Association between Treatment Factors and Metabolic syndrome in Iraqi Patients with Rheumatoid Arthritis

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Abstract
Rheumatoid Arthritis is a systemic disease characterized by massive joint destruction and deformity. The disease leads to increased morbidity and mortality especially if associated with other diseases like Metabolic Syndrome. Metabolic syndrome is a cluster of risk factors caused by abdominal obesity, such as hyperglycemia, hypertension, dyslipidemia, and insulin resistance. Rheumatoid arthritis has been found to be associated with metabolic syndrome. The present paper aims to assess the correlation between metabolic syndrome and different treatment modalities like steroids or methotrexate that are used to treat Iraqi patients with Rheumatoid Arthritis.
Keywords: metabolic syndrome, rheumatoid arthritis, steroids, methotrexate

1. Introduction

1.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality (Wolfe 1996). Given the presence of autoantibodies, such as rheumatoid factor (RF) and anti–citrullinated protein antibody (ACPA), which can precede the clinical manifestation of RA by many years (Nielen *et al*.2004), RA is considered an autoimmune disease; autoimmunity and the overall systemic and articular inflammatory load drive the destructive progression of the disease (Firestein 2003). Joint damage is rarely apparent in the very early stages of disease, but rather accumulates consistently over time (Machold 2002).

Over the last decade, the optimal use of disease-modifying antirheumatic drugs (DMARDs), in particular the anchor DMARD methotrexate (MTX) (Visser *et al*. 2009), and the availability of new biologic agents (Smolen et al. 2007; Doan & Massarotti 2005), have dramatically enhanced the success of RA management. Moreover, it has been recognized that early therapeutic intervention improves clinical outcomes and reduces the accrual of joint damage and disability (Bukhari *et al*. 2003; Van Dongen *et al*. 2007).

1.2 Metabolic syndrome

Metabolic syndrome (MetS) is a constellation of interrelated risk factors of metabolic origin (Sattar *et al*. 2003). The features of MetS include: Central obesity, Insulin resistance, dyslipidemia, high blood pressure, prothrombotic state, and proinflammatory state (Wang *et al*. 2007).

The appropriate way to define MetS is still under debate, Several groups including the world health organization (WHO) (Alberti and Zimmet 1998), The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) (Third Report of the NCEP ATPIII 2002), and the International Diabetes Federation (IDF) (The IDF consensus worldwide definition of metabolic syndrome 2005) have proposed criteria to define this syndrome for research purpose or early clinical identification. In 2001, the (NCEP ATP III) simplified the WHO criteria by requiring three of five simple clinical measures, increased waist circumference (WC), elevated triglycerides (TG), reduced high density lipoprotein cholesterol (HDL-C), elevated blood pressure (Bp), and elevated plasma glucose. The various MetS definitions include the same core criteria: obesity, insulin resistance, dyslipidemia and hypertention, but differ in the cut-off points for individual criteria and in the inclusion of additional factors (eg. microalbuminuria). The WHO, for instance, requires evidence of insulin resistance or DM to make a diagnosis of MetS, while the IDF requires a certain degree of abdominal obesity. The NCEP, however, considers the five components equal in importance (Reaven 2006). According to Scott Grundy, University of Texas Southwestern Medical School, Dallas, Texas, the intent was just to update the NCEP ATP III definition and not create a new definition (Grundy *et al. 2004*). These include the following:
1. increase waist circumference:
    *   Men — Equal to or greater than 40 inches (102 cm)
    *   Women — Equal to or greater than 35 inches (88 cm)
2. Elevated triglycerides: Equal to or greater than 150 mg/dL (1.7 mmol/L)
3. Reduced HDL ("good") cholesterol:
    *   Men — Less than 40 mg/dL (1.03 mmol/L)

- Women — Less than 50 mg/dL (1.29 mmol/L)
4. Elevated blood pressure: Equal to or greater than 130/85 mm Hg or use of medication for hypertension
5. Elevated fasting glucose: Equal to or greater than 100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia

2. Material & Methods

2.1 Study population

A total number of 203 patients with RA meeting the American College of Rheumatology Criteria for the classification of rheumatoid arthritis participated in the study. The patients attended the Rheumatology & Rehabilitation Department of Baghdad Teaching Hospital during 2010. All patients gave their informed written consents prior to commencement of the study.

2.2 Assessment of the metabolic syndrome

The metabolic syndrome was diagnosed according to NCEP III criteria (Third Report of the NCEP ATPIII 2002). All participants had an extensive baseline assessment including a detailed record of their medical history, physical examination, and measurements of basic demographics: (age, gender, height, weight, body mass index (BMI), waist circumference and smoking status).

2.3 Laboratory tests

Baseline blood samples were obtained from each patient and were analyzed in the same laboratory. Blood samples were taken in the morning after 10 hours of overnight fasting. Blood tests included: C reactive protein (CRP), erythrocyte sedimentation rate (ESR), fasting lipid profile: [total cholesterol (TC), high density lipoprotein (HDL), low density lipoproteins (LDL) and triglycerides (TG)], rheumatoid factor, liver function tests, renal function tests, and fasting glucose.

2.4 Rheumatoid arthritis disease characteristics

Patients' data were obtained via case note analysis and a face - to- face interview performed by rheumatologist. Rheumatoid arthritis disease-related data, such as disease duration, extra-articular manifestations (as a marker of disease severity), physical activity and drug use (all anti-rheumatic drugs and glucocorticoid use), were recorded.

3. Results

3.1 Descriptive characteristics of study population

Among the 203 patients with RA, 162 (79.8%) were women and 41 (20.2%) were men, with a mean (SD) age of 46.9±11.5 years. No significant differences between the mean age of men than that of women among patients with RA (48.0±12.6 versus 46.6±11.3 p=0.507).

3.2 Prevalence of MetS

The prevalence of MetS was 51.2% in study subjects being 29.3% in male and 56.8% in female. When the prevalence of MetS was analyzed in various age groups, there was no significant difference between male and female prevalence in any specific age group while a significant difference was depicted comparing the total number (p=0.046) as shown in table 1.

3.3 Correlations

The study found a significant correlation between age and BMI (p<0.001) along with number of metabolic syndrome components in RA patients (p<0.001). Also a significant positive correlation was found between duration of RA disease and the number of criteria related to metabolic syndrome (p<0.05).

3.4 Therapy and MetS

Regarding the possible association between treatment factors and MetS in RA patients; table 2 shows that the usage of steroid dose ≥ 10mg for more than 3 months duration were more common in patients with MetS (p <0.001), similarly the MetS tend to be more common in patients that don't take or on irregular uses of methotrexate (p=0.032). Biological treatment did not seem to have an effect on MetS in this study (p=0.532).

4. Discussion

This study reported a high prevalence of MetS among Iraqi rheumatoid patients according to the NCEP 2001, as agreed by previous studies (Chung *et al.* 2007; Karvounaris *et al.* 2007). This prevalence was significantly higher in women than in men which differ from previous studies on the prevalence of MetS done by Chung *et al* (2007), Karvounaris *et al* (2007), and Toms *et al* (2009) who showed the same prevalence rate between men and women.

This study showed a linear correlation between high BMI and age; which agrees with previous studies (Dessein *et al*. 2002; Chung *et al*. 2007; Chung *et al*. 2008). The economic growth of the Gulf region has resulted in increases in health problems and related diseases especially obesity in Asian population. This was first noted in developed states (Pischon *et al*. 2008), but has rapidly spread to third world countries in the past few years (Chung *et al*. 2008; WHO Expert Committee). The hot climates and sand storms largely discourage outdoor activities while indoor activities (such as TV watching) and socializing frequently involve eating and snacking; subsequently resulting in obesity (Chung *et al*. 2008).

This study found a significant relation between RA and the number of components of MetS in agreement with a study done in Brazil (Da Cunha *et al.* 2012) and the QUEST-RA Study (Sokka *et al*. 2009). Moreover, in a multivariate model assessment, the risk of having severe relapses was found to be significantly higher for patients with MetS compared to those without MetS even after further adjusting for RA treatments, demographics and behavioral factors.

The present data suggested that RA disease duration correlates posatively with MetS, implicating a significant role for the inflammatory burden in the evolution of metabolic disturbances in patients with RA. This finding is in agreement with the study done by Karvounaris *et al* (2007).

The results concerning treatment agents and MetS showed lack of significant association between glucocorticoid use at any dose and the presence of MetS but when the dose increased to ≥10mg/day for more than 3 months duration there was a significant increase in the risk of development of MetS; this result in part differ from data presented by Toms *et al*. (2008) which may be due to effects of other drugs such as biological agents in that study leaving little scope for additive effects of glucocorticoid. The present study also demonstrated that patients on regular doses of methotrexate were less likely to developed MetS than those who don't take or on irregular uses of the drug; this finding is in agreement to previous studies (Zonana-Nacach *et al*. 2008; Toms *et al* 2009). About 2% of patients in this study were on biological treatment while the study done by Karvounaris *et al* (2007) reported 40% taking anti-TNFα agents this may be due to the limited availability of these drugs in our hospital.

5. Conclusion

This paper confirms a positive correlation between metabolic syndrome components and duration of rheumatoid arthritis. Chronic inflammatory state of metabolic syndrome may be correlated to treatment by high doses of steroids or irregular uses of methotrexate in Rheumatoid arthritis patients.

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Table 1. Prevalence of the Metabolic Syndrome in patients with Rheumatoid Arthritis

Age Group (years)	Metabolic Syndrome			
	Women	Men	Total	
	N (%)	N (%)	N (%)	P *
< 40	46/105 (43.8)	6/25 (24.0)	52/130 (40.0)	0.101
40 – 59	29/40 (72.5)	2/10 (20.0)	31/50 (62.0)	0.791
≥60	17/17 (100.0)	4/6 (66.7)	21/23 (91.3)	0.064
Total	92/162 (56.8)	12/41 (29.3)	104/203 (51.2)	**0.046**

*Significant P values (< 0.05) are highlighted in bold.

Table 2. Association between Treatment factors and Metabolic Syndrome in patients with Rheumatoid Arthritis.

Variables	Women with RA			Men with RA			All with RA		
	MetS +	MetS-	P *	MetS +	MetS-	P *	MetS +	MetS-	P *
	(n=92;%)	(n=70;%)		(n=12;%)	(n=29;%)		(n=104;%)	(n=99;%)	
Steroids; any dose;, n (%)									
take	51(56.7)	31(44.3)	0.120	5(45.5)	14(48.3)	0.873	56(55.4)	45(45.5)	0.158
Not take	39(43.3)	39(55.7)		6(54.5)	15(51.7)		45(44.6)	54(54.5)	
Steroid dose (mg/day), > 3 months; n (%)									
≥10	36(81.8)	13(43.3)	**0.001**	1(50.0)	5(38.5)	1.000	37(80.4)	18(41.9)	**0.000**
< 10	8(18.2)	17(56.7)		1(50.0)	8(61.5)		9(19.6)	25(58.1)	
Methotrexate: Under Treatment; n (%)									
Irregular/ Not used	57(63.3)	34(48.6)	0.061	6(66.7)	14(48.3)	0.454	63(63.6)	48(48.5)	**0.032**
Regular use	33(36.7)	36(51.4)		3(33.3)	15(51.7)		36 (36.4)	51(51.5)	
Biologic agents; n (%)									
take	1(1.1)	1(1.4)	1.000	0(0.0)	1(3.4)	0.515	1(1.0)	2(2.0)	0.532
Not take	91(98.9)	69(98.6)		12(100.0)	28(96.9)		103(99.0)	97(98.0)	

RF, rheumatoid factor; MetS+, metabolic syndrome; MetS-, no metabolic syndrome; RA, rheumatoid arthritis.

*Difference between patients with RA with and without MetS.

Significant P values (< 0.05) are highlighted in bold.

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