rheumatoid disease (Del Rincon et al., 2001; Gabriel et al., 1999; Kremers & Gabriel, 2006; McEntegart et al., 2001).

The metabolic syndrome (MetS) is a composite diagnosis, combining phenotypic features that portend an increased risk for cardiovascular disease (CVD). The syndrome consists of visceral obesity, atherogenic dyslipidemia, hypertension, and impaired fasting glucose/glucose tolerance test or overt diabetes mellitus (DM) (National Cholesterol Education Program, 2001). Studies have reported the presence of MetS to be associated with an approximate 2- fold increased risk for incident cardiovascular morbidity and mortality (Lakka et al., 2002), a 2.1 fold increase for initial stroke (Najarian et al., 2006), and 3.5 fold increased risk for Type II DM (Lorenzo et al., 2003). The complex interplay of genetic and environmental factors, insulin resistance and inflammation, are all believed to contribute to the pathogenesis of the syndrome.

The overall prevalence of MetS in the US population, as evaluated by the National Health and Nutrition Examination Survey (NHANES III), is 23.1%, and increases with age to as high as 44% in those 65 years or older (Ford et al., 2002). Several studies have established an increased prevalence of insulin resistance and increased risk for CVD in RA patients (Dessein et al., 2002a, 2002b). However, there are few reports regarding MetS in RA, and the

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existing data reflect variations in the populations studied (Crowson et al., 2011; Karvounaris et al., 2007). Data from Europe and the US have shown associations between the syndrome and the inflammatory burden of RA.

Most data on RA, including reports related to MetS and CVD, are comprised mainly of females. The few reports on RA in males indicate a more severe course of disease, and worse outcome (Ford et al., 2002; Janghorbani et al., 1993; Jawaheer et al., 2006; Mikuls et al., 2011). Further, elderly males more often have comorbid diseases such as diabetes mellitus and hypertension that places them at even greater risk for CVD.

Therefore we sought to examine the prevalence and relationship of MetS to RA disease burden and CVD in a primarily elderly, male RA cohort.

2. Patients and methods

2.1 Study population

Study patients enrolled in the ongoing Veterans Affairs Rheumatoid Arthritis (VARA) Registry prior to January 2009 were included in the study. The characteristics of this population have been previously described (Mikuls et al., 2007). Briefly, VARA is a multi-center chronic disease registry initiated in 2003 now including collection sites at VA Medical Centers across the U.S. The current study included participants from VA sites in Dallas, Denver, Jackson, Omaha, Salt Lake City, and Washington, DC. Rheumatoid arthritis (RA) patients with disease onset after age 18 years who fulfill American College of Rheumatology (ACR) classification criteria for RA (Arnett et al., 1988) are invited to enroll. Participating sites prospectively collect and archive clinical and laboratory observations associated with RA during routine visits and standard of care. VARA has been approved by the Institutional Review Board (IRB) and VA Research and Development Committee at each participating site. All subjects provide written consent for a single blood draw and ongoing review of their electronic medical records.

2.2 Metabolic syndrome definition

The NCEP/ATPIII criteria (National Cholesterol Education Program, 2001) for MetS were modified so that a body mass index (BMI) of ≥ 30 kg/m^2 replaced waist/hip circumference. Because waist and hip measurements are not routinely available on study subjects, BMI was used as a surrogate for waist-to-hip circumference with the following rationale: a) weight and annual height measurements are routinely obtained on all our patients, b) data support BMI to be as accurate as waist circumference in identifying individuals for risk of CVD (Farin et al, 2006), c) BMI is included in the WHO definition for MetS (World Health Organization [WHO], 1999) and there appears to be at least modest levels of agreement between BMI and waist-to-hip ratio in both men and women (Balkau et al., 2006), and d) to obviate the varied cut off points for waist circumference for different ethnic groups (Alberti et al., 2005). Additionally, documented prior use of disease specific medications were used as surrogates for the other three MetS components. Hence MetS was defined as presence of ≥ 3 of 4 criteria (BMI ≥ 30 kg/m^2, anti-hypertensive, lipid lowering, and/or diabetes agents) (Grundy et al., 2005).

2.3 Clinical measures

RA disease severity was assessed by rheumatoid factor (RF) positivity, duration of disease, presence of radiographic changes suggestive of RA (based on ACR criteria) and nodules at enrollment. Disease activity was assessed at the time of the most recent clinic visit by

erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), total swollen and tender joint count (0-28 joints), patient global well-being 100 mm visual analog scale, modified health assessment questionnaire (MD-HAQ, 0-3) and three-variable Disease Activity Score (DAS28-3v; a composite measure based on swollen/tender joint counts and ESR) (Bawa et al., 2005; Prevoo et al., 1995). The three-variable DAS was used in place of a four variable DAS to minimize the impact of missing data from patient global scores.

Disease-modifying anti-rheumatic therapy (DMARD), biologic treatments, and prednisone use were also recorded at the most recent visit. DMARD agents included methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide; biologic treatments included anti-tumor necrosis factor (adalimumab, etanercept, infliximab), anti-signal 2 inhibitor (abatacept) and anti-CD20 (rituximab) agents. Patient report of ever or never smoking was tabulated, and subjects were categorized based on a history of CVD (documentation of prior coronary artery disease, myocardial infarction, angina, cerebrovascular event, transient ischemic attack, or peripheral vascular disease).

2.4 Statistical analysis

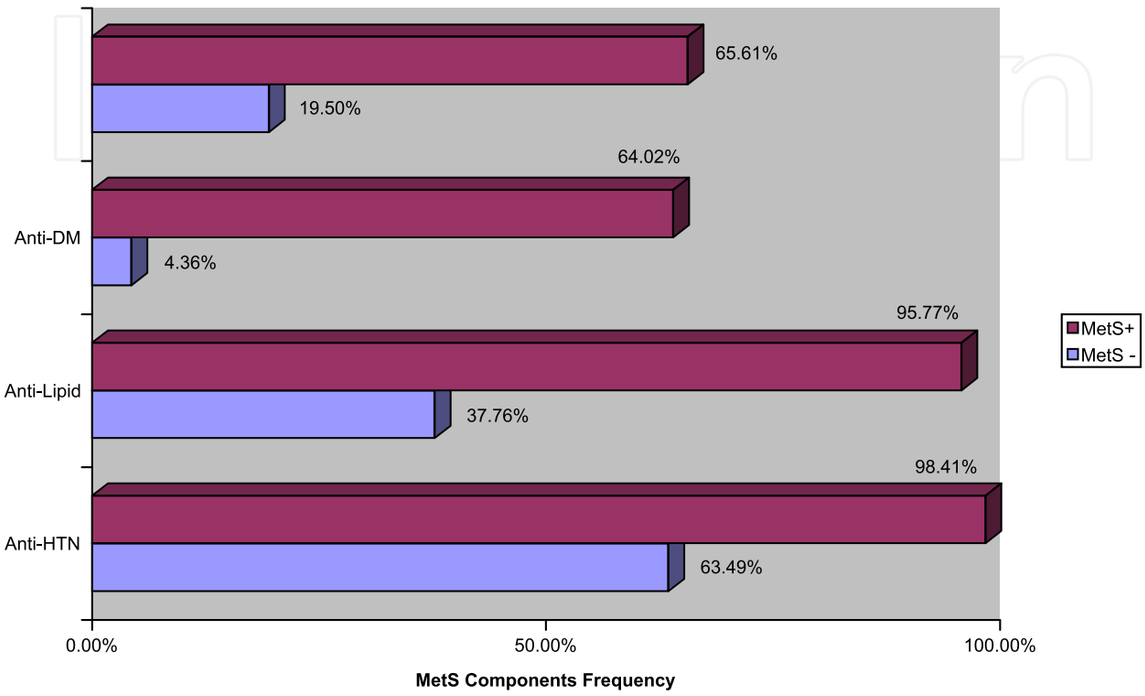
Descriptive statistics were used to define the group. Group comparisons, based on the presence/absence of MetS, were performed using Chi-square for categorical variables and a one-way ANOVA for continuous data. Odds ratios (OR) and 95% confidence intervals were used to assess the association of MetS with prevalent CVD and were calculated using multivariable logistic regression, adjusting for age, sex, smoking status (ever vs. never), and the current use of DMARDs and/or biologic therapies. Given the reported anti-inflammatory effect of select lipid lowering agents (statins) in RA, we performed a subanalysis in subjects with MetS to examine the association of statin use with measures of disease activity. All analyses were performed using SAS (SAS Inc, Cary, NC).

3. Results

Six-hundred seventy-one patients were included in this study (Table 1). The study cohort included 53 (7.9%) women, had a mean age of 65.4 years [SD10.8], and a mean disease duration of 13.7 years [SD 11.5]. The majority were Caucasian (n = 543, 80.9%). Four hundred and twelve (61.4%) had radiographic changes consistent with RA, and 312 (46.5%) had nodules. Approximately 58.3% were on a traditional DMARD at their most recent clinic visit, while an additional 25.8% were receiving a combination of a biologic agent with a traditional DMARD. Fifty three percent of the study cohort was receiving prednisone.

The mean DAS28 was 3.2 [SD 1.3] and CRP was 1.3 [SD 1.9] mg/dl. The majority (78.8%) were either previous or current smokers. One-hundred eighty-nine subjects satisfied the modified criteria for MetS, corresponding to a prevalence of 28.2% (95 % CI 24.7-31.7). There were no significant differences in subject demographics, measures of disease severity or activity, use of biologic agents or DMARDS, prednisone use, or smoking status in RA subjects with MetS compared to those without MetS (Table 1). In a subanalysis of subjects with and without MetS, there were no significant differences in measures of disease activity in those taking statins compared to individuals not taking statins (data not shown). As expected, disease components of MetS were far more common in those with the syndrome in comparison to those without MetS (Figure 1). Of note, a BMI that exceeded 30 kg/m^2 was present in only one-third of study patients, but comprised 66% of MetS patients and only 20% of individuals without MetS. The use of anti-hypertensive and lipid lowering agents

were nearly universal among those meeting criteria for MetS, with over 95% use. Logistic regression analysis revealed MetS to be associated with an approximately three-fold risk of CVD (OR=2.9; 95% CI 1.95-4.34), after adjusting for age, sex, DMARD / biologic use, and smoking status (Table 2). There was no increased CVD risk with individual components of the metabolic syndrome.



MetS= Metabolic Syndrome
BMI = Body Mass Index
Anti-DM = Treatment for diabetes with insulin and/or oral hypoglycemic medications
Anti-Lipid = Treatment for dyslipidemia with cholesterol lowering medications
Anti-HTN = Treatment for high blood pressure with medications

Fig. 1. MetS Components Frequency in VARA cohort

4. Discussion

In our cohort, the prevalence of MetS was 28.2% and had significant association with CVD. The few existing studies that have examined the relationship of RA with MetS primarily involved women, and indicated increased mortality from CVD among those satisfying criteria for MetS. Men with RA have more extra-articular disease and a greater overall mortality (Janghorbani et al., 1993; Jawaheer et al., 2006; Mikuls et al., 2011). In general, there is a disproportionate individual impact of MetS, CVD, and RA in men. Our findings provide data previously lacking regarding the frequency of MetS in older men with RA and its relationship with RA-specific factors and CVD co-morbidity.

In non-RA populations, MetS has been reported to increase the risk for CVD by two fold, and death by as much as 4 fold (Dekker et al., 2005; Lakka et al., 2002). In a Finnish cohort of men aged 42 to 60 years of age, MetS was found in only 14.3%, but with a 2.9 to 4.3 greater risk of death from coronary heart disease (Lakka et al., 2002). In a population-based cohort

	VARA Cohort **% (n), mean [SD]**		
	% (Number)	MetS Absent	MetS Present
Variables	(N=671)	78% (482)	28% (189)
Age	65.35 [SD 10.75]	65.23 [SD11.43]	65.66 [8.79]
Female	7.9 (53)	9.8 (47)	3.2 (7)
Caucasian	80.6 (543)	80.3 (387)	82.5 (156)
African American	14.6 (98)	15.4 (74)	12.7 (24)
Erosions present	61.4 (412)	63.9 (308)	55 (104)
Disease Duratio	13.74 [SD 11.5]	14.08 [SD 11.61]	12.89 [SD 11.21]
Nodules present	46.5 (312)	47.5 (229)	43.9 (83)
RF Positive	88.4 (593)	89 (429)	86.8 (164)
DAS28(3v)†	3.20 [SD 1.34]	3.21 [SD 1.33]	3.18 [SD 1.38]
CRP	1.29 [SD 1.87]	1.37 [SD 1.98]	1.09 [SD 1.53]
DMARDS	58.3 (391)	56.2 (271)	63.5 (120)
DMARDS+Biologic*	25.8 (173)	26.4 (127)	24.3 (46)
Prednisone	43.5 (292)	46.7 (225)	35.5 (67)
Ever Smoke	78.8 (529)	78.7 (379)	79.4 (150)

P values not statically significant for all variables
Veteran **A**ffairs **R**hematoid **A**rthritis Registry
MetS = Metabolic Syndrome DMARDS=Disease-Modifying Anti-Rheumatic Drugs
*Biological Agents (mainly anti-tumor necrosis factor) †Disease Activity Score, 28 joints
SD = Standard Deviation

Table 1. Demographics and Parameters of Disease Severity and Activity of Veterans Affairs Rheumatoid Arthritis Patients with and without the Metabolic Syndrome

Variables	*OR*	*95% C.I.*		*P value*
		Lower	Upper	
MetS Present	2.91	1.95	4.34	<0.001
DMARDS	2.27	1.47	3.50	<0.001
Age	1.04	1.02	1.07	<0.001
Ever Smoking	1.67	0.99	2.82	0.05
Gender (male)	0.38	0.11	1.29	0.12
DMARDS+Biologic*	1.06	0.66	1.72	0.80

DMARDS (Disease Modifying Anti-rheumatic drugs)
*Biologic Agents (mainly anti-tumor necrosis factor)
CI = Confidence Interval

Table 2. Multivariable Logistic Regression Model examining the association of Metabolic Syndrome with Cardiovascular Disease in VARA cohort

of 615 men aged 50 to 75 years, the prevalence of MetS varied from 17% - 32% when assessing the agreement in the various definitions of MetS (Dekker et al., 2005). When using NCEP-ATPIII criteria, the hazard ratio for fatal and non-fatal CVD in men with MetS was 1.91 (1.31–2.79), compared to 1.68 (1.11–2.55) in the 749 women.
A similar risk for CVD occurs for RA patients with MetS, but these results are obtained from cohorts consisting primarily of female patients (Dessein et al., 2002; Karvounaris et al., 2007).

Further, as in the non-RA study cohorts, the definitions and criteria of both MetS and CVD varied. In one study, MetS, as defined by WHO criteria, was a better predictor of coronary calcification than NCEP-ATPIII criteria (Pandya et al., 2006). Though coronary calcification detection by electron beam computer tomography is a more sensitive means of detecting atherosclerosis than clinical diagnoses, the association with MetS achieved an odds ratio of 2.02, (95% CI: 1.03-3.97, p=0.04.), less than the 2.91 (95% CI: 1.95-4.34, p<0.001) in our cohort. In that study (Pandya et al, 2006), almost 50% of the patients had longstanding disease (median = 20 years), were younger than our cohort (median 59 years), and were majority female. The almost three-fold risk for CVD in our cohort was independent of anti-rheumatic treatment, smoking, age or gender. There was, however, a trend to increased risk with increasing age and DMARD therapy alone, the latter perhaps related to channeling bias or confounding by indication.

Given the notable comorbidity in our study population, and the historically age-matched prevalence of MetS in 44% of the US NHANES III population aged 65 years, our prevalence of 28% was unexpected. The limited data from other disease cohorts involving U.S. veteran populations report higher frequencies on the order of 50% (Meyer et al., 2006; Pandya et al., 2006). However, our results are similar to another US RA cohort, 40% of whom were male. The prevalence of MetS was approximately 26% as defined by NCEP-ATPIII criteria, and was almost half that of controls (Rodriguez-Pla et al., 2007). In that study, the difference in prevalence between RA and controls could not be explained by differences in physical activity. In contrast, in 200 similarly aged but primarily female RA patients, MetS occurred in 44% of patients at a similar rate to the age- and sex- matched controls, but used ATPIII criteria (National Cholesterol Education Program, 2001). Of the 53 men in the study, approximately 30% with MetS had coronary disease (p=0.02). Not only do differences in MetS classifications make comparisons amongst cohorts difficult, but the disparate muscle loss with fat retention that occurs in RA patients, affects BMI assessments. Rheumatoid cachexia, which is present in most (two-thirds) RA patients, doesn't merely involve fat "retention"; there is exacerbated fat gain. When body composition is assessed (i.e. % body fat), up to 80% of RA patients satisfy BMI criteria for obesity i.e. ≥27% for males, and ≥38% for females (Baumgartner et al., 1999). This prevalence of obesity in RA is not reflected by BMI because of the concomitant loss of muscle. Thus, for individuals with the same BMI, an RA patient will have, on average, 4.3% higher % body fat than a healthy, age- and sex-matched subject. Therefore, in RA patients, a BMI greater than 28kg/m^2 has been proposed to define obesity, and may, and may therefore lead to higher, and more accurate, estimations of MetS in RA cohorts. (Stavropoulos-Kalinoglou et al., 2007).

Our modified definition of MetS based on NCEP-ATPIII criteria though highly specific, may have lacked sensitivity by excluding otherwise eligible patients with discordance between waist-to-hip ratio and BMI, or those who had not received pharmacological treatment for component diseases. We recognize therefore that our prevalence estimate may have trended towards the conservative and underestimated the true impact of MetS in this population; an important concern given the strong association between MetS and CVD. However, of note is the rigor with which VA patients are screened and treated for diabetes mellitus, hypertension and hyperlipidemia based on adherence to select process indicators (Steven, 2004). Therefore it is likely that our use of medication is a reasonable surrogate for the select comorbidities of MetS. Surprisingly, our study found no significant risk of any of the individual components of MetS, and may indicate that traditional risk factors do not impart the same risk for CVD in RA as in the general population.

The role of adipose tissue and BMI in inflammatory disease is evolving as is its impact on response to disease-modifying therapies (Klaasen et al., 2011; Ouchi et al., 2011). Yet the association of MetS with RA disease activity and severity is equivocal. One study has reported an increase of nine-fold in odds ratio correlation between MetS and disease activity, but not with severity (Karvounaris et al., 2007). A relationship between MetS and disease activity and severity was not found in our cohort, but the mean disease activity was low and the effect of DMARD therapies on MetS is unknown. Aware that statin use may be more frequent in the context of MetS and of its potential anti-inflammatory and immunomodulatory effects, we explored but were unable to find an association between statin use and disease activity in RA patients with and without MetS.

There are limitations to our study. The use of BMI in place of waist-to-hip circumference may have limited the sensitivity of our criteria. However, the use of BMI in lieu of waist-to-hip circumference allows pragmatic application in clinical practice, and thereby easier identification of MetS. There is a reported positive correlation between BMI and CVD and increased CRP levels, and BMI is inversely related to functional status in inflammatory rheumatic diseases (Choi et al., 2002; Kremer & Reed, 2006). There was no difference in disease activity amongst the cohort, and the increased risk for CVD in RA patients with MetS was independent of disease activity. Whether a lower DAS score is found in RA patients with MetS, regardless of traditional or biologic DMARD, remains to be determined.

Strengths of the study include that it is of a well-characterized group of males with RA, a group that to date has been vastly underrepresented in clinical research. Moreover, the patients treated at these sites have equal access to medical care and RA therapies, hence providing the unique opportunity to explore disease related outcomes in a uniform health system. Although premature atherosclerosis occurs in RA independent of traditional risk factors, our findings indicate that it is the composite entity of the metabolic syndrome rather than its individual components that pose the risk for CVD. Optimum control of all individual components is required to minimize cardiovascular morbidity.

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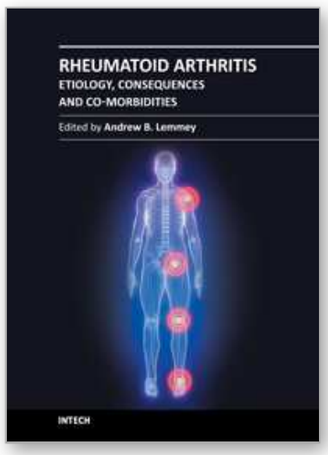
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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 16 chapters, with contributions from numerous countries (e.g. UK, USA, Japan, Sweden, Spain, Ireland, Poland, Norway), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Etiology, Consequences and Co-Morbidities will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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