Rheumatoid arthritis and metabolic syndrome

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ABSTRACT

In the past 20 years, the life expectancy of patients with rheumatoid arthritis (RA) has been shown to be reduced by three to ten years as compared to that of the general population. Currently, cardiovascular disease (CVD) is the major cause of death in patients with RA, and acute myocardial infarction can be up to four times more frequent in these patients. The autoimmune systemic inflammatory response, along with the presence of metabolic syndrome (MetS), doubles the risk for fatal or non-fatal CVD and coronary atherosclerosis, regardless of age and sex. Rheumatoid arthritis has been associated with increased prevalence of MetS, but its role in the different characteristics of the disease, such as disease duration, activity, and treatment with glucocorticoids, is not well defined. This study aimed at reviewing the prevalence of MetS and the factors implicated in the development of atherosclerosis in RA patients, assessing the clinical aspects of RA and its association with the development of MetS.

Keywords: metabolic syndrome X, rheumatoid arthritis, cardiovascular diseases.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disorder characterized by chronic symmetric and erosive synovitis that affects preferentially peripheral joints.[1] Patients with RA have a reduced life expectancy,[2] which is associated with an increased risk for cardiovascular events.[3,4] They have a four-fold increased frequency of acute myocardial infarction.[5] Accelerated coronary[3] and extracoronary[2] atherosclerosis is a characteristic of RA, and its pathogenesis has not been clearly defined.[6] The high prevalence of traditional cardiovascular risk factors and the systemic inflammatory process play a role in this pathogenesis. There is evidence of an inflammatory basis for atherosclerosis, which has led many researchers to study the relationship between systemic inflammatory conditions, such as RA, and the risk for coronary heart disease.[7-9] Metabolic syndrome (MetS), a set of cardiovascular risk factors (such as central obesity, dyslipidemia, hypertension, and hyperglycemia), has been assessed aiming at predicting the risk for cardiovascular disease (CVD).[3] There is evidence showing the association between RA, its inflammatory activity, and MetS,[2,3] but the results on the prevalence of this syndrome in RA are conflicting.[2,3,6,10,11]

This study aimed at reviewing the prevalence of MetS and the factors involved in the development of atherosclerosis in RA patients, assessing the clinical aspects of RA and their association with the development of MetS.

DEFINITION CRITERIA OF METABOLIC SYNDROME

Metabolic syndrome can increase up to two fold the risk for CVD.[12] The most accepted hypothesis for the development of MetS indicates insulin resistance (IR) as the major pathophysiological mediator.[13]

There have been several attempts to define MetS in literature (Table 1). The World Health Organization (WHO) established in 1999 the criteria for defining MetS (modified in 2004).[14] Alternative definitions have been subsequently proposed by the European Group for the Study of Insulin Resistance

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(EGIR)[15] in 1999 and by the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP ATP III) - American Heart Association (AHA) in 2001. The NCEP III was last updated in 2005.[16] The American Association of Clinical Endocrinologists (AACE),[17] in 2003, and the International Diabetes Federation (IDF),[18] in 2004, have also proposed their criteria for defining MetS.

All definitions include measuring systemic blood pressure, triglycerides, high-density lipoprotein cholesterol (HDL-C), and fasting glycemia. They differ regarding the cutoff points of their components and the criteria of obesity. The WHO and EGIR definitions require the presence of IR in the first, and IR or hyperinsulinemia in the second. The definition of the NCEP-ATP III is based only on the number of abnormalities,[3] while the IDF definition is based on central obesity, which requires an increased waist circumference. The AACE definition of MetS requires high risk for IR or body mass index (BMI) ≥ 25 kg/m^2 or waist ≥ 102 cm (men)/ ≥ 88 cm (women).

PREVALENCE OF METABOLIC SYNDROME IN BRAZIL

A study carried out by Nakazone *et al.*[19] in the city of São José do Rio Preto, São Paulo state, in 2007, assessed 340 individuals (200 patients and 140 controls), paired for sex and age. The patients were on regular follow-up with a cardiologist, and the presence of risk factors for CVD was considered, aiming at primary or secondary prevention. Individuals with no routine cardiology follow-up were included in the control group. According to the NCEP-ATPIII (2001) criteria, 35.5% of patients and 8.6% of controls ($P < 0.0001$) had MetS. The IDF criteria evidenced MetS in 46% of patients and in 17.9% of controls ($P < 0.0001$).

Another Brazilian study, assessing the existence of an association between periodontal disease and MetS in 1,315 Japanese-Brazilians aged between 30 and 92 years, regardless of oral health conditions, has reported a 54% prevalence of MetS according to the NCEP 2001 definition.[20]

Table 1
Current definitions of metabolic syndrome

Parameters	NCEP ATP III 2005	IDF 2005	EGIR 1999	WHO 1999 modified	AACE 2003
Required		Waist ≥ 94 cm (men) or ≥ 80 cm (women) *	IR or fasting hyperinsulinemia at the top of the 25th percentile	IR: HOMA at the top of the 25th percentile, fasting glycemia ≥ 110 or DM	At high risk for IR Δ or BMI ≥ 25 or waist ≥ 102 (men) or ≥ 88 (women)
Number of abnormalities	≥ 3 of:	≥ 2 of:	≥ 2 of:	≥ 2 of:	≥ 2 of:
Glucose	≥ 100 mg/dL or treatment with a drug for high glycemia	≥ 100 mg/dL or DM diagnosis	110-125 mg/dL		≥ 110; ≥ 140 mg/dL 2h after glucose
HDL-c	< 40 (men);< 50 (women) or treatment with a drug for low HDL-c ◊	< 40 (men); < 50 (women) or treatment with a drug for low HDL-c	< 40 mg/dL	< 35 (men); < 40 (women)	< 40 (men); < 50 (women)
Triglycerides	≥ 150 mg/dL or treatment with a drug for high triglycerides ◊	≥ 150 mg/dL or treatment with a drug for high triglycerides	Or ≥ 180 mg/dL or treatment with a drug for dyslipidemia	Or ≥ 150 mg/dL	≥ 150 mg/dL
Obesity	Waist ≥ 102 cm (men) or ≥ 88 cm (women) §		Waist ≥ 94 cm (men) or ≥ 80 cm (women)	Waist ≥ 94 cm (men) or ≥ 88 cm (women)	
Hypertension	≥ 130/85 mmHg or treatment with a drug for SAH	≥ 130/85 mmHg or treatment with a drug for SAH	≥ 140/90 mmHg or treatment with a drug for SAH	≥ 140/90 mmHg or treatment with a drug for SAH	≥ 130/85 mmHg

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance; WHO: World Health Organization; AACE: American Association of Clinical Endocrinologists; HDL-c: high-density lipoprotein cholesterol; HOMA: homeostasis model assessment; BMI: body mass index; SAH: systemic arterial hypertension; IR: insulin resistance; DM: diabetes mellitus.

* For South-Asian and Chinese patients, waist ≥ 90 cm (men) or ≥ 80 cm (women); for Japanese patients, waist ≥ 90 (men) or ≥ 80 cm (women).

Δ At high risk for IR, indicated by the presence of at least one of the following: diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease, or *acanthosis nigricans;* family history of type 2 diabetes, hypertension or CVD; history of gestational diabetes or glucose intolerance; non-white ethnicity; sedentary lifestyle; BMI = 25 kg/m^2 or waist circumference = 94 cm for men and = 80 cm for women; and age de 40 years.

◊Treatment with one or more fibrates or niacin.

§ In Asian patients, waist ≥ 90 cm (men) or ≥ 80 cm (women).

Adapted from Meigs.[25]

In 2004, Velásquez-Meléndez *et al.*[21] carried out a cross-sectional population-based study in Virgem das Graças, a rural community located in Vale do Jequitinhonha, state of Minas Gerais. The study comprised 251 individuals (117 men and 134 women), whose ages ranged from 20 to 88 years. The prevalence of MetS according to the NCEP 2001 definition was 21.6% (7.7% for men and 33.6% for women). The overall prevalence adjusted for age was 19.0%.

In 2006, a population-based study conducted in the rural district of Cavunge, in the semi-arid region of the state of Bahia, assessed the prevalence of MetS according to the NCEP/ATPIII 2001 criteria in a random sample consisting of 240 individuals (102 men and 138 women; age range, 25 to 87 years). The raw prevalence of MetS was 30.0%, and, after adjusting for age, 24.8%.[22]

Salaroli *et al.*[23] have reported a 29.8% prevalence of MetS (without difference between sexes) in a random sample of 1,663 individuals (25-64 years) in the city of Vitoria, state of Espírito Santo, according to the NCEP/ATPIII 2001 criteria.

CRITICAL OVERVIEW OF METABOLIC SYNDROME

In addition to the sum of the individual components of MetS,[2] this cluster of risk factors is believed to play an important role in increasing the risk for CVD. Likewise, the existence of a single pathophysiological basis, IR,[3] is believed to explain the syndrome. However, a consensus about it has not been achieved.

The American Diabetes Association and the European Association for the Study of Diabetes have issued a joint declaration questioning the classification of the components of MetS as a true "syndrome". The arguments were as follows: lack of definition clarity, with different criteria in existing definitions; different and multiple phenotypes included in MetS, with consequent different treatment strategies; lack of a consistent evidence basis for entering several components in the definitions; inclusion of patients with clinical CVD or diabetes as part of the syndrome, which is intended to define risk for these diseases; unclear pathogenesis linking the components of MetS: there is the possibility that IR is not the underlying condition of all factors, and it is not a consistent finding in some definitions; other risk factors for CVD, which are not components of MetS, such as inflammatory markers, may carry an equal or greater risk; and, finally, the MetS-associated risk for CVD has not shown to be greater than the sum of the individual components.[24]

Despite questions about the existence of MetS, it is undoubtedly paramount to identify the presence of its components and establish the adequate management strategies so that the morbidity and mortality associated with diabetes and CVD can be reduced.[25]

The etiology of MetS is unknown, but it is likely to involve a complex interaction of genetic, environmental, and metabolic factors. Results of several studies have suggested that the pro-inflammatory state can contribute to the development of MetS.[20]

METABOLIC SYNDROME IN RHEUMATOID ARTHRITIS

The interest in identifying MetS in patients with RA has emerged recently, justified by the need to better understand the determinant factors of CVD in these patients (Table 2).

In 2002, the first study assessing the hypothesis that the increased prevalence of interrelated cardiovascular risk (CV risk factors) factors determines the presence of MetS in RA had patients with osteoarthritis (OA) as the control group. The authors reported that more patients with RA had IR and low HDL levels as compared with patients with OA, and both were directly associated with C-reactive protein levels. Moreover, IR, low HDL levels, hypertriglyceridemia, and hypertension were associated with each other in the rheumatoid group, which was not observed in patients with OA.[26]

To assess the effects of glucocorticoids on CVD of patients with RA, Dessein *et al.*[5] have tested the effects of glucocorticoids on traditional CV risk factors factors. The use of prednisone and its frequent intramuscular, intra-articular, and intravenous doses have been associated with the presence of IR ($P < 0.05$). The use of glucocorticoids has not been associated with obesity, dyslipidemia, or hypertension. In 2006, the same research team assessed the association of MetS-related CV risk factors factors with the presence of subclinical atherosclerosis using ultrasound measurement of plaques and the common carotid intima and media layer thickness. Hypertension, IR, and hypertriglyceridemia were independent risk factors for subclinical atherosclerosis ($P = 0.02$, 0.04, and 0.05, respectively). In this study, individual risk factors were more strongly associated with subclinical atherosclerosis than with the MetS definitions.[10]

In 2008, Chung *et al.*[2] demonstrated for the first time an increase in MetS prevalence in patients with RA when compared with controls adjusted for age, race, and sex. Using the WHO definition, the frequency of MetS was greater in patients with long-term disease (42%) when compared to patients with early arthritis (30%) and controls (11%) ($P < 0.001$). The authors

Table 2
Prevalence of metabolic syndrome in rheumatoid arthritis

Author, year (reference)	Study	Sample	Criteria for defining MetS	Prevalence of MetS
Chung *et al.,* 2008[2]	Case-control	154 patients 85 controls	NCEP 2001 and WHO modified	Long-term RA 42%, initial RA 30%, and controls 22% (NCEP 2001); Long-term RA 42%, initial RA 31%, and controls 11% (WHO)
Karvounaris *et al.,* 2007[3]	Case-control	200 patients 400 controls	NCEP 2001	RA 44% Controls 41%
Dessein *et al.,* 2006[10]	Cross-sectional	74 patients	NCEP 2005 and WHO modified	RA 19% (NCEP 2005); RA 14% (WHO)
Elkan *et al.,* 2009[11]	Cross-sectional	80 patients	IDF	Women with RA 20% Men with RA 63%
La Montagna *et al.,* 2007[6]	Case-control	45 patients 48 controls	NCEP 2005	RA 55.5% Controls 45.8%
Toms *et al.,* 2009[29]	Cross-sectional	400 patients	IDF, NCEP 2004, NCEP 2001, WHO, EGIR	45.3% (IDF) 40.1% (NCEP 2004) 38.3 % (NCEP 2001) 19.4% (WHO) 12.1% (EGIR)
Giles *et al.,* 2010[28]	Case-control	131 patients 121 controls	NCEP 2005	RA 36% Controls 27%

NCEP: National Cholesterol Education Program; WHO: World Health Organization; IDF: International Diabetes Federation; EGIR: Group for the Study of Insulin Resistance.

also assessed the presence of atherosclerosis using detection of coronary calcifications on electron beam computed tomography. In RA group, patients with MetS according to the WHO definition were at an increased risk for higher coronary artery calcification scores, regardless of age and sex (OR = 2.02; 95% CI: 1.03-3.97; P = 0.04).

Some authors have found conflicting results regarding the aforementioned studies. Karvounaris *et al*.[3] reported no statistically significant difference between cases and controls regarding the presence of MetS. The authors have studied 200 patients with RA and 400 controls adjusted for age and sex. The total prevalence of MetS, according to the NCEP 2001 definition, was 44% in patients with RA and 41% in controls (P = 0.5). In another study, La Montagna *et al*.[6] assessed 45 patients with RA and 48 controls with no systemic rheumatologic disease. The prevalence of MetS, according to the updated NCEP definition, was 55.5% in patients with RA and 45.8% in patients without RA. In the study, no significant difference was observed between cases and controls.

In 2010, North-American researchers assessed the presence of CV risk factors factors and the NCEP III criteria for MetS in a case-control study with 131 patients with RA and 121 controls.[27] The difference in prevalence of MetS was not statistically significant between patients and controls (36% *versus* 27%; P = 0.12; respectively). These authors quantified the visceral and subcutaneous fat by use of computed tomography. The abdominal fat distribution differed significantly depending on RA activity, and was more significantly associated with CV risk factors factors in patients than in controls.

Non-controlled studies have also assessed the prevalence of MetS in RA. Elkan *et al.,*[11] differently from the previous studies, used the IDF criteria for determining the prevalence of MetS in 80 patients (61 women and 19 men) with RA. They have reported a MetS prevalence of 20% for women and 63% for men. In 2009, Toms *et al*.[28] assessed the prevalence of MetS in 400 patients with RA using five definitions (NCEP 2004 and 2001, IDF, WHO, and EGIR). The highest prevalence was 45.3% according to IDF, and the lowest prevalence was 12.1% according to EGIR.

CONCLUSIONS

Based on current knowledge, one can state that patients with RA are at a higher risk for developing CVD than general population. Studies about the prevalence of MetS in this population of patients have not achieved definitive conclusions, although its presence has been directly associated with a worse prognosis and disease activity. By itself, the later aspect suggests that a better control of underlying disease inflammatory process may improve both articular and CV prognoses in these patients. Monitoring and early identification of CV risk factors factors should be a necessary and constant preoccupation of rheumatologists caring for patients with RA.

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