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Prevalence of Metabolic Syndrome in a Sample of Iraqi Patients with Ankylosing Spondylitis treated with Anti TNF-a Therapy

ABSTRACT

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease, which mainly affects the axial joints, including the spine, sacroiliac joints, and entheses. The aim of the study was to detect the prevalence of metabolic syndrome (MetS) in Iraqi patients with AS, in comparison to healthy controls and to assess their relationships with demographic and clinical characteristics. A cross-sectional study was conducted at the rheumatology unit of Baghdad Teaching Hospital in Medical City from October 2019 to March 2020.The study included a total of 100 patients diagnosed with AS, according to the modified New York diagnostic criteria, and 100 age and sex matched controls. Demographic data, disease activity scores, comorbidities, current medications were reported. Waist circumference, blood pressure, fasting blood sugar, triglyceride and high-density lipoprotein cholesterol were measured and MetS was diagnosed according to the NCEP ATPIII criteria. The prevalence of MetS in AS patients was (51%) which is higher than that of the controls (46%), but the difference was insignificant (p=0.4). The mean HDL-c, FBS, systolic and diastolic blood pressure were significantly lower in AS patients compared to controls (p=0.03; p=0.005; p=0.05; p=0.01, respectively). AS patients with MetS had significantly higher incidence of low HDL-c (P=0.03), and lower incidence of high FBS (P=0.01) and TG (P=0.04) than controls with MetS. The mean age and body mass index in patients with AS and MetS were significantly higher compared to patients with AS without MetS (p=0.005; p=0.001). Multivariate regression analysis showed that age of the patients was the only significant predictor for the risk of MetS (odds ratio [OR] =1.6, confidence interval [95% CI] = 1.2 - 1.8, P=0.03). It was concluded that, the prevalence of metabolic syndrome in AS patients was higher than in the general population but statistically insignificant. Low HDL-c is the most important component of MetS in AS. AS patients with MetS were older in age and had higher BMI than AS without MetS.

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Introduction:

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease, which mainly affects the axial joints, including the spine, sacroiliac joints, and entheses, but it may also involve peripheral joints [1-3]. AS affects young people (about 80% of patients develop the first symptoms at an age younger than 30 years), it affects men more than woman (the ratio is approximately 2:1) [4-10].

Metabolic syndrome (MetS) represents a clustering of specific cardiovascular risk factors including abdominal obesity, arterial hypertension, fasting hyperglycemia, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-c). presence of three or more of five risk factors is required to define MetS [11-13]. Development of metabolic syndrome depends on two elements: first, adult weight gain, with bodyfat accumulation and secondly a predisposition to locate fat in intra-abdominal sites[14-16] The most accepted and unifying hypothesis to describe the pathophysiology of MetS is insulin resistance (IR), which is defined as a decrease in the sensitivity or responsiveness to the metabolic actions of insulin on its target organs, leading to hyperinsulinemia whose objective is to maintain normal glucose in fasting state. As a consequence, glucotoxicity, lipotoxicity and inflammation occur, leading to generalized endothelial dysfunction, mainly at the cardiovascular level [17-18]. Patients with rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis, have increased prevalence of CVDs when compared to general population, which is one of the main causes of mortality in these patients. Moreover, CVD risk is increased when obesity is present in these patients. However, traditional cardiovascular risk factors do not completely explain the enhanced cardiovascular risk in this population. Thus, MetS and the altered secretion patterns of proinflammatory

adipokines present in obesity could be the link between CVDs and rheumatic diseases [19]. Furthermore, adipokines have been linked to the pathogenesis of MetS and its comorbidities through their effects on vascular function and inflammation [20]. Systemic inflammation and the increased production of pro-inflammatory cytokines in these patients may favor the onset of metabolic syndrome. In patients affected by chronic arthritis, TNF-alpha is considered as one of the factors responsible for favoring insulin resistance and dyslipidemia, which are important features of the metabolic syndrome [21]. TNFi, currently used in the treatment of several inflammatory diseases, may have a role in the reduction in plasma glucose by increasing insulin sensitivity, and in ameliorating lipid profile in dyslipidemic patients [21]. The great majority of the studies demonstrated that AS patients have higher risk of experiencing MetS and CVDs than in healthy controls, even after receiving anti-tumor necrosis factor (anti-TNF) therapy. Moreover, in these patients, MetS was associated with higher disease activity [22-25]. Aim of the study was to detect the prevalence of metabolic syndrome in Iraqi patients with ankylosing spondylitis, in comparison to healthy controls and to assess their relationships with demographic and clinical characteristics.

Patients and methods:

This case-control study was conducted at the Rheumatology Unit of Baghdad Teaching hospital in Medical City from October 2019 to March 2020. A total of 100 consecutive patients diagnosed to have AS, according to the modified New York diagnostic criteria [7] (appendix 1), were included in the study and compared to 100 healthy controls matched for age and sex. The control group was recruited from healthy relatives of the patients not known to have MetS previously and not taking drugs that may cause MetS. Oral informed consent was obtained from each participant. The age of the

participants ranged from 16 to 60 years. Individuals were excluded from the study if they had one of the following [10]: Other autoimmune inflammatory diseases, history of coronary artery disease, cerebrovascular or peripheral vascular disease, coronary artery bypass and chronic kidney disease. Data were collected using a pre-constructed data collection sheet (appendix 5). Age, gender, marital status, education, smoking and co-morbidity were reported. Disease duration, disease activity and medications were recorded for all patients. Waist circumference was measured in centimeters at the level of the umbilicus, height in meters and weight in kilograms were measured for all participants, body mass index (BMI) was calculated according to the equation BMI= weight /height^2. Blood pressure was measured in sitting position using pneumatic device, blood samples were taken after at least 10 hours fasting from individuals in both groups to test for fasting blood sugar (FBS), triglycerides (TG), and HDL-cholesterol (HDL-c), all measured in mg/dl. ESR was measured for all patients, CRP was unavailable. Metabolic syndrome was determined using the NCEP ATPIII criteria [11-14].

SPSS version 23 was used for data entry and analysis. Numerical data was expressed as mean and standard deviation while categorical data was expressed and number and percentage. Suitable tests (independent sample student t test, chi-square (Fischer exact test if not applicable), multivariate and logistic regression) were used to confirm significance. P value ≤0.05 was considered as significant.

Results

The mean age for patients and controls were (39.8 vs. 37.5, p=0.1) and the difference was insignificant. The mean value of waist circumference for patients and controls were 103.1±12.2, 101.4±13.1 cm respectively, the difference was also insignificant (p=0.3). Thirty five percent of patients and 26% of controls were active smokers while 38% of patients and 57%

of controls were non–smokers, the difference was statistically significant (p=0.04). The results demonstrated there was no significant difference between patients and controls in term of presence or absence of comorbidities (Hypertension, diabetes mellitus and hyperlipidemia), where the significance levels (P-value) were 0.4, 0.2 and 0.4 respectively. All AS patients were on anti TNF treatment, 62 out of total 100 patients were on Etanerecept (62%), 25 patients on Infliximab (25%) and 13 patients were on Adalimumab (13%). The results showed that 51out of 100 AS patients (51%) and 46 out of 100 controls (46%) had MetS and this difference was statistically insignificant, p=0.4. Moreover, Triglycerides were higher among controls compared to AS patients but the difference was insignificant (p=0.1). FBS and HDL-c were significantly lower in AS group (p=0.005, 0.03 respectively). Systolic and diastolic blood pressures were also significantly lower in AS patients compared to controls (p=0.05, 0.01 respectively) as seen in table 1 and fig.1.

Table.1; Demographic characteristics of ankylosing spondylitis patients and controls

		AS		Controls		p-value
		Mean	SD	Mean	SD	
Age/year		39.8	9.47	37.5	11.57	0.1
Gender	Male	90	90.0%	90	90.0%	1.0
	Female	10	10.0%	10	10.0%	
Education	Illiterate	5	5.0%	4	4.0%	0.6
	Primary	25	25.0%	32	32.0%	
	Secondary	37	37.0%	28	28.0%	
	College	26	26.0%	30	30.0%	

	Post-graduate	7	7.0%	6	6.0%	
Smoking	Active	35	35.0%	26	26.0%	0.04
	ex-smoker	22	22.0%	15	15.0%	
	Passive	5	5.0%	2	2.0%	
	Absent	38	38.0%	57	57.0%	
Hypertension		11	11.0%	15	15.0%	0.4
Diabetes mellitus		8	8.0%	13	13.0%	0.2
Hyperlipidemia		2	2.0%	4	4.0%	0.4
BMI (kg/m^2)		29.17	5.2	28.10	4.95	0.1
Waist/cm		103.1	12.2	101.4	13.1	0.3
Fasting blood sugar(mg/dl)		105.61	23.30	120.7	48.17	0.005
Triglyceride(mg/dl)		130.29	70.54	148.73	95.27	0.1
HDL-c(mg/dl)		41.13	8.96	44.06	9.89	0.03
Systolic blood pressure(mmHg)		120.40	16.33	124.70	15.38	0.05
Diastolic blood pressure(mmHg)		77.60	11.44	82.15	8.17	0.01
Metabolic syndrome		51	51.0%	46	46.0%	0.4

AS, ankylosing spondylitis; SD, standard deviation; BMI, body mass index; HDL-c, high density lipoprotein cholesterol.

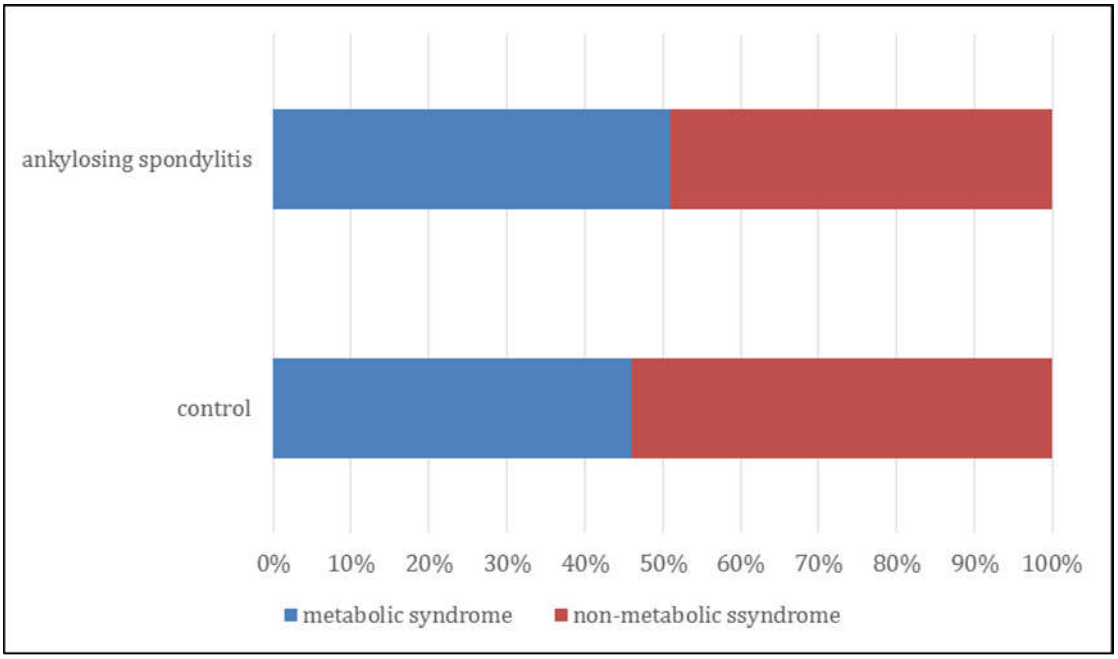

Fig.1; Prevalence of metabolic syndrome for ankylosing spondylitis (AS) patients and controls

For metabolic syndrome-related features, the incidence of patients with fasting blood sugar of ≥100 was significantly higher in controls compared to patients (91.3 vs 72.5%). The incidence of low HDL-c serum levels was significantly higher among AS patients compared to controls (78.4% vs. 58.7%; p=0.03). The incidence of high TG (≥150) was significantly higher in controls in comparison to patients (71.7 vs 52.9 %, p=0.04). There were no significant differences in the frequencies of other metabolic syndrome components as displaced in table 2.

Table.2; Prevalence of various metabolic syndrome components among subjects who have metabolic syndrome.

		AS(n=51)		Controls(n=46)		p-value
		No.	%	No.	%	
FBS	>100	37	72.5%	42	91.3%	0.01
Triglyceride	>150	27	52.9%	33	71.7%	0.04
HDL-c	Low	40	78.4%	27	58.7%	0.03
Waist/cm	High	46	90.2%	38	82.6%	0.2
Bp>130/80	present	15	29.4%	15	32.6%	0.7

AS, ankylosing spondylitis; FBS, fasting blood sugar; HDL-c, high density lipoprotein cholesterol; Bp, blood pressure.

AS patients with metabolic syndrome were significantly older than those without MetS (p=0.005). The results revealed that there was no significant association between smoking status and MetS (p=0.4). The BMI of patients with MetS was significantly higher than that of patients without MetS (p=0.001). The ESR, BASDAI and ASDAS also not differed significantly between patients with and without metabolic syndrome (p=0.2, 0.9 and 0.5 respectively), even though the ESR of patients with MetS was slightly higher than that of patients without MetS. Patients with MetS had insignificantly longer disease duration (p=0.7) in comparison to those without MetS.

Table.3; Demographic characteristics and disease-related features of patients with ankylosing spondylitis divided into 2 groups according to the presence of metabolic syndrome

		Metabolic syndrome				p-value
		Present (n=51)		**Absent (n=49)**		
		Mean/no.	SD/%	Mean/no	SD/%	
Age/year		42.3	8.8	37.2	9.4	0.005
Smoking status	Active	18	35.3%	17	34.7%	0.4
	ex-smoker	14	27.4%	8	16.3%	
	Passive	3	5.9%	2	4.1%	
	Absent	16	31.4%	22	44.9%	
BMI ($kg/m^{2)}$		31.1	4.6	27.2	5.3	0.001

ESR mm/Hr.		19.7	17.04	16.1	16.1	0.2
BASDAI		3.7	1.4	3.8	1.7	0.9
ASDAS		2.5	0.8	2.4	0.9	0.5
Disease duration		4.3	1.2	4.7	1.4	0.7
NSAID	present	9	17.6%	13	26.5%	0.2
Biology	Etanerecept	34	66.7%	28	57.1%	0.4
	Infliximab	10	19.6%	15	30.6%	
	Adalimumab	7	13.7%	6	12.2%	

BMI, body mass index; ESR, erythrocyte sedimentation rate; BASDAI, bath ankylosing spondylitis disease activity index; ASDAS, ankylosing spondylitis disease activity score; NSAID, non-steroidal anti-inflammatory drug.

Discussion:

Metabolic syndrome represents the tip of the iceberg for the development of CVD, DM2 and stroke. Therefore, early detection, prevention and treatment of MetS is of crucial importance especially for AS patients who are at increased risk for CVD [14].To our knowledge this is the first study in Iraq to assess the prevalence of MetS in patients with AS, receiving TNFi. In this cross-sectional study, the prevalence of MetS in AS was higher than that of the controls (51% vs 46%). This result, although statistically insignificant, goes with the results of similar studies [15-18]. However, a study by Mok et al found no increase in the prevalence of MetS in AS patients [26]. Perhaps one of the major causes of the increased prevalence of MetS is residual disease activity, which leads to persistent elevation of proinflammatory cytokines that contributes to insulin

resistance, impaired glucose tolerance, dyslipidemia, and accelerated atherosclerosis [26]. Also, the significantly higher prevalence of smokers in the AS group may influence the parameters of MetS. The average disease duration in this study was 4.5 years which is less than that of previous studies (16 years in Malesci and Papadakis, 9 years in Maia and Liu, 6 years in Mok) [22-26], which means less effect of the inflammation and treatment on the features of MetS. This may explain the decreased difference between patients and controls. Strikingly the prevalence (51%) was much higher than that of previous studies (46% in Italy [22], 35% in Greece [23], 27% in Brazil [24] and 20% in China [25]). However, the prevalence of MetS in the control group was also higher than that of the previous studies. This may indicate that the differences are attributed to other factors as genetics and racial variations. HDL-c was significantly lower in AS group than the control group and this is consistent with the finding of previous studies [22-25]. A meta-analysis by Mathieu et al [29] that included 38 studies and a total of 34132 AS patients and 83705 controls reported that decreased total cholesterol and HDL-c occurred in AS patients and that the low HDL-c levels appeared to play a crucial role in developing myocardial infarctions in AS patients. They also reported a higher frequency of metabolic syndrome and lower triglyceride levels in AS patients.

A study by Gkolfinopoulou et al [30] found that serum total cholesterol, HDL-c and LDL-c concentrations did not differ statistically between patients with AS and controls. while serum triglycerides levels were lower in patients with AS compared to controls.

In contrary to previous studies [22-25], FBS, systolic and diastolic blood pressures were significantly lower in AS group. In addition, triglycerides were non-significantly lower in this group. This may, in part, be due to the higher incidence of comorbidity (hypertension, DM2 and hyperlipidemia) in the control group.

Another explanation of these rather favorable findings is the effect of anti TNF therapy. Anti TNFα biologics have been shown by controlled trials to reduce the levels of biomarkers for cardiovascular risk in PsA, RA and AS by neutralizing the inflammatory effects of TNFα [26-28]. An increase in HDL-c serum levels has been described in patients affected by inflammatory arthritides after 6 months of therapy with infliximab [14]. A study by Alosami et al showed that treatment of AS patients with Anti TNFα for 6 months was associated with an increase in HDL-c levels [31], Moreover, TNF-α blockade in AS patients has been shown to improve insulin sensitivity in non-diabetic patients and may slow atherosclerosis progression, with beneficial effects on adipokines, biomarkers of atherosclerosis, and MetS-related biomarkers [19].

An important component of the MetS in AS patients is low HDL-c, the incidence of which was significantly higher in AS patients who had MetS than in controls with MetS. a similar finding was reported in previous studies that measured HDL-c in AS patients [22, 23]. HDL cholesterol could be protective against atherosclerosis and the mechanisms are numerous. In addition to its role in the process of reverse cholesterol transport (from the atheroma plaque to the liver), HDL cholesterol has antioxidant (reducing oxidation of LDL, making them less atherogenic) and anti-inflammatory properties (inhibition of the expression of adhesion molecules on endothelial cells) [29]. Patients with AS and MetS in this study had significantly lower incidence of increased FBS and TG levels than controls with MetS. most of the previous studies didn't find significant difference in these parameters, except Mok et al [26]. When comparing patients with AS who have MetS with those who do not have MetS the formers were significantly older (mean age =42.3 ± 8.8 Vs 37.2 ± 9.4). that goes in line with the findings of Papadakis et al [23] and Maia et al [24]. However, Liu et al [25] did not find a difference in age. Aging is

known to be associated with greater prevalence of MetS mainly because of growing insulin resistance and intra-abdominal fat deposition [24]. In addition, age of the patients was the only significant predictor for the risk of metabolic syndrome (OR=1.6, [95% CI] = 1.2 -1.8, P=0.03), and this was independent of disease duration as shown in multivariate regression analysis. Also, patients with AS and MetS had significantly higher BMI than AS without MetS, this is similar to the finding of Liu et al [25]. However, it is important to point out that BMI is not a strong predictor of body fat. waist circumference is a somewhat better guide to cardiometabolic disease risks because waist circumference identifies people with relatively low BMI but with increased intra-abdominal fat accumulation [17]. There were no significant differences between AS with and AS without MetS regarding disease duration, disease activity and ESR. Also, Malesci [22], Maia [24] and Liu [25] found no difference regarding disease activity, duration and ESR. while Papadakis [23] found higher BASDAI and longer disease duration in AS with MetS compared to non-metabolic AS. One of the limitations encountered in this study is the cross-sectional design of the study that does not allow for adequate evaluation of the relation between disease activity and the parameters of MetS. Another limitation is that all the patients were on anti TNFi, so that we could not study the effect of treatment on the development of MetS.

Conclusions:

•The prevalence of metabolic syndrome in AS patients was higher than in the general population but the difference was statistically insignificant.

•Low HDL-c is the most important component of MetS in AS.

•AS patients with MetS were older in age and had higher BMI than AS without MetS.

Recommendations:

1- Early detection, prevention and treatment of metabolic syndrome in ankylosing spondylitis are of paramount

importance.

2- Larger sample size and longer disease duration is recommended in future studies to further validate the results of this study

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