Review Article:

Metabolic syndrome in patients with rheumatoid arthritis: clinical implications

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by swelling, tenderness, and destruction of synovial joints, leading to severe disability and premature mortality. The severity of inflammation is linked to an increased risk of cardiovascular mortality in the affected persons. Patients with RA are more prone for accelerated atherosclerosis than the general population. Atherosclerosis is in turn a risk factor for cardiovascular disease (CVD). Metabolic syndrome (MetS) is a major risk factor for the development of CVD. Evaluation of patients with RA for MetS appears to be clinically relevent because, not only are patients with RA more prone to develop atherosclerotic CVD, but when an associated MetS coexists this risk is further amplified. Investigations into the relationship between RA and the MetS have yielded conflicting results. While some studies reported a higher prevalence of MetS in patients with RA, others did not document such association. It has also been demonstrated that drugs which decrease rheumatoid inflammation are also useful in decreasing the MetS component of the disease.

Key words: *Rheumatoid arthritis, Metabolic syndrome, Atherosclerosis, Cardiovascular disease*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease, in which there is swelling, tenderness, and destruction of synovial joints, leading to severe disability and premature mortality.[1-6] RA is considered an autoimmune disease[6,7] and the overall systemic and articular inflammatory load drives the destructive progression of the disease. In addition, the extent of inflammation has been linked to an increased risk of cardiovascular mortality in patients with RA as compared to general population.[8] This is because patients with RA are more prone for accelerated atherosclerosis which in turn is a risk factor for cardiovascular disease (CVD) and thus there is decreased survival in them.[9]

The metabolic syndrome (MetS) is considered as one of the best known risk factor to the development of CVD. Evaluation of patients with RA for MetS is clinically important. This is because, not only are patients with RA significantly more prone to develop atherosclerotic CVD, but when there is an associated MetS this risk is likely to be further amplified.

Rheumatoid arthritis

RA has been in this world since the beginning of civilization. Although the term "rheumatoid arthritis" was proposed only in 1859,[10] evidence indicates that RA existed long before 1800.[11] In India the earliest description of arthritis can be seen in *Atharva Veda* composed around 1000 BC. Charaka, the great Indian physician, described RA in his *Charaka Samhita*. He described that RA first strikes hands and feet and then spreads in the entire body.[12]

Studies on RA show a considerable variation of the disease frequency among different populations. The established RA can be distinguished from other forms of arthritis by multiple criteria; and those agreed by the American Rheumatism Association (ARA) in 1987 are usually used.[13] The median prevalence es-

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timate of RA for the total population in south European countries is 3.3 (range 3.1-5.0) cases per 1000, for north European countries 5.0 (range 4.4-8.0), and for developing countries 3.5 (range 2.4-3.6).[14] RA affects 0·5-1·0% of adults in developed countries and is 2 to 3 times more frequent in women than men.[15,16] The basis of gender difference is probably related to effects of hormonal milieu on the function of the immune system.

In 1993, Malaviya et al[17] observed that the prevalence of RA among adults in India was 0.75%. In 1980, the World Health Organization (WHO) and the International League of Associations for Rheumatalogy (ILAR) designed the concept of the Community Oriented Programme for Control of Rheumatic Disease (COPCORD).[18] In an earlier report from India,[19] the prevalence of RA was 0.5% [95% confidence intervals (CI): 0.3-0.7)] while a recent COPCORD study from Bikaner[20] showed prevalence of RA as 2.54% (95% CI: 2.8-6.8). These studies, though providing good projections of the rheumatological burden in India, cannot be considered to represent the national scenario in total.

The primary site of immune activation in RA is the synovium. Infiltration of the synovium with mononuclear cells, especially T-cells and macrophages, and synovial hyperplasia are hallmarks of the disease.[21,22] RA predominantly affects the synovial joints. Despite its predominant articular manifestations, RA is a systemic disease, which is often associated with extra-articular manifestations. In patients with RA extra-articular manifestations occur in 17.8%-40.9%, either in the beginning or during the course of the disease.[23,24] RA is associated with a high morbidity and premature death because of early development of cardiovascular and/or lung diseases.

Metabolic syndrome

The MetS consists of a constellation of abnormalities that leads to increased risk of CVD and diabetes mellitus. The major features of the MetS include central obesity, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, hyperglycaemia, and hypertension. Most commonly, five definitions for the MetS are used worldwide: The National Cholesterol Education Programme-Adult Treatment Panel III (NCEP-ATP III) 2001,[25] NCEP-ATP III 2004,[26,27] the WHO,[28,29] the International Diabetes Federation (IDF) [30,31] and the European Group for Study of Insulin Resistance (EGIR).[32] These definitions are having many similarities, however, they differ in some of their components and cut-offs. In the general population, prevalence of the MetS vary according to the definition used[33] and its prevalence increases with age.[34,35] The prevalence of MetS in patients with RA in various published studies is shown in Table 1.[36-42]

In various studies around the world, the prevalence of MetS (based on NCEP-ATP III criteria, 2001) varied from 8%-43% in men and from 7%-56% in women.[43] A study from north India[44] showed that overall prevalence of MetS [based on NCEP-ATP III criteria (2001)] was 38.5% and its prevalence was more among females (44.8%) than in males (39.5%). Higher socioeconomic status, sedentary lifestyle and high body mass index (BMI) were significantly associated with MetS. Another study from west India[45] showed the prevalence of MetS [based on NCEP-ATP III criteria (2001)] as 12.8%. Chow et al[46] found a prevalence of MetS [based on NCEP-ATP III criteria (2004)] of 26.9% in males and 18.4% in females in southern India. In a community-based study (n=350) from eastern India[47] the prevalence of MetS [based on NCEP-ATP III criteria (2004)] was found to be 31.4%; gender-wise comparison revealed that the prevalence of MetS was higher among women (80/166; 48.2%) than in men (30/184; 16.3%). MetS is one of the best known risk factor to the development of CVD. A recent systematic review and meta-analysis of the lit-

Table 1: Comparison of prevalence of metabolic syndrome in patients with rheumatoid arthritis in various studies

	Study						
	Karvounaris et al[36]	**Chung et al[37]**	**Toms et al[38]**	**Dao et al[39]**	**Karimi et al[40]**	**Sahebari et al[41]**	**da Cunha et al[42]**
Year of publication	2007	2008	2009	2010	2011	2011	2012
Place of study	Heraklion, Greece	Tennessee,United States of America	Dudley, United Kingdom	Hanoi, Vietnam	Zanjan, Iran	Mashhad, Iran	Porto Aleg Brazil
No. of cases studied	200	154	387	105	92	120	283
No. of controls studied	400	85	None	105	96	500	226
Age of cases (years)	63±11*	ND	63.1 (55.5-69.6)†	56.3 (26 -73)†	48.3±14.6*	45.5±13*	56.8±12.3*
Females [No. (%)]	147 (73.5)	ND	282 (72.9)	105 (100)	92 (100)	106 (88.3)	233 (82.3)
Prevalence of MetS as per WHO criteria (cases Vs controls) [No. (%)]	ND	55 (35.7) Vs 9 (10.6) (p=0.001)	70 (18.1)	20 (19.0) Vs 13 (12.4) (p<0.001)	18 (19.6) Vs 21 (21.9) (p=0.70)	ND	ND
Prevalence of MetS as per NCEP-ATP III criteria (2001) (cases Vs controls) [No. (%)]	88 (44) Vs 164 (41) (p=0.5)	54 (35.1) Vs 19 (22.4) (p=0.03)	149 (38.5)	26 (24.7) Vs 15 (14.2) (p<0.001)	25 (27.2) Vs 34 (35.4) (p=0.22)	45.2% Vs 53.8% (p=0.0001)	ND
Prevalence of MetS as per NCEP-ATP III criteria (2004) (cases Vs controls) [No. (%)]	ND	ND	156 (40.3)	34 (32.4) Vs 19 (18.1) (p<0.001)	ND	ND	111 (39.2) Vs 44 (19.5) (p< 0.001)
Prevalence of MetS as per IDF criteria (cases Vs controls) [No. (%)]	ND	ND	159 (41.1)	43 (40.9) Vs 24 (22.9) (p<0.001)	ND	30.8% Vs 34.2% (p=0.005)	ND
Prevalence of MetS as per EGIR criteria (cases Vs controls) [No. (%)]	ND	ND	47(12.1)	17 (16.2) Vs 11 (10.5) (p<0.001)	ND	ND	ND

*expressed as mean±SD; †expressed as median (IQR)

MetS = metabolic syndrome; WHO = World Health Organization; NCEP-ATP III = National Cholesterol Education Programme Adult Treatment Panel III; IDF = International Diabetes Federation; EGIR=European Group for Study of Insulin Resistance; ND = not described; SD = standard deviation; IQR = interquartile range;

Source: references 36-42

erature,[48] involving 951,083 patients, has shown that the MetS is associated with a 2-fold increased risk of CVD, cardiovascular mortality, myocardial infarction and stroke.

Rheumatoid arthritis, metabolic syndrome and cardiovascular disease

Several groups have documented a high prevalence of MetS in patients with systemic rheumatic diseases like RA and systemic lupus erythematosus (SLE). Chronic inflammation seen in patients with RA is one of the important factors which links it to both MetS and atherosclerosis.[49] Proinflammatory cytokines, tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) seen in patients with RA contribute to insulin resistance[50,51] which is the basic metabolic disorder seen in MetS. Insulin resistance leads to other metabolic disturbances like hyperglycaemia, dyslipidaemia[52] which independently contribute to atherosclerosis and cardiovascular risk. Proinflammatory cytokines are also independently involved in the pathogenesis of atherosclerosis through the production of acute-phase reactant C-reactive protein.[53] Thus multiple mechanisms inflammation, insulin resistance and dyslipidaemia increase the burden of cardiovascular risk in these patients.

The basic pathology in RA is inflammation which in turn is basis for atherosclerosis and this has led to study the relationship between systemic inflammatory conditions, such as RA, and the risk for CVD. It was seen that even in the absence of traditional coronary risk factors, women with RA have a 2-3 fold higher risk of CVD.[54,55] Also another study showed that patients with RA are 50% more likely to suffer a cardiovascular event than subjects from the general population.[56] Investigations into the relationship between RA and the MetS have yielded conflicting results. While some studies[42-44] reported a higher prevalence of MetS in patients with RA, others[45,46] did not document any such association. A recent study[42] showed that MetS was significantly more prevalent in American patients with long-standing RA [42% by both WHO and NCEP-ATP III criteria (2001)] as well as in early RA [31% and 30% by WHO and NCEP-ATP III criteria (2001), respectively] than in controls [11% and 22% by WHO and NCEP-ATP III criteria (2001), respectively]. However, a study from Iran[45] showed statistically significant higher prevalence of MetS in controls as compared to patients with RA. These data suggest that it is necessary to treat both conditions (RA and MetS) simultaneously and effectively.

It has been demonstrated that use of methotrexate,[48] hydroxychloroquine[57,58] and anti-TNF-α drugs[59] decrease the prevalence of components of MetS in patients with RA and thus reduces the risk of development of CVD. Methotrexate is thought to exert its effects through its anti-inflammatory action mediated through adenosine[60] which is known to enhance glucose metabolism through insulin and alters lipid metabolism.[61] Anti-TNF-α drugs have been shown to improve insulin resistance and insulin sensitivity[59] apart from decreasing inflammation while hydroxychloroquine decreases blood glucose levels[62] and total cholesterol levels.[63]

But well designed studies comparing the prevalence of MetS in patients with RA on treatment with disease modifying antirheumatic drugs (DMARDs) and those who are treatment naïve are lacking.

Studies about the prevalence of MetS in patients with RA have yielded conflicting results. However, based on current knowledge, one can conclude that patients with RA are at a higher risk for development of CVD than the general population. So, by looking for and treating MetS associated with RA the control of overall inflammatory process and the associated risk of CVD is better.

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