Modifiable cardiovascular risk factors in patients with Behçet's disease: a multicenter experience

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Background
Vascular involvement in Behçet's disease (BD) is one of the major causes of mortality and morbidity. Modifiable cardiovascular risk factors such as high blood pressure, dyslipidemia, hyperglycemia, overweight, and smoking have been demonstrated to have a significant impact on cardiovascular disease in the general population with or without other diseases.

Objective
The aim of this study was to evaluate whether modifiable cardiovascular disease risk factors differ among patients with BD in comparison with the general population.

Patients and methods
This was a multicenter case–control study carried out on 182 BD patients identified by analysis of the databases of the International Study Group Classification Criteria. The patients were compared with 80 controls matched for age, sex, and study period. Full clinical history taking and medical examination were carried out for all patients, and investigations including lipid profile and blood glucose were carried out and data on hypertension, height, weight, and smoking were collected and recorded.

Results
Levels of serum low-density lipoprotein ($P<0.005$) and cholesterol ($P<0.005$) were significantly high in the Behçet patient group, but no statistical difference was detected as regards triglycerides, diabetes mellitus, or BMI. Smoking and hypertension increase the risk of cardiovascular manifestations in our patients. The mean±SD age of BD patients was 31.6±9.008, 76.9% were male individuals and 23.1% were female individuals.

Conclusion
Patients with BD had a high prevalence of cardiovascular comorbidities. Optimal control of blood pressure, lipids and blood sugar with reduction in body weight and stoppage of smoking may be an effective strategy to reduce vascular complications in these populations.

Keywords:
Behçet's disease, cardiovascular disease, hypertension, modifiable risk factors

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Introduction

Behçet's disease (BD) is a chronic multisystem disease described as both an autoimmune and an autoinflammatory disorder, primarily characterized by oral and genital ulcerations but also affecting other body systems including the eye (uveitis), joints (arthritis), and skin. BD can be life-threatening in severe forms wherein the disease progresses to involve the large blood vessels, central nervous system, or the gastrointestinal tract (GIT) [1,2]. BD mostly affects ethnic groups of Mediterranean and East Asian origin who have settled along the Silk Road route regions [3].

Vascular involvement is observed in up to 40% of the patients with BD, especially in young male individuals and is one of the major causes of mortality and morbidity [4]. Several types of vascular manifestation tend to occur in the same individual; for example, cerebral venous sinus thrombosis and pulmonary artery involvement tend to occur, as do intracardiac thrombosis and pulmonary artery involvement, and Budd–Chiari syndrome and inferior vena cava syndrome. Lower extremity vein thrombosis (superficial and deep) is the most common form of vascular involvement and leads to severe postthrombotic syndrome and venous claudication [5]. Advanced vascular wall destruction with aneurysm formation causes local blood flow

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abnormalities. Endothelial dysfunction, release of von Willebrand factor, platelet activation, enhanced thrombin and fibrin generation, antithrombin deficiency, and impaired fibrinolysis are the pathological factors that associated with vasculitis (perivasculitis) in BD. Actually, pathological thrombosis in BD can be best viewed within the classical Virchow's triad [6]. Cardiac manifestations include pericarditis, myocarditis, endocarditis, mitral valve prolapse, valve lesions, intracardiac thrombosis, endomyocardial fibrosis, myocardiopathy, and coronary artery lesions. The prognosis in these cases is unfavorable with frequent recurrences. The highest direct mortality rate in cardiovascular involvement was attributed to large-vessel vasculitis as a result of sudden death by aneurysm rupture or thrombosis [7].

Traditional risk factors associated with cardiovascular disease (CVD) and prevalent in BD patients included age, hypertension, dyslipidemia, diabetes mellitus, smoking, and obesity but were comparable to what was expected in the overall population [8]. In the general population, modifiable risk factors such as blood pressure, dyslipidemia, hyperglycemia, weight, and smoking have been demonstrated to have a significant impact for CVD [9]. The prevalence of risk factors associated with coronary artery disease is similar, as compared with the overall population; however, the high incidence of CVD at a relatively young age in these BD patients suggests that atherosclerosis might be accelerated in BD patients [10].

The aim of this study was to evaluate whether modifiable risk factors for CVD, such as hypertension, hyperglycemia and dyslipidemia, or life-style–related risk factors such as smoking, diabetes mellitus, and obesity, differ among BD patients compared with those of the general population.

Patients and methods

A multicenter case–control study was performed on 182 Egyptian patients suffering from BD, who were selected from the outpatient clinics of rheumatology, ophthalmology, dermatology and neurology in Menoufia University Hospital, Tanta University Hospital, Mansoura University Hospital and Beni Suef University Hospital during the period spanning from April 2018 to August 2019. The diagnosis of BD was made according to the International Study Group Criteria of Behçet's Disease. We included 80 healthy adult individuals as controls. All controls and patients were subjected to medical history taking and complete physical examination. Investigations were carried out for all patients and controls, including random blood glucose, fasting blood glucose, lipid profile [cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)], C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Informed consent from all patients was obtained in accordance with the local ethical committee principles.

All participants completed questionnaires concerning any diagnosis of diabetes mellitus, previous myocardial infarction, medications, and smoking habits. Classification and handling of data: the patients were classified as smokers when reporting a consumption of an average of one or more cigarettes per day. Hypertension was defined by either a systolic pressure over 140 mmHg, diastolic pressure greater than 90 mmHg or medication with antihypertensive effects. Increased serum cholesterol was defined as a level over 200 mg/dl and increased serum triglycerides as over 150 mg/dl. Hyperglycemia was defined by the following (and they are): (a) a fasting blood glucose level of over 126 mg/dl, (b) 2-h glucose loading test over 200 mg/dl, (e) medication, or (d) a reported diagnosis of diabetes mellitus. The BMI was calculated by dividing weight (kg) by the square of height (m^2). Elevated BMI was defined as BMI equal or higher than 30 kg/m^2 [9].

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 23.0 for Windows (IBM Corp., Armonk, New York, USA). Quantitative data were expressed as mean±SD. These data were analyzed by applying t test for comparison between two groups of normally distributed variables. For the qualitative data, they were expressed in the form of number and percentage and then analyzed by applying χ^2 for comparison between two independent qualitative variables that were normally distributed.

Results

Demographic data of Behçet's disease patients and controls

There was no significant statistical difference between the studied groups as regards age and sex. Age range in the control group was 9–64 years, with a mean age of 31.6±9.008 years. Male individuals comprised 140 (76.9%) BD patients and 56 (70%) participants in the control group. Female individuals comprised 42 (23.1%) BD patients and 24 (30%) participants in the

control group. BD patients showed male predominance with a male : female ratio of 3.3 : 1 (Table 1) (Fig. 1).

Clinical manifestations of the studied Behçet's disease patients

Distribution of diagnostic features of BD among studied patients revealed that oral and genital ulcers were predominant features in all patients. Eye lesions were present in 61.6 in the form of anterior uveitis (35.7%), posterior uveitis (6.5%), anteroposterior uveitis (9.8%), retinal artery vasculitis (2.7%), retinal artery occlusion (2.1%), vitritis (1.65%), and 0.5% each for blindness, retinitis, dry eye, papilloedema and optic atrophy. The Pathergy phenomenon was positive in 34.6%. Vascular involvement was present in 26.8% in the form of arterial and venous thrombosis (0.5 and 23.3%, respectively). Neuro-Behçet manifestations were present in 16.4%. Articular manifestations were present in 26.9%. There was no GIT, cardiac, or renal involvement in the studied patients (Figs 2–4).

Table 1 Demographic data of the studied patients (patients and controls)

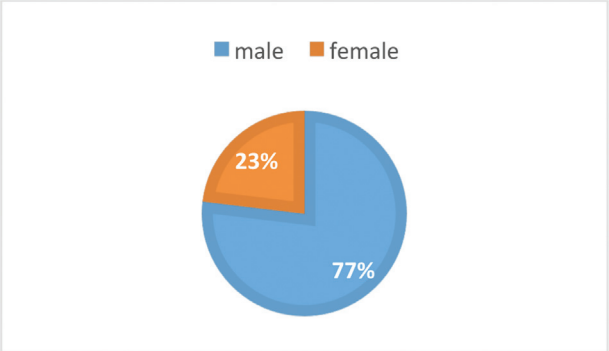
	BD patients (*N*=182)	Control group (*N*=80)	Test of significance	*P* value
Age (mean ±SD)	31.6 ±9.008	30.1±6.4	1.3	0.1
Sex [*n* (%)]				
Male	140 (76.9)	56 (70)	1.4	0.2
Female	42 (23.1)	24 (30)		

BD, Behçet's disease.

Modifiable traditional cardiovascular risk factors among patients and controls

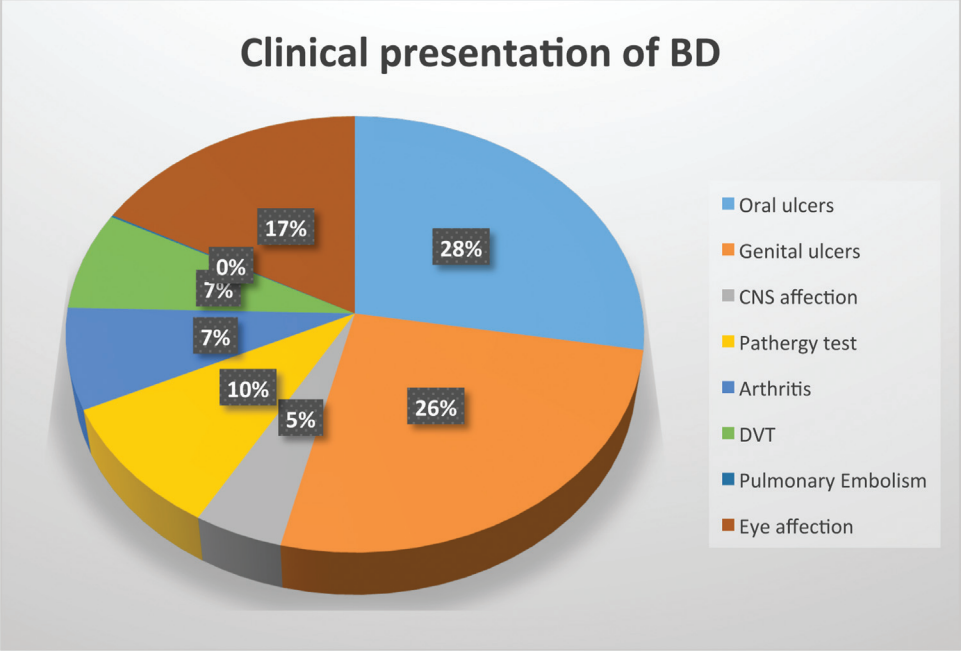
There was significant statistical difference between family history of premature coronary heart disease, hypertension, and smoking between healthy controls and BD patients according to clinical manifestations (Table 2). There was the significant statistical difference between lower HDL, and higher LDL and cholesterol concentrations compared with controls. However, no statistical difference was detected as regards triglycerides (Table 2). There was no significant statistical difference in obesity and diabetes mellitus between healthy controls and BD patients (Table 2).

Figure 1



Sex differences in Behçet disease.

Figure 2



Clinical presentations of patients with BD. BD, Behçet's disease.

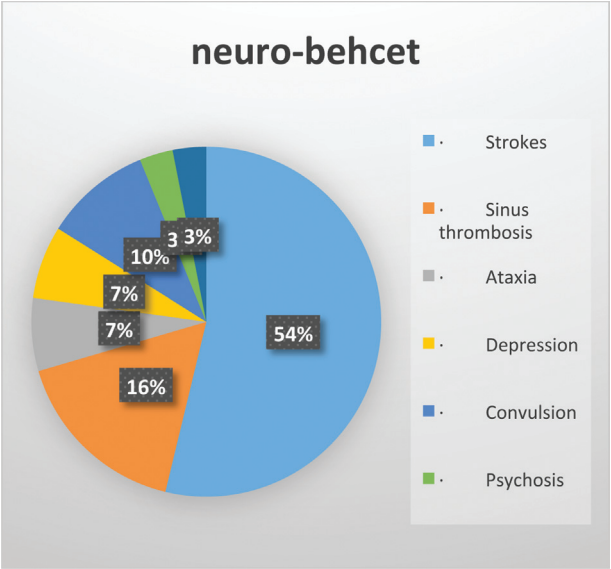
Laboratory investigations (markers of inflammation)

The laboratory investigations of the studied population revealed an ESR of 31.7±19.3 mm/first hour, and CRP was positive in 42.9% (Table 3).

Discussion

This is a multicenter study that was carried out on 182 patients of BD, including patients from Menoufia University Hospital, Tanta University Hospital, Mansoura University Hospital and Beni Suef University Hospital. Their ages ranged from 9 to 64 years of age with an average age of 31.6±9.008.

Figure 3



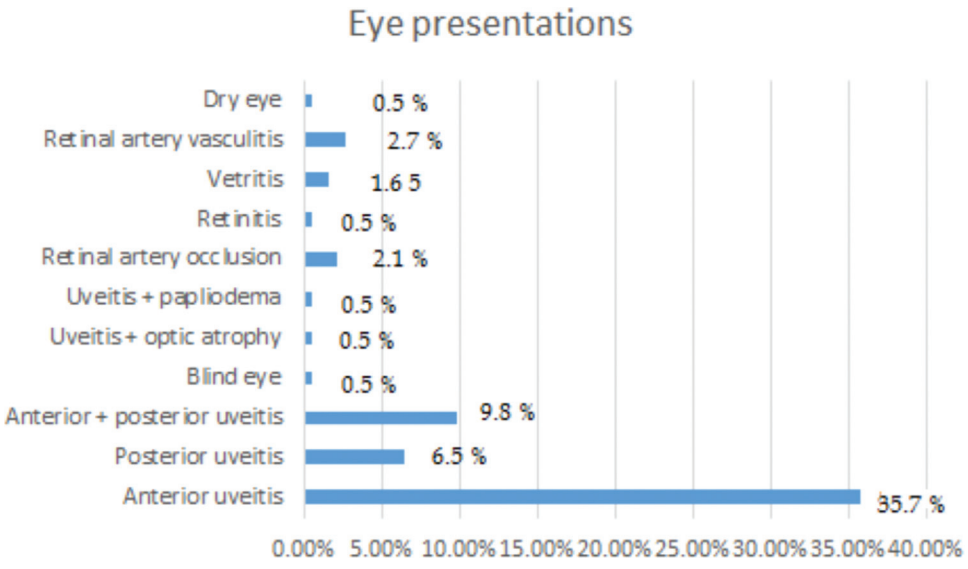
Neuro-Behçet manifestations.

Cardiac and vascular involvement of BD, also referred to as vasculo Behçet's, is frequent and affects all sizes of arteries and veins and all the cardiac layers, accounting for the major cause of mortality [11]. In the general population, modifiable risk factors such as hypertension, dyslipidemia, hyperglycemia, weight, smoking, diet, and exercise have been demonstrated to have a significant impact for CVD. In patients with rheumatic disease, CVD has been suggested to be linked to the presence of inflammation, which is considered to be a risk factor in its own right, in addition to the classic risk factors [9].

Although acute myocardial infarction commonly results from coronary atherothrombosis, there are several other etiologies that should be taken initially into account, especially in young adults without significant atherosclerotic risk factors. Thrombophilia and coronary arteritis are, in this context, examples of etiologies that should be taken care of. There is a reported case of BD with arterial involvement diagnosed after myocardial infarction resulting from thrombosis of the left main coronary artery in a 38-year-old young man without any particular past medical history [12].

As regards the demographic data of the studied groups, our study showed that there was no significant statistical difference between the studied groups with regard to age and sex. BD patients showed male predominance with a male : female ratio of 3.3 : 1. A multicenter nationwide Egyptian study on 1526 BD patients reported that the male-to-female ratio was 2.6 : 1 from 26 specialized Egyptian rheumatology centers

Figure 4



Eye affection in Behçet's disease.

Table 2 Modifiable cardiovascular risk factors among Behçet's disease patients and controls

	Behçet's disease patients Mean±SD	Control Mean±SD	Test of significance	*P* value
Family history [*n* (%)]				
Yes	16 (8.7)	0	7.4	0.004*
No	166 (91.3)	80 (100)		
Smoking [*n* (%)]				
Yes	60 (32.9)	0	34.2	0.000*
No	122 (67.1)	80 (100)		
BMI (kg/m^2)	26.7±3.8	26.3±3.3	0.8	0.3
BMI (kg/m^2) [*n* (%)]				
Normal	47 (25.8)	21 (26.3)	1.1	0.5
Over weight	103 (56.6)	49 (61.2)		
Obese	32 (17.6)	10 (12.5)		
RBG (mg/dl)	140.9±28.3	124.5±23.8	4.3	0.000*
BG (mg/dl) [*n* (%)]				
Normal	150 (82.4)	75 (93.7)	5.8	0.02*
Prediabetic/diabetic	32 (17.6)	5 (6.3)		
Systolic BP (mmHg)	122.5±12.7	110±9	7.9	0.000*
Diastolic BP (mmHg)	80.3±8.9	70±6.3	9.4	0.000*
HTN (mmHg) [*n* (%)]				
Normal BP	105 (57.7)	80 (100)	Fisher exact	
Pre-HTN	55 (30.2)	0	47.1	0.000*
HTN	22 (12.1)	0		
Total cholesterol (mg/dl)	177.02±35.9	145.5±15.1	7.4	0.000*
TG (mg/dl)	112.5±35.5	103.2±4.6	2.3	0.02*
HDL (mg/dl)	47.9±7.9	57.4±2.4	10.1	0.000*
LDL (mg/dl)	98.3±34.2	80.4±3.5	4.6	0.000*

BG, blood glucose; BP, blood pressure; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; RBG, random blood sugar; TG, triglycerides.

Table 3 Markers of Inflammation among patients

	Mean±SD
ESR	31.7±19.3
CRP [*n* (%)]	
Negative	104 (57.1)
Positive	78 (42.9)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

[13]. Another study showed that the male-to-female ratio was 1.3 : 1, in Egypt, 31.8 for the Middle East, 4.5 for Asia, and 3.3 for Europe; in Tunisia, it was 2.7 : 1, while in Senegal a ratio of 2.4 : 1 was reported. In Turkey, there was a female preponderance with an female : male of 1.2 : 1, and, in Korea, there was a female predominance (male : female, 0.56 : 1) [14].

According to the distribution of clinical criteria of BD in studied BD patients, this study showed that oral and genital ulcers were predominant features in all patients. Eye lesions were present in 61.6 in the form of anterior uveitis (35.7%), posterior uveitis (6.5%), anteroposterior uveitis (9.8%), retinal artery vasculitis (2.7%), retinal artery occlusion (2.1%), vitritis (1.65%), and 0.5% each for blindness, retinitis, dry eye, papilloedema and optic atrophy. The pathergy phenomenon was positive in 34.6%. Vascular involvement was present in 26.8% in the form of arterial and venous thrombosis (0.5 and 23.3%, respectively). Neuro-Behçet manifestations were present in 16.4%. Articular manifestations were present in 26.9%. There was no GIT, cardiac, or renal involvement in the studied patients. A multicenter nationwide Egyptian study concluded that there was a high frequency of genital ulcers (85.1%) followed by eye involvement (70.8%), skin affection (49.4%), musculoskeletal (48.9%), and DVT in 23.6%, while CNS and GIT involvement were the least frequent (13.1 and 9.5%, respectively) [12]. In another study, oral ulcers were present in all followed by genital (96.8%), vascular (57.1%), cutaneous (55.5%), ocular (47.6%), joint (36.5%), neurological (34.9%), gastrointestinal (19%), and cardiac (6.3%) lesions [15]. In another study, it was reported that the prevalence of BD manifestations was as follows: oral ulcer, 100%; genital ulcers, 94%; pathergy positivity, 75%; erythema nodosum, 43.2%; papulopustular lesions, 74.2%; and vascular involvement, 6.8%. Systemic involvement was present in the form of articular involvement in 79.5%, ocular involvement in 28.8%, pulmonary involvement in 2.3%, vascular involvement in 9.8%, neurologic involvement in 2.3%, and genitourinary system involvement in 0.8% [16].

In our study, a family history of premature coronary heart disease significantly increased the risk of vascular manifestations. Another study reported that family history of premature coronary heart disease (<55 years in first-degree male relatives and <65 years in female relatives) is a traditional risk factor for future coronary artery disease [17].

Hypertension is a major risk factor for CVD; in our study, both systolic and diastolic blood pressure measurements were significantly higher in the Behçet group. Another study agreed with our study and reported that the increased blood pressure in BD might be caused by changes in normal responsiveness of the vascular bed to pressure stimuli because of vasculitis or autonomic nervous dysfunction [18]. Another study reported that old age and hypertension were found to be independent factors contributing to ischemic stroke in BD patients. In addition, BD patients with older age and hypertension had a higher risk of stroke [19].

In our study, the prevalence of obesity was not higher in the BD group than in the healthy control group. A European study agreed with our study and reported that the close associations of obesity with inflammatory status and increased atherosclerotic complication lead to a great interest in the body composition in chronic inflammatory diseases. The prevalence of overweight and obesity in patients is common in cases of rheumatoid arthritis and systemic lupus. The prevalence of obesity was not higher in the BD group than in the healthy control group. The causes of obesity are associated with a sedentary lifestyle, physical inactivity, and glucocorticoid usages in rheumatoid arthritis and systemic lupus. BD may have a milder disease course than RA and SLE [20].

In our study, the prevalence of diabetes mellitus was not higher in the BD group than in the healthy control group. Another study that does not agree with our study reported that increased glucose levels result in increased oxidative stress and protein glycation of vessel walls, accelerating the atherosclerotic process and arterial thrombosis. Endothelial dysfunction is one of the steps of this pathway. Endothelium activation/damage has been postulated both in the pathogenesis and the course of BD in terms of vascular involvement [21]. Another study reported that BD is significantly associated with peripheral insulin resistance. This might be explained by the diverse consequences of inflammation and endothelial dysfunction in BD [22].

In the present study, BD patients had a high atherogenic potential, as marked by the significantly lower HDL, and higher LDL and cholesterol concentrations compared with controls. However, no statistical difference was detected as regards triglycerides. Two studies that agreed with our finding reported that BD patients had an atherogenic lipid profile [23,24]. However, in another study, while investigating the risk of atherosclerosis in patients with BD, blood lipid levels were not significantly different from the levels found in the healthy population [25]. Another study reported low blood lipid levels as a protector against atherosclerosis in BD. This may give a new insight that the inflammation, lipid profile and the development of atherosclerosis in BD may develop through a different mechanism from that associated with other inflammatory conditions [26].Our study concludes that smoking increases vascular manifestations of BD. In another study, 16.8% of patients with BD were smokers. The frequencies of vascular lesions in smokers were significantly more than in nonsmokers (odds ratio, 3.3) [27].

Another study on 209 patients with BD showed that, in smokers, BD activity according to Behçet's Syndrome Activity Scale and frequency of erythema nodosum, uveitis, arthritis, and neurological involvements are more than those observed in nonsmokers [28].

There is a logical mechanism that may explain the association between smoking and BD activity. Cigarette smoke is a complex mixture of compounds. Although nicotine itself may have anti-inflammatory properties resulting from the inhibitory effect of nicotine exposure on interleukin 8 (IL-8) and its actions on the parasympathetic neural system, cigarette smoke has a proinflammatory effect mainly via the promotion of vascular inflammation related to the increase of neutrophil chemotaxis and recruitment of polymorphs, monocytes and macrophages, release of H_2O_2, activation of NF-κB and upregulation of IL-1β, IL-6, and TNF-α [28].

CRP is an acute-phase protein of hepatic origin that increases following IL-6 secretion by macrophages and T cells, reflecting the level of inflammation. This indicates the increased CRP more commonly seen in acute or active inflammatory reactions in BD patients. In our study, CRP was positive in 42.9%. Another study reported that CRP was a significant predictor of the risk of cardiovascular events in women [29]. Another study reported that acute thrombophlebitis,

with its easy access to the blood circulation, was associated significantly with raised levels of CRP and ESR [30].

A major strength of this study was the new vision of assessment of modifiable cardiovascular risk factors in BD patients together with data for randomly selected matched controls drawn from the general population. The main limitation of the present study is the limited cardiovascular profile available about patients, including vascular imaging, and certainly more data on physical activity and diet would be of great interest, including data on the consumption of medications such as lipid-lowering medications.

Conclusion

BD is characterized by a high prevalence of cardiovascular comorbidities such as hypertension, dyslipidemia, obesity, and diabetes mellitus. Optimal control of blood pressure, lipids and blood sugar with reducing body weight, adequate exercise, and decreasing smoking may be an effective strategy to reduce the incidence of CVD in this population.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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