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Metabolic Syndrome and Cardiovascular Diseases in Seronegative Spondyloarthropathy and Rheumatoid Arthritis Patients: A Comparative Study

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ABSTRACT

Background: Spondyloarthritis (SpA) and rheumatoid arthritis (RA) are ones of the most rheumatic diseases with chronic inflammatory damaging processes that have a great risk for metabolic syndrome (MS) and cardiovascular diseases. Several studies have indicated higher cardiovascular disease (CVD) risk and mortality rates among these patients compared to the general population.

Objective: To identify the prevalence and early detection of metabolic syndrome and cardiovascular disease in seronegative spondyloarthropathy and rheumatoid arthritis patients and their relation to disease activity.

Patients and Methods: Our study was carried out on sixty rheumatoid arthritis patients (54 female and 6 males with mean age 46.7 ± 5.5 years) and sixty spondyloarthroapathy patients (27 female and 33 males with mean age 44.9 ± 5.9 years).

Results: In RA group, there were 23 patients (38.3%) with metabolic syndrome and 37 patients (61.7%) without metabolic syndrome. In SPA group, there were 21 patients (35%) with metabolic syndrome and 39 patients (65%) without metabolic syndrome. There was no statistical significant difference (p-value > 0.05) between studied groups as regards metabolic syndrome prevalence. There was high statistical significant difference (p-value < 0.001) between patients with MS and patients without MS in RA group regarding age, duration, BMI, FBS, ESR, CRP and DAS28. High statistical significant difference (p-value < 0.001) was detected between patients with MS and patients without MS in SPA group as regards duration, BMI, FBS and BASDI. There was increase in cIMT in RA (0.8 ± 0.2) and SPA groups (0.7 ± 0.1) with high statistical significant difference (p-value < 0.001).

Conclusion: MS prevalence increased in patients with RA and SPA, whereas the cardiovascular risks increased in RA patients. The disease activity of both were associated with metabolic syndrome, implicating the role of chronic inflammation in metabolic syndrome development.

Keywords: Metabolic Syndrome, Cardiovascular Diseases, Seronegative Spondyloarthropathy, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by progressive joint destruction, associated with extra-articular manifestations, affecting different internal organs [(1)]. Interestingly, these patients showed an increased risk of mortality when compared to general population and recent evidence clearly confirmed that this risk is large due to cerebro-cardiovascular events (CVEs) [(2)]. In addition, several studies showed the close relationship between RA and specific cardiovascular (CV) events, including myocardial infarction (MI), cerebrovascular accident (CVA) and congestive heart failure [(3)].

It is now well-known that increased subclinical atherosclerosis, mainly carotid artery plaques, may be observed in RA patients, which may be easily recognized by ultrasound, thus identifying those patients with higher CVEs risk [(4)]. Rheumatoid arthritis and metabolic syndrome are considered diseases with common traits that can increase the risk of cardiovascular disease [(5)] with previous research showing an association between the two [(6)].

The spondyloarthropathies form a heterogeneous group includes ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease associated arthritis, and the 'reactive' arthritis, which follows a very specific set of infectious diseases [(7)]. The axial skeleton is a dominant site of pathology in these conditions, with inflammation of the ligamentous attachments in the affected spine, which results in pain, stiffness and poor mobility. In contrast to other articular diseases such as rheumatoid arthritis where inflammation is accompanied by bony erosion and destruction [(8)], spondyloarthropathy is not only characterized by such destruction, but by new bone formation [(9)]. Psoriatic arthritis (PsA) one of the most common spondyloarthropathies in which systemic inflammation extends beyond the skin and joints. Recent research highlighted the increased risk of major adverse cardiovascular events (combined end-point of myocardial infarction, stroke, and cardiovascular death) in patients with PsA [(10)].

Cardiovascular involvement has been demonstrated as the most important cause of mortality

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in both Rheumatoid arthritis and spondyloarthropathies. It is considered that systemic inflammation, circulating proinflammatory cytokines, and traditional risk factors may be effective on accelerated atherosclerosis, hypertension, dyslipidemia, obesity, and insulin resistance [(11)].

This study aimed to identify the prevalence and early detection of metabolic syndrome and cardiovascular disease in seronegative spondyloarthropathy and rheumatoid arthritis patients and their relation to disease activity.

PATIENTS AND METHODS

This study was carried out on sixty rheumatoid arthritis patients (54 female and 6 males with mean age 46.7 ± 5.5 years) who fulfilled 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA. In addition, sixty spondyloarthropathy patients (27 female and 33males with mean age 44.9 ± 5.9 years) who fulfilled the 2010 ASAS (Assessment of SpondyloArthritis international society Axial Spondyloarthritis) classification criteria of spondyloarthropathy [(7)].

All patients were selected from those attending the Outpatient Clinic and inpatients of Rheumatology and Rehabilitation Department at Al-Azhar-Assiut University Hospital from December 2017 to January 2020.

Exclusion criteria:

Age < 18 years old. Patients with history of malignancy. Patients with an active infection. Chronic kidney disease and thyroid dysfunction patients. Pregnant patients and other autoimmune diseases.

All patients were subjected to the following:

Full History taking including age, sex, disease duration (years), history of present illness and history of chronic diseases including diabetes mellitus, hypertension and dyslipidaemia. In addition, drug history [non-steroidal anti-inflammatory drugs (NSAIDs), steroids, conventional and biological disease-modifying antirheumatic drugs (DMARDs) and drugs for diabetes, hypertension, and hyperlipidemia.

BMI was measured before clinical examination: Body mass index (BMI): weight in kgs/ (Height in m) ^{2} according to **World Health Organization (WHO)** classification of BMI [(12)].

Clinical Examination including:

(i) General examination: general condition, vital signs (pulse, blood pressure, respiratory rate and temperature) and waist circumference.

(ii) (ii) Locomotor examination.

- **Assessment of RA disease activity** using DAS-28 score.
- **Assessment of SPA disease activity** using BASDAI score.
- **Laboratory investigations:** CBC, ESR, CRP, lipid profile (Total cholesterol, TG, LDL, HDL), serum uric acid and serum rheumatoid factor (RF).
- **Carotid intima-media thickness (CIMT**) was measured using real-time gray-scale sonography. The intima-media thickness (IMT) of common carotid artery, carotid bulb and internal carotid artery was determined.

Ethical consideration

An approval of the study was obtained from Al-Azhar University Academic and Ethical Committee. The aim of the study was explained to each participate before collection of data. Verbal and written consent were obtained from those who welcomed to participate in the study. Privacy of the data was assured.

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 15.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Chi-square test was used when comparing between non-parametric data. A one-way analysis of variance (ANOVA) was used when comparing between more than two means. P-value ≤ 0.05 was considered significant, P-value < 0.001 was considered as highly significant and P-value > 0.05 was considered insignificant.

RESULTS

This study was carried out on sixty rheumatoid arthritis patients (54 female and 6 males with mean age 46.7 ± 5.5 years) and disease duration of 6.8 ± 1.8 years and sixty spondyloarthroapathy patients (27 female and 33 males with mean age 44.9 ± 5.9 years) and disease duration of 6.9 ± 1.9 years.

Table (1): Comparison between studied groups as regards demographic data

Demographic data		RA Group (N = 60)		SPA Group (N = 60)		P-value
Sex	Male	6	10%	33	55%	< 0.001 HS
	Female	54	90%	27	45%	
Age (years)	Mean	46.7		44.9		0.107 NS
	± SD	5.5		5.9		
Duration (years)	Mean	6.8		6.9		0.867 NS
	± SD	1.8		1.9		

NS: p-value > 0.05 is considered non-significant. HS: p-value < 0.001 is considered highly significant.

This table showed no statistical significant difference **(p-value > 0.05)** between studied groups as regards demographic data (age and duration of disease), while there was high statistical significant difference **(p-value < 0.001)** between studied groups as regards sex.

Table (2): Comparison between studied groups as regards drugs used for treatment

Drugs		RA Group (N = 60)		SPA Group (N = 60)		P-value
Methotrexate	No	27	45%	54	90%	< 0.001 HS
	Yes	33	55%	6	10%	
Leflunomide	No	34	56.7%	59	98.3%	< 0.001 HS
	Yes	26	43.3%	1	1.7%	
Sulfasalazine	No	45	75%	42	70%	0.540 NS
	Yes	15	25%	18	30%	
Hydroxy-chloroquine	No	18	30%	52	86%	< 0.001 HS
	Yes	42	70%	8	14%	
Corticosteroids	No	21	35%	54	90%	< 0.001 HS
	Yes	39	65%	6	10%	
NSAID	No	54	90%	18	30%	< 0.001 HS
	Yes	6	10%	42	70%	
Biological agents	No	59	98.3%	54	90%	0.008 S
	Yes	1	1.7%	6	10%	

S: p-value < 0.05 is considered significant. NS: p-value > 0.05 is considered non-significant.
HS: p-value < 0.001 is considered highly significant.

This table showed no statistical significant difference **(p-value > 0.05)** between studied groups as regards sulfasalazine and biological agents. There was statistical significant difference **(p-value < 0.05)** between studied groups as regards biological agents. Moreover, there was high statistical significant difference **(p-value < 0.001)** between studied groups as regards methotrexate, Leflunomide, hydroxyl-choloquine, corticosteroids & NSAID.

Table (3): Prevalence of metabolic syndrome in studied groups

	RA Group (N = 60)	SPA Group (N = 60)
Metabolic syndrome (n and %)	23 (38.3%)	21 (35%)
Abdominal obesity (%)	65%	63.3%
Hypertension ≥130/85mmHg or under treatment (%)	35%	26.6%
Fasting glucose ≥100 mg/dL or under treatment Type II DM (%)	16.5%	11.5%
HDL lowering level %	35%	40%

This table showed the description of metabolic syndrome in studied groups. In RA group, there were 23 patients (38.3%) with metabolic syndrome and 37 patients (61.7%) without metabolic syndrome. In SPA group, there were 21 patients (35%) with metabolic syndrome and 39 patients (65%) without metabolic syndrome.

Table (4): Comparison between studied groups as regards CIMT

		RA Group (N = 60)	SPA Group (N = 60)	P-value
CIMT (mm)	Mean	0.8	0.7	< 0.001 HS
	± SD	0.1	0.1	

HS: p-value < 0.001 is considered highly significant.
This table showed high statistical significant difference **(p-value < 0.001)** between studied groups as regards CIMT.

Table (5): Comparison of studied data in RA group as regards metabolic syndrome

RA group		Metabolic syndrome				P-value
		With (n = 23)		Without (n = 37)		
Age (years)	**Mean ± SD**	43.4 ± 5.6		39.1 ± 6.9		**0.014 S**
Duration (years)	**Mean ± SD**	7.3 ± 1.8		3.3 ± 0.6		**< 0.001 HS**
BMI	**Mean ± SD**	29.7 ± 5.3		24.6 ± 4.9		**< 0.001 HS**
W.C	**Mean ± SD**	104.8 ± 8.6		98.5 ± 7.4		**0.003 S**
FBS (mg/dl)	**Mean ± SD**	107.5 ± 12.4		90.8 ± 10.3		**< 0.001 HS**
U.A (mg/dl)	**Mean ± SD**	5.2 ± 1.3		4.7 ± 1.7		0.464 NS
ESR (mm/h)	**Mean ± SD**	40.2 ± 2.8		15.7 ± 2.7		**< 0.001 HS**
CRP (mg/dl)	**Mean ± SD**	11.6 ± 3.5		8.9 ± 2.3		**< 0.001 HS**
Methotrexate	**Yes**	13	56.5%	30	81.1%	**0.04 S**
Steroid	**Yes**	20	87%	23	62.2%	**0.038 S**
DAS28	**Mean ± SD**	4.4 ± 1.1		2.8 ± 0.9		**< 0.001 HS**

S: p-value < 0.05 is considered significant. HS: p-value < 0.001 is considered highly significant.
NS: p-value > 0.05 is considered non-significant.

This table showed no statistical significant difference **(p-value > 0.05)** between patients with MS and patients without MS in RA group as regards U.A. While, there was statistical significant difference **(p-value < 0.05)** between patients with MS and patients without MS in RA group as regards age, W.C and methotrexate and steroid use. In addition, there was high statistical significant difference **(p-value < 0.001)** between patients with MS and patients without MS in RA group as regards duration, BMI, FBS, ESR, CRP and DAS28.

Table (6): Comparison of studied data in SPA group as regards metabolic syndrome

SPA group		Metabolic syndrome				P-value
		With (n = 21)		Without (n = 39)		
Age (years)	**Mean ± SD**	41.4 ± 6.7		38.6 ± 7.4		0.154 NS
Duration (years)	**Mean ± SD**	8.2 ± 2.1		4.5 ± 1.2		**< 0.001 HS**
BMI	**Mean ± SD**	30.3 ± 6.3		24.7 ± 5.2		**< 0.001 HS**
W.C	**Mean ± SD**	102.4 ± 7.8		97.3 ± 8.4		**0.025 S**
FBS (mg/dl)	**Mean ± SD**	110.5 ± 11.8		92.8 ± 12.3		**< 0.001 HS**
U.A (mg/dl)	**Mean ± SD**	5.4 ± 1.9		4.5 ± 1.3		0.131 NS
ESR (mm/h)	**Mean ± SD**	14.3 ± 3.8		12.3 ± 4.2		**0.142NS**
CRP (mg/dl)	**Mean ± SD**	17.2 ± 4.1		8.2 ± 1.3		**< 0.001 HS**
Methotrexate	**Yes**	6	28.6%	9	23.1%	0.639 NS
NSAID	**Yes**	19	31.6%	23	38.3%	0.806 NS
BASDI	**Mean ±SD**	4.3 ± 0.1		3.1 ± 0.3		**< 0.001 HS**

S: p-value < 0.05 is considered significant. HS: p-value < 0.001 is considered highly significant.
NS: p-value > 0.05 is considered non-significant.

This table showed no statistical significant difference **(p-value > 0.05)** between patients with MS and patients without MS in SPA group as regards age, U.A, ESR and methotrexate and NSAID use. While, there was statistically significant difference **(p-value < 0.05)** between patients with MS and patients without MS in SPA group as regards W.C. In addition, there was high statistical significant difference **(p-value < 0.001)** between patients with MS and patients without MS in SPA group as regards duration, BMI, FBS, CRP and BASDI.

DISCUSSION

In our study, the prevalence of MS in patients with RA was 38.3% according to NCEPIII criteria. Several studies report variable prevalence of MS among RA patients depending upon the MS definition used. **Müller** [13] and his colleagues reported that the prevalence of MS in patients with RA using NCEP criteria was 35.16 %, which is similar to our results. Moreover, our study has the similar results reported by **Da Cunha *et al.*** [14] whose study carried out on 283 RA patients and the prevalence of MS among patients was 39.2%. Another study was done by **Karakoc *et al.*** [15] on 54 RA patients and reported similar results (42.6%) of metabolic syndrome in those patients. Similar results are reported by **de Oliveira *et al.*** [16] in their study, which was carried out on 110 RA patients but with a higher prevalence with 50% of those patients had MS according to NCEPIII criteria. In addition, another study was done by **Labitigan *et al.*** [17] reported different MS prevalence (19%) among 1162 RA patients. Therefore, it is likely that other factors related to the characteristics of the study population such as genetic, ethnic, cultural, demographic, socioeconomic and clinical factors also are affecting the prevalence. Thus, studies conducted

using different populations are critical in order to identify other factors related to MS.

In our study, assessment of the individual components of MS among RA patients, we found that the abdominal obesity was the highest prevalence component (65%) while the lowest one was high FBS (16.5%). These findings are in agreement with study done by **Zafar *et al.* [18],** which reported that high FBS (21.9%) was the least prevalent component, while a high WC (46.1%) was the most prevalent component.

In our study, we reported high statistical significant difference **(p-value < 0.001)** between patients with MS and patients without MS in RA group as regards disease duration. Our result is in agreement with **Karimi *et al.* [19]** and his colleagues whose study reported that RA duration was also significantly different between patients with and without metabolic syndrome (p-value 0.008).

In our study, we found high statistical significant difference (p-value < 0.001) between patients with MS and patients without MS in RA group as regards disease activity (DAS28). We agree with **Pandey *et al.* [20]** in their study, which carried out on 84 RA patients and reported that MS in RA patients increase with higher DAS28 score (p < 0.001). **Karvounaris *et al.* [21]** also reported that high DAS28 was found to be significantly higher for patients with MS compared to those without MS components (p=0.016). On the other hand, **Ağaday *et al.* [22]** reporteded that DAS 28 was not found to be associated with MS in RA patients (P-value0.15). We disagree also with **Karimi *et al.* [19]** in their study, which reported that no significant difference was found in DAS28 between patients with and without metabolic syndrome (p-value 0.8).

In our study, the prevalence of MS in our patients with SPA was 35% according to NCEPIII criteria. Similar result was reported by **Ağaday *et al.* [22]** whose study was carried out on 41 SPA patients and the prevalence of MS among patients was 41.5%. **Morales *et al.* [25]** also reported 37% of 410 of SPA patients included in their study fulfilled MS criteria, which is similar to our results. Another study done by **Gunawan *et al.* [23]** who reported significant prevalence of MS of 54.5% among 33 SPA patients but their result was higher than our study.

In our study, we found that high WC had the highest prevalence (63.3%), while the high FBS (11.5%) was the lowest prevalent metabolic syndrome component in SPA patients with metabolic syndrome. We agree with study done by **Gunawan *et al.* [23]** who reported that central obesity was the most common metabolic syndrome's component found in SPA metabolic patients and impaired glucose tolerance was the least one.

We report high statistical significant difference **(p-value < 0.001)** between patients with MS and patients without MS in SPA group as regards disease duration. We agree with **Gunawan *et al.* [23]** in their study, which reported that SPA duration was also significantly different between patients with and without metabolic syndrome (P-value 0.000). While, this disagrees with **Malesci *et al.* [24]** who found no significant relationship in metabolic syndrome prevalence in AS patients regarding disease duration.

In our study, we found high statistical significant difference (p-value < 0.001) between patients with MS and patients without MS in SPA group as regards disease activity (BASDI). We agree with **Morales *et al.* [25]** in their study, which reported that SPA MS was related with higher BASDAI. On the other hand, study done by **Ağaday *et al.* [22]** and reported that BASDI were not found to be associated with MS.

In our study, we reported no statistically significant difference between RA group and SPA group as regards MS prevalence. We agree with **Ağaday *et al.* [22]** in their study, which reported that MS prevalence among 98 RA patients was 43.9% versus 41.5% among SPA patients with no statistically significant difference (p-value .0510). On the other hand, our study disagrees with **Özkan *et al.* [26]** who carried out their study on 102 PSA patients and 102 RA patients and reported that the prevalence of MS was higher in patients with PsA than in those with RA (40.6% vs. 24.7%, respectively; p=0.019). In our study, we found increase in CIMT in RA (0.8 ± 0.2) and SPA groups (0.7 ± 0.1) with highly statistical significant difference (p-value < 0.001). We agree with **Abdel-Monem *et al.* [27]** who reported an increase in CIMT in 30 RA patients (0.7 ± 0.71 mm) with P < 0.001) compared to control group. In addition, we agree with **Skare *et al.* [28]** in their study on 36 SPA patients and reported a significant increase of CIMT in these patients (0.72 ± 0.21 mm with P = 0.0007) compared to control group.

CONCLUSIONS

MS prevalence increased in patients with RA and SPA, whereas the cardiovascular risks increase in RA patients. The disease activity of both were associated with metabolic syndrome, implicating the role of chronic inflammation in metabolic syndrome development.

RECOMMENDATIONS

Lipid profile is recommended for all RA and SPA patients on diagnosis and during follow up of the disease. IMT of common carotid artery could be added as further investigation for detection and follow up of atherosclerosis in RA and SPA patients. Early diagnosis and treatment of metabolic syndrome in RA and SPA patients are needed to prevent cardiovascular complications.

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