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Original Article

Clinical significance of metabolic syndrome and carotid intima-media thickness in Behçet's disease patients: Relation to disease activity

Iman El-Gazzar [a,*], Al-Hussein El-Dakrony [a], Safaa Sayed [a], Hussein El-Fishawy [b], Hanan Fathi [c], Mohamed Shaaban [d], Rehab Abdel Rahman [e]

[a] Rheumatology Department, Faculty of Medicine, Cairo University, Egypt
[b] Internal Medicine Department, Faculty of Medicine, Cairo University, Egypt
[c] Rheumatology Department, Faculty of Medicine, Fayoum University, Egypt
[d] Radiodiagnosis Department, Faculty of Medicine, Cairo University, Egypt
[e] Radiodiagnosis Department, Faculty of Medicine, Ain Shams University, Egypt

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ABSTRACT

Aim of the work: The aim of the present work was to assess the effect of metabolic syndrome (MetS) co-morbidity and the carotid intima-media thickness (cIMT) in Behçet's disease (BD) patients and to study their relation to clinical manifestations and disease activity.
Patients and methods: Thirty-eight BD patients and another 38 age and sex matched controls were studied. The disease activity was assessed using BD Current Activity Form (BDCAF) score and the adult treatment panel criteria were used to define the presence of MetS. The cIMT was measured by ultrasonographic scanning.
Results: The BD patients were 30 males and 8 females with a mean age of 36.2 ± 7.8 years and disease duration of 7.6 ± 5.1 years. MetS was more frequent in BD patients (28.9%; 7 males and 4 females) compared to the control (10.5%; 2 males and 2 females). The mean IMT in the patients (0.78 ± 0.32 mm) was significantly increased compared to the control (0.42 ± 0.12 mm) ($p < 0.001$). The IMT was thickened in 9 (23.7%) patients and atherosclerotic plaques present in 6 (15.8%) with MetS. The IMT and BDCAF tended to be increased in those with MetS compared to those without. The IMT in the BD patients significantly correlated with the BDCAF ($r = 0.47$, $p = 0.003$), serum creatinine ($r = 0.33$, $p = 0.04$), urea ($r = 0.53$, $p = 0.001$) and triglycerides ($r = 0.45$, $p = 0.005$). The IMT tended to be increased in the male patients.
Conclusion: Metabolic syndrome is an important co-morbidity in BD patients and measuring the IMT is essential to avoid an increase in flares or the consequent development of cardiovascular diseases or renal impairment.

1. Introduction

Behçet's disease (BD) is a chronic, immuno-inflammatory disease and vasculitis with multisystemic involvement [1,2]. It primarily affects the vascular system and the increased inflammatory response may lead to endothelial dysfunction which results in vasculopathy [3]. The main cause of mortality is large vessel disease, especially bleeding pulmonary artery aneurysms and central nervous system disease comes second [4]. Evidence for increased atherosclerosis has been observed [1], however, given the chronic inflammatory background of BD; the issue of premature atherosclerosis was addressed with conflicting evidence [5].

The metabolic syndrome (MetS) is a cluster of cardiometabolic disorders that result from the increasing prevalence of obesity [6]. The major components of MetS include central obesity, dyslipidemia including elevated triglycerides (TG) and reduced high-density lipoproteins (HDL), insulin resistance and impaired fasting blood glucose (FBG) as well as hypertension [2,6]. MetS identifies those with increased risk for cardiovascular diseases (CVDs) and type-2 diabetes mellitus [6].

Patients with rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) have increased prevalence of CVDs with an increased risk when obesity is present in these patients. Traditional factors do

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* Corresponding author.
E-mail address: imanalgazzar@hotmail.com (I. El-Gazzar).

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not completely explain the enhanced cardiovascular risk; however, MetS could be the link between CVDs and rheumatic diseases [6]. Chronic inflammatory diseases such as psoriasis, RA, inflammatory bowel diseases, SLE, gout and osteoporosis have been reported to be associated with the development of MetS [2,6–11].

Being a systemic vasculitis, BD may also be associated with cardiovascular involvement [12]. Dyslipidemia, especially hypertriglyceridemia, has proven to be a risk factor and superlative marker for the occurrence of atherothrombosis in BD patients [13,14]. Because systemic inflammation and dyslipidemia are involved in the pathogenesis of atherosclerosis, BD may play a part in the development of atherosclerosis [15].

The superficial location, large size and relative immobility of the carotid arteries make them amenable to noninvasive ultrasound imaging that may offer valuable insight into the atherosclerosis status in other vascular beds to assess cardiovascular risk. As a consequence, carotid intima-media thickness (cIMT) became a popular clinical measurement [16] and an important biomarker of subclinical atherosclerosis [17]. In BD, cIMT represents a key event in atherosclerosis and may enlighten the increased development of cardiovascular diseases [18]. The IMT may be a useful parameter in defining BD progression and identifying those at high risk [19]. The aim of the present work was to assess the effect of metabolic syndrome co-morbidity and the cIMT in BD patients and to study their relation to clinical manifestations and disease activity.

2. Patients and methods

Thirty-eight BD patients, satisfying the International Study Group for BD new set of diagnostic criteria [20] were recruited from Cairo University Hospitals' outpatient clinics. None of the patients were receiving insulin. Another 38 age and sex matched healthy volunteers served as controls. Full history taking, clinical examination and relevant investigations were carried out for all patients. The body mass index (BMI) and waist circumference (WC) were recorded and the disease activity was assessed using BD Current Activity Form (BDCAF) score [21]. The study conforms to the 1995 Helsinki declaration and all patients gave their informed consent prior to their inclusion. Adult Treatment Panel (ATP III) criteria [22] were used to define the presence of MetS.

2.1. Measurement of the cIMT

Ultrasonographic scanning of the carotid artery, extracranial common carotid artery, carotid bulb and the internal carotid artery in the neck was performed bilaterally using an echographic system (ATL HDI 5000, USA) with an electric linear transducer (mid- frequency 7.5 MHz). The detection limit was 0.1 mm. And the IMT was defined as the distance between the leading edges of the 2 echogenic lines separated by a hypoechogenic space; the first line represented luminal-intimal transition and the second medial-adventitial. Three determinations of IMT were conducted at the site of the thickest and two adjacent points (1 cm up and downstream from the thickest point) and were averaged (mean IMT). According to a previous study, the IMT was considered normal when <0.9 mm and thickened when $\geqslant$0.9 mm. A thickness >1.3 mm was indicative of atherosclerotic plaque [23].

2.2. Statistical analysis

Statistical Package for Social Science (SPSS) program version 15 was used for analysis of data. Data were presented as mean ± SD. Mann–Whitney test was used for analysis of 2 quantitative data. Spearman's correlation was used for detection of the relation between 2 variables. p-value <0.05 was considered significant.

3. Results

The study included 38 BD patients (M:F 30:8) with a mean age of 36.2 ± 7.8 years, disease duration of 7.6 ± 5.1 years and an age of onset of 28.6 ± 5.6 years. The Clinical manifestations, medications received and disease activity in BD patients are presented in Table 1. The 38 control were of matched age (35.4 ± 6.5 years) (p = 0.62) and gender (M:F 30:8). Metabolic syndrome was more frequent in BD patients (28.9%; 7 males and 4 females) compared to the control (10.5%; 2 males and 2 females). None of the patients was known to have any renal involvement. Demographic and laboratory features of the BD patients and control are shown in Table 2. The mean IMT in the BD patients (0.78 ± 0.32 mm) was significantly increased compared to the control (0.42 ± 0.12 mm) (p < 0.001). The IMT was thickened in 9 (23.7%) patients and atherosclerotic plaques present in 6 (15.8%) with MetS. None of the control had thickened IMT or had plaques.

The IMT and BDCAF tended to be increased in those with MetS (0.93 ± 0.35 mm and 3.1 ± 1.4) compared to those without (0.72 ± 0.29 mm and 2.3 ± 1.3) (p = 0.1 and p = 0.12 respectively). Fig. 1 shows the IMT in the BD patients and control. There was no significant difference between the demographic features, clinical manifestations and disease activity of those with and without MetS.

The IMT in the BD patients significantly correlated with the BDCAF (r = 0.47, p = 0.003), serum creatinine (r = 0.33, p = 0.04), BUN (r = 0.53, p = 0.001) and serum triglycerides (r = 0.45, p = 0.005). The BDCAF further correlated with the steroid dose (r = 0.47, p = 0.003), ESR (r = 0.37, p = 0.02), BUN (r = 0.34, r = 0.04) and FBS (r = 0.58, p = 0.002). The IMT tended to be increased in the male BD patients (0.78 ± 0.32 mm) compared to females (0.76 ± 0.32 mm) (p = 0.87). All other parameters were also comparable.

4. Discussion

Evidence for accelerated atherosclerosis in BD has been observed [24]. In the present study, BD patients had a higher frequency of MetS and increased IMT with atherosclerotic plaques present especially in those with MetS. The males with BD were more with a M:F of 3.75:1 and tended to have an increased IMT. Besides its significant morbidity profile, BD is reported to be a cause of accelerated atherosclerosis and increased mortality among young male patients [4,25–27]. The gender associated clinical variations in BD usually involves a meaningful risk of cardiovascular involvement for men. [3,28]. Subclinical atherosclerosis

Table 1
Clinical manifestations, medications received and disease activity in Behçet's disease patients.

Parameter		BD patients (n = 38)
Manifestations	Oral ulcers	38 (100)
	Genital ulcers	34 (89.5)
	Ocular	20 (52.6)
	Cutaneous	32 (84.2)
	Arthralgia/Arthritis	30 (78.9)
	CNS	19 (50)
	DVT	12 (31.6)
	Pulmonary	6 (15.8)
	GIT	11 (28.9)
Steroids (mg/d)		16.8 ± 8.9
Colchicine (mg/d)		0.9 ± 0.5
BDCAF		2.5 ± 1.4

Results are presented as n (%) or mean ± SD. BD: Behçet's disease, CNS: central nervous system, DVT: deep venous thrombosis, GIT: gastrointestinal, BDCAF: BD Current Activity Form.

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Table 2
Demographic characteristics, laboratory features metabolic syndrome (MetS) and intima media thickness (IMT) in Behçet's disease patients and control.

Parameter mean ± SD		BD patients (n = 38)	Control (n = 38)	p
Age (years)		36.2 ± 7.8	35.4 ± 6.5	0.62
BMI		26.9 ± 3.9	25.4 ± 3.1	0.08
WC (cm)		88.3 ± 11.8	85.6 ± 9.8	0.27
SBP (mmHg)		125 ± 15	115.1 ± 12.1	0.002
DBP (mmHg)		85.5 ± 13.3	80.4 ± 7.1	0.04
Laboratory investigations	Hb (g/dl)	12.7 ± 1.1	13.1 ± 1.04	0.17
	WBC ($x10^3/mm^3$)	7.9 ± 2.3	8.2 ± 2.2	0.57
	Pl ($x10^3/mm^3$)	307.5 ± 81.7	317.4 ± 63.8	0.56
	ESR (mm/1st hr)	28 ± 18.6	14.3 ± 5.3	<0.001
	AST (U/L)	22.9 ± 9.1	21.2 ± 8.6	0.41
	ALT (U/L)	24.1 ± 13.4	16.9 ± 7.4	0.005
	BUN (mg/dl)	23.6 ± 8.2	22.8 ± 7.6	0.67
	Creatinine (mg/dl)	0.74 ± 0.13	0.68 ± 0.12	0.04
	FBS (mg/dl)	103.1 ± 32.01	85.6 ± 12.6	0.01
	Chol. (mg/dl)	184.1 ± 49.3	145.8 ± 32.9	<0.001
	TG (mg/dl)	121.2 ± 33.5	95.6 ± 17.5	<0.001
	HDL (mg/dl)	54.3 ± 17.3	63.4 ± 13.1	0.04
	LDL (mg/dl)	117.2 ± 48.8	69.6 ± 20.2	<0.001
MetS n (%)		11 (28.9)	4 (10.5)	0.045
IMT (mm)		0.78 ± 0.32	0.42 ± 0.12	<0.001

BD: Behçet's disease, BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, Hb: hemoglobin, WBC: white blood cells, Pl: platelets, ESR: erythrocyte sedimentation rate, AST: aspartate transaminase, ALT: alanine transaminase, BUN: blood urea nitrogen, FBS: fasting blood sugar, Chol.: Cholesterol, TG: triglycerides, HDL: high density lipoprotein, LDL: low density lipoprotein, MetS: metabolic syndrome, IMT: intima-media thickness.

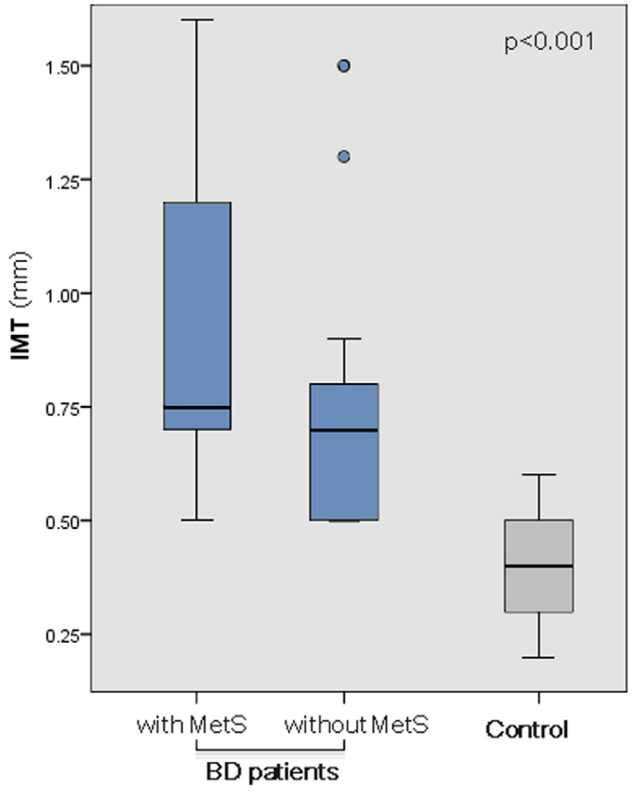

Figure 1. Intima media thickness in Behçet's disease patients with and without metabolic syndrome and control.

was evidenced in BD patients [23,29] even when there is no significant cardiovascular involvement [30]. The cIMT was significantly increased in BD patients [31] and can be a good marker of subclinical atherosclerosis especially in males [29,32] and is useful in detecting structural and functional vascular damage [1]. On the other hand, increased atherosclerosis, assessed by IMT and plaque formation, was not a prominent feature of BD even among patients with major organ involvement [5]. Genetic predisposition and HLAB51 positivity are associated with vascular involvement and predict morbidity and mortality in BD [3] which may account for the variable findings. The frequency of plaque formation was significantly higher in BD patients compared to the control but lower than in SLE [18].

In the current study, the IMT significantly correlated with the serum triglycerides. Dyslipidemia, particularly hypertriglyceridemia, may be a risk factor for thrombosis in BD. An association between increased levels of plasma lipids and deep-vein thrombosis has been suggested although the pathogenic mechanism is controversial [33]. Hyperlipidemia was found to be an independent predictor of coronary artery disease (CAD) [26] and increased autoantibodies against LDL may be responsible for endothelial dysfunction in BD [34]. In this work, the FBS significantly correlated with the BDCAF. An increased susceptibility to insulin resistance in Korean [35] and Turkish [36] patients with BD has been reported. On the contrary, in another study dyslipidemia and insulin resistance were not associated with an increased risk for atherosclerotic CVD in BD patients [12]. Traditional risk factors associated with CAD and prevalent in BD patients included hypertension, dyslipidemia, diabetes mellitus, smoking and obesity but were comparable to what was expected in the overall population [26].

It is currently clear that MetS, a cluster of risk factors for CVD, diabetes and stroke, is becoming endemic. A potential role for MetS, an important risk factor for pro-inflammatory immune imbalance is characterized by chronic inflammation and altered self-immune tolerance [37]. In accordance to the present results, MetS was detected in 35.4% of Turkish BD patients and 20% of controls. Furthermore, BD was found to be a significant risk factor for developing MetS [2].

There was no significant difference between those with and without MetS or thickened IMT as regards the age, disease duration or clinical manifestations. In agreement, increased arterial wall thickness was not associated with the disease duration, clinical manifestations or immunosuppressive therapy [29]. However, in another study, age at onset, disease duration, BMI, gastrointestinal system and neurological involvements correlated with increased MetS risk Yalçın. All BD patients should be closely monitored for

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hypertension, hyperlipidemia and diabetes mellitus to avoid the development of MetS [2].

In the present study, the IMT significantly correlated with the BUN and serum creatinine. This is in accordance with the work of others were the IMT significantly correlated with the renal function tests [23] and with the creatinine clearance [29].

In this study, the IMT significantly correlated with the BDCAF. Similarly, the IMT significantly correlated with the disease activity [23]. Moreover, active BD was compatible with the serum lipid profile, which is accepted as a risk for the development of atherothrombosis [13]. Endothelial dysfunction was also found to contribute to the risk of atherosclerosis in active BD patients [38]. Conversely, it has been reported that active BD patients may be less susceptible to atherogenic events [15].

In conclusion, MetS is an important co-morbidity in BD patients and measuring the IMT is essential to avoid an increase in flares or the consequent development of CVD. Future longitudinal larger scale studies are required to confirm the present results and further elucidate the cardiovascular risk of MetS and relation to disease activity and subclinical renal impairment in BD patients.

Conflict of interest

None.

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