Ischaemic heart disease in Behçet's syndrome: a systematic review and meta-analysis

Y. Yang, Y. Yu, C. Sun, M. Jiang, J. Lin

Division of Rheumatology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Abstract

Objective

Behçet's syndrome (BS) has been reported with cardiovascular involvement. It's still unclear that BS is associated with the increased risk of ischaemic heart disease (IHD). We aimed to conduct a meta-analysis concerning the incidence of IHD in BS and identify the relationship between IHD and BS.

Methods

We performed a comprehensive literature search based on PubMed and Embase databases up to 7 July, 2021. Incidence of IHD was calculated by metaproportion. Pooled risk ratio and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method of DerSimonian and Laird.

Results

Four studies with 9237 patients with IHD in BS and 40353 controls were identified and included in our meta-analysis. The pooled risk ratio of IHD in patients with BS was 1.30 and achieved statistical significance (95% CI 1.04–1.64). The statistical heterogeneity was low with an I^2 of 39% (p=0.18).

Conclusion

In this meta-analysis the presence of BS was associated with an increased risk of IHD. Prospective researches should be done to determine the pathophysiological and prognostic implications of increased IHD in BS.

Key words

Behçet's syndrome, ischaemic heart disease, coronary artery disease, meta-analysis

*Yang Yang, BD**
*Ye Yu, MD**
Chuanyin Sun, MD
Mengdi Jiang, PhD
Jin Lin, PhD

**These authors contributed equally.*

Please address correspondence to:
Jin Lin,
Division of Rheumatology,
The First Affiliated Hospital,
College of Medicine,
Zhejiang University,
Hangzhou 310006, China.
E-mail: linjinzju@zju.edu.cn

Received on August 17, 2021; accepted in revised form on January 20, 2022.

Competing interests: none declared.

Introduction

Behçet's syndrome (BS), also known as Behçet's disease (BD), is a systemic variable vasculitis involving skin, mucosa, joints, eyes, arteries, veins, nervous system and gastrointestinal system (1). BS occurs most frequently in Eurasian populations along the ancient Silk Road which extends from eastern Asia to the Mediterranean basin (2). The origin of BS is still unclear, but it is recently believed that the pathogenesis of BS is related to the uncontrolled autoimmune and autoinflammatory response in genetically susceptible individuals (3).

Vascular involvement is a common complication of BS, affecting up to 40% of patients according to ethnicity. The most frequent complication is venous involvement accounting for nearly 14% to 40%, followed by arterial complications ranging from 2% to 17%. Cardiac complications occur relatively rare with less than 6% (4). Cardiac involvement including coronary artery disease (also known as ischaemic heart disease, IHD), often manifested in the form of silent myocardial ischaemia (5), angina pectoris or myocardial infarction (6), which deserves special attention because it occurs in relatively young patients with BS around 30 years old. The prognosis of coronary artery involvement is poor, leading to myocardial infarction in all cases and accounting for 25% of all deaths (7). Coronary lesions complicated to myocardial infarction are the most severe cardiac complications (4).

Recently, the understanding of atherosclerosis has changed fundamentally that systemic inflammation increases the risk of cardiovascular disease through an atherosclerosis-accelerating pathway (8) and today it is generally accepted that IHD originates from chronic inflammatory endothelial environment (9). Therefore, possibility existed that the micro-inflammation mediated vascular injury in BS can accelerate the development of coronary artery disease and lead to IHD. However, the data on IHD risk in BS patients remain unclear with conflicting epidemiological studies (10, 11). Here, we performed a systematic review and meta-analysis of literature aiming to calculate the prevalence of IHD in BS and identify the impact of BS on the risk of IHD.

Methods

Search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement protocol.

Two investigators independently searched published studies indexed in PubMed and Embase databases from inception to 7 July 2021 using the MeSH terms "Behçet's syndrome" and "Myocardial ischemia". Search terms included indexed terms from Medical Subject Headings (MeSH) in PubMed, Emtree in Embase.com as well as free-text terms. A hand search of references was also carried out. Unpublished studies were not included.

Inclusion and exclusion criteria

All articles that focused on IHD in BS were identified. Specifically, the following criteria were required to be met: 1) cohort or case control studies; 2) diagnosed BS patients according to well-defined criteria, such as the International study group criteria; 3) report of IHD. IHD was defined in included studies based on medical diagnostic codes and included acute coronary syndrome, myocardial infarction, and/or angina, etc.; 4) obtained data met the needs of research of the association of BS and IHD; and articles were published in English. Reviews, case reports, case series, and other studies that lacked systematic inclusion criteria of patients were excluded.

Data extraction and quality assessment

Two investigators independently extracted data from each study using a standardised data collection form. Following information was extracted: last name of the first author, title, publication year, country where the study was conducted, study design, criteria used for diagnosis of BS and IHD, number of cases and controls, number of IHD in BS, basic epidemiological data of the studies (mean age of subjects, proportion of males and follow-up duration) and control group. Any discrep-

ancies in data extraction were resolved by consensus.

Study quality was assessed using the 9-star Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiol-ogy/oxford.asp) by two investigators (12). The maximum attainable score was 9, and studies were classified as being low (0–2), medium (3–6), or high quality (7–9) in our study. Disagreements were resolved by discussion.

Statistical analysis

Review Manager Version 5.3 software produced by the Cochrane Collaboration was used for the data analysis. Adjusted point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird which assigned study's weight based on its standard error (13). A random-effect model was used in light of the high likelihood of between study variance with the different study designs and inclusion criteria. Statistical heterogeneity was determined by Cochran's Q test. This test was complemented with the I^2 statistic, which quantified the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0–25% indicates insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity and 76-100% high heterogeneity (14). STATA 15.1 (StataCorp.) was used to calculate Begg's test to assess the possibility of publication bias. In addition, sensitivity analysis was applied to evaluate whether the meta-analysis results were stable and reliable.

Results

Basic characteristics

Up to 7 July 2021, a total of 1018 potentially eligible articles (371 articles from PubMed and 647 articles from Embase) were retrieved using the search strategy described, of which 303 were excluded due to duplicate publication. Review of the titles and abstracts according to the inclusion criteria resulted in exclusion of 704 records. Reading of the full text of the remaining 11 articles for further evaluation resulted in the selection of 4 studies, including 1 case control studies and 3 retrospective cohort studies with 9237 cases of BS and 40353 controls for subjection to meta-analysis (10, 11, 15, 16) . A flowchart of article screening for the meta-analysis are summarised in Figure 1.

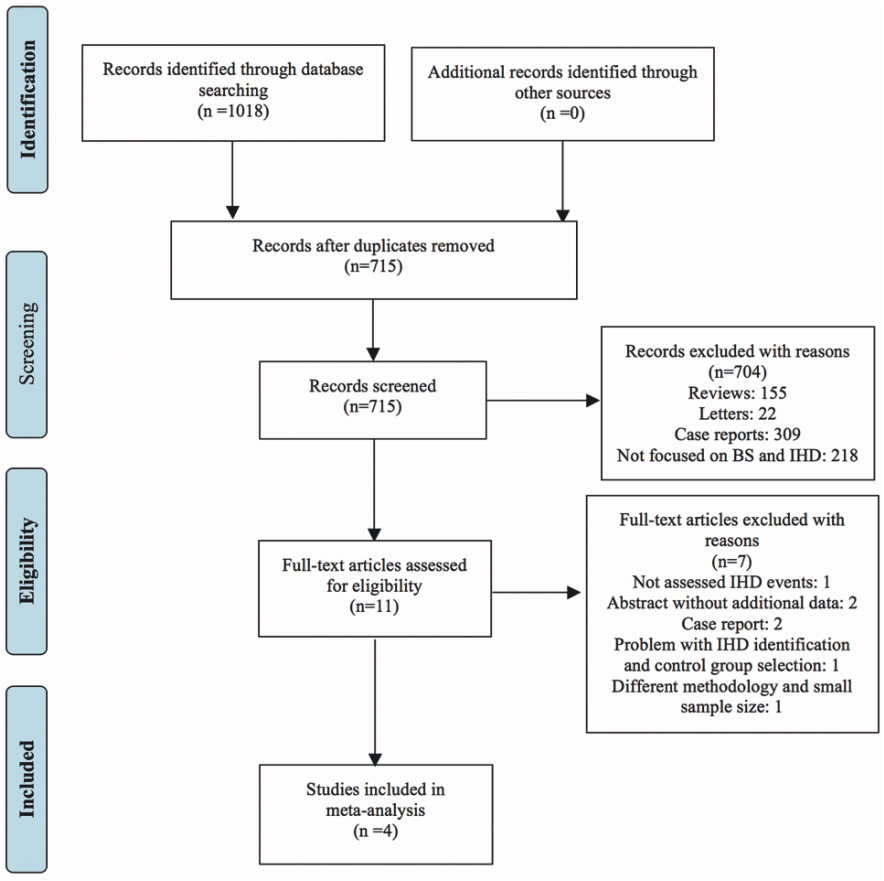

Fig. 1. Study flow diagram.

Table I summarised the characteristics of included studies and participants. All studies used national registry databases from Israel, Korea, the UK and Taiwan. The three cohort studies did exclude patients with a history of cardiovascular events. All studies compared BS patients with the non-BS controls and were of high quality with Newcastle-Ottawa score of 7 to 9.

Table II showed the distribution of cardiovascular risk factors in patients with BS and non-BS controls for the included studies. The mean age of study subjects at symptom onset or at diagnosis was <50 years. The male to female ratio was approximately 1:1.4 across all studies. There was no difference with regard to the prevalence of diabetes between BS patients and normal controls. As for the prevalence rate of hypertension and smoking, the results were inconsistent. However, the prevalence rate of dyslipidaemia was ranged from 2.6% to 50.1% and 3 studies reported statistically significant higher rate of dyslipidaemia in BS patients versus in controls; in the remaining studies, the related information was not provided.

Relationship between BS and IHD

The total incidence rate of IHD was 1.51% (751/49588), of which the BS group was 1.95% (95% CI=1.67%-2.23%) (180/9237) and the control group was 1.42% (95% CI=1.30%-1.53%) (571/40353). The pooled risk ratio of IHD in patients with BS versus controls was 1.30 (95% CI=1.04-1.64, I^2=39%, p=0.18; Fig. 2).

Sensitivity analysis and publication bias

Begg's test showed no publication bias (p=1.00) (Fig. 3A). In addition, sensitivity analysis results showed that the results were stable and reliable (Fig. 3B).

Table I. Main characteristics of the studies included in the meta-analysis.

Study	Year	Country	Study design	Follow-up, years	Classification criteria for BS	Diagnosis of IHD	Number of BS patients	Number of IHD in BS	Number of controls	Number of IHD in controls	Control group	Quality score
Yavne (16)	2017	Israel	Case control	NA	Medical records or hospital discharge papers	Medical records or hospital discharge papers for IHD	871	95	4349	327	Age- and gender-matched general population	7
Ahn (11)	2019	Korea	Retrospective cohort	3.6	ICD-10 codes	ICD-10 code for acute myocardial infarction	5576	24	27880	70	Age- and sex-matched general population	9
Thomas (15)	2020	UK	Retrospective cohort	5.3	The read codes	The read codes for IHD	1236	32	5016	111	Age- and gender-matched general population	9
Lin (10)	2021	Taiwan	Retrospective cohort	NA	International study group criteria and ICD-9-CM code	ICD-9-CM codes for acute myocardial infarction and IHD	1554	29	3108	63	propensity score matched non-BS cohort	9

IHD: ischaemic heart disease; NA: not applicable.

Table II. Distribution of traditional cardiovascular risk factors in patients with BS and patients without BS in the included studies.

Study	Mean age of cases, years		Sex, male, %		Hypertension, % total		Diabetes, % total		Dyslipidaemia, % total		Smoking, % total	
	BS	Control	BS	Control	BS	Control	BS	Control	BS	Control	BS	Control
Yavne (16)	49.0	49.8	52.6	52.6	28.6	24.1 [b]	16.2	14.3 [c]	50.1	41.9 [b]	42.4	38.1 [b]
Ahn (11)	43.4	43.4	32.5	32.5	11.4	10.2 [b]	4.1	3.9 [c]	[a] 10.3	[a] 7.0 [b]	NA	NA
Thomas (15)	42.3	42.3	36.2	36.2	10.2	9.3 [c]	3.8	2.9 [c]	9.4	6.6 [b]	23.8	24.4 [b]
Lin (10)	39.2	39.1	42.0	44.0	6.6	6.7 [d]	2.5	2.8 [d]	2.6	3.1 [d]	NA	NA

NA: not applicable; a: lipid-regulating medication use; b: p-value <0.05; c: p-value >0.05; d: the BS and non-BS cohorts were matched by propensity score, accounting for the following confounders: age, sex, year of index date, comorbidities, and drug exposure.

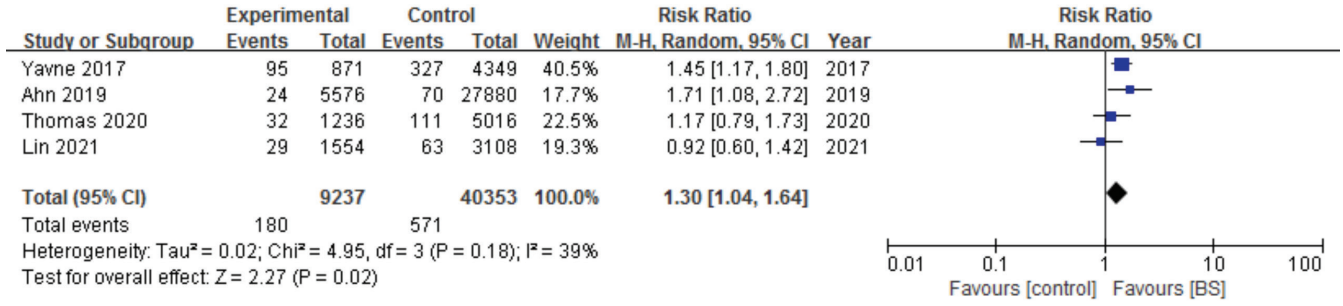

Fig. 2. Prevalence of ischaemic heart disease in Behçet's syndrome.

Discussion

To the best of our knowledge, this study is the first meta-analysis concerning the association between IHD and BS. The results demonstrated that patients with BS have a 30% increased risk of IHD. Although we have concluded BS has a high rate of IHD, the pathophysiological mechanisms are not clear.

IHD refers to a group of closely related syndromes by an imbalance between the myocardial oxygen demand and the blood supply. The most common cause is narrowing of the lumen of the coronary arteries by atherosclerosis. Accelerated subclinical atherosclerosis has been observed in multiple studies in BS. Several studies found the increased intima-media thickness (IMT) in BS patients (17, 18). Increased arterial stiffness by measurement of the pulse wave velocity (PWV) of carotid arteries (19, 20) and greater carotid plaque frequency were also reported (21).

Inflammation and endothelial dysfunction play paramount roles in all stages of atherosclerosis, including initiation, progression, and thrombotic complications of the lesion (8, 22).

Endothelial dysfunction is an early critical step in the formation of atherosclerosis (23). Several studies have demonstrated the detrimental effect of activated inflammatory cells (such as dendritic cells and T cells), inflammatory cytokines (such as TNF-α) and

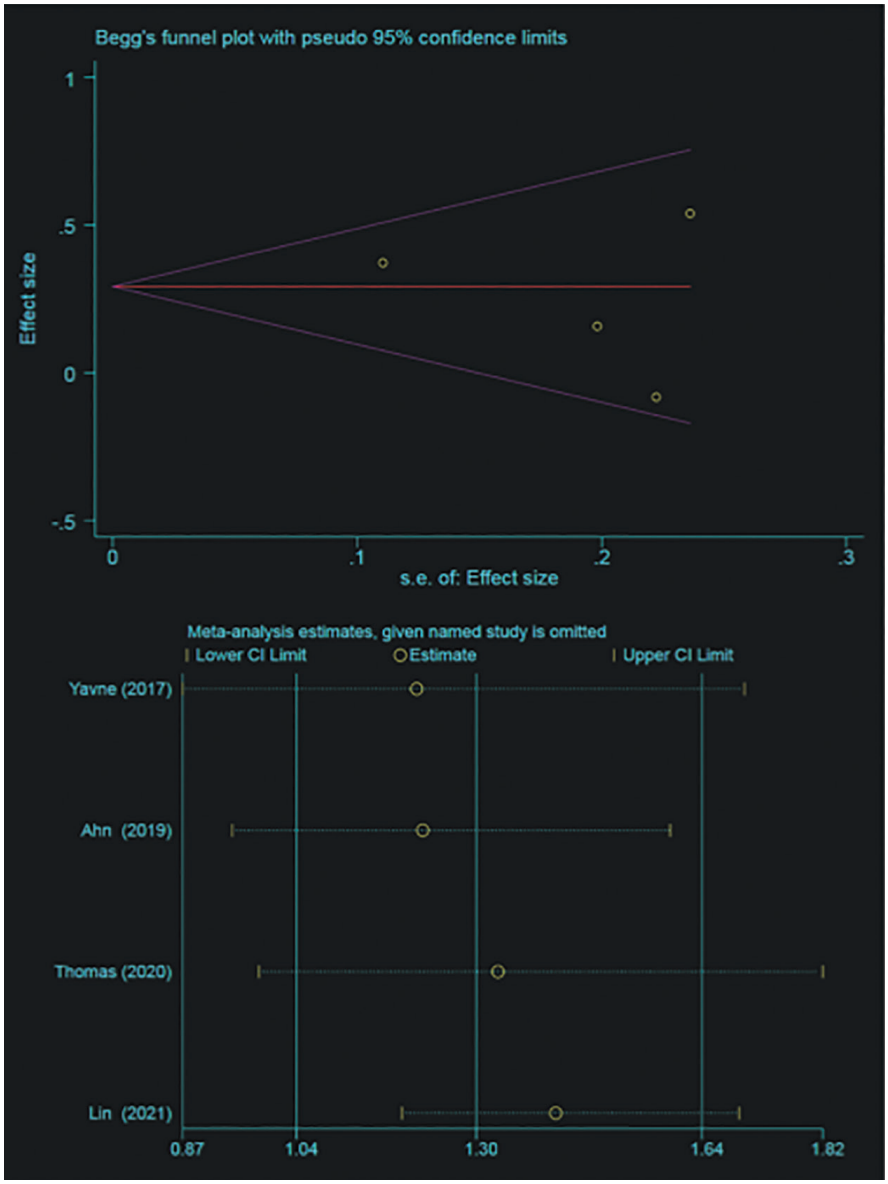

Fig. 3. A: Begg's test for the assessment of potential publication bias between studies; **B**: Sensitivity analysis.

oxidative stress on endothelial function, resulting in the acceleration of atherosclerosis (24-26). Infection-related trigger factors, including antigens and autoantigens, are believed to mediate the development of BS in patients with a genetic predisposition and subsequently activate the innate and adaptive immune systems (such as neutrophil cells and Th1 cells), resulting in the production of numerous cytokines (such as IL-1, IL-6, and tumour necrosis factor-α [TNF-α]) and chemokines to combat the infection-related factors (27, 28). Histopathological analysis shows that neutrophils and lymphocytes infiltrate arteries and veins in BS patients, leading to vascular endothelial dysfunction (29). In addition, BS patients have reduced antioxidant capacity and increased reactive oxygen species (ROS) levels (the production of ROS is a normal characteristic of neutrophils) that contribute to endothelial cell damage and induce platelet, leukocyte, and endothelial cell activation through the release of proinflammatory cytokines and chemokines, causing endothelial damage and lipid peroxidation, which results in a high atherogenic state (30). Endothelial activation, otherwise, can cause increased cytokine secretion and enhanced adhesion molecule expression, thus accelerating monocyte and leukocyte adhesion and consequently, plaque formation (31). Many studies have indeed found vascular endothelial dysfunction in BS patients, as measured by flow-mediated vasodilation (FMD) and endothelial-mediated vasodilation (EMD) (32-35). Merashli *et al*. (36) demonstrated a greater degree of FMD impairment in patients with higher disease activity; however, FMD impairment during inactive disease means that BS patients are at risk of arterial damage in the long term.

It is reported that cardiovascular risk factors are common in BS patients. Researches demonstrated increased homocysteine (hcy), a prothrombotic molecule, which predispose to coronary artery disease, in BS patients (37, 38). Hcy can destroy endothelial cells directly or indirectly (39). Excessive hcy cause loss of endothelial function by producing toxic hydrogen peroxide, superoxide and hydroxyl (40). Besides, many drugs used to treat BS patients, especially glucocorticoids, have various metabolic side effects (such as obesity, hyperglycaemia, hypertension, and dyslipidaemia), which may increase the incidence of atherosclerosis and cardiovascular events (41, 42); however, this relationship is complicated because glucorticosteroids also have active anti-inflammatory effects and could reduce tissue damage during coronary ischaemia and after myocardial infarction (43, 44). In most of the included studies of our meta-analysis, the distribution of hypertension, smoking, and dyslipidaemia in patients with BS seems to be more prevalent compared to patients without BS, although not all results reach a statistically significant difference. Pandey *et al*. (45) showed that hypertension (OR=2.20, p=0.03) and hyperlipidaemia (OR=2.34, p=0.02) were independent predictors of coronary artery disease in patients with BS in a multimodel regression analysis. In addition, the physical activity of BS patients decreased due to pain and fatigue (46). Current researches seem to indicate that exercise training is an effective therapeutic modality for mitigating endothelial dysfunction and vascular wall inflammation (47).

Although atherosclerosis remains the major cause of acute coronary syn-

drome (ACS), there are many other aetiologies that should be taken into account, especially in young patients with no atherosclerotic risk factors. IHD in BS may be due to coronary vasculitis in the absence of coronary atherosclerosis. Silent myocardial ischaemia was found in 8 out of 41(19.5%) BS patients [as compared to 1 out of 35 (2.9%) controls] with treadmill exercise test and thallium-201 myocardial perfusion single photon emission computed tomography (SPECT) without evidence of coronary stenosis in coronary angiography (48). The pathological findings of coronary involvement in BS include arteritis and inflammatory endarteritis obliterans of the vasa vasorum, which can lead to destruction and fibrosis of the media, with ensuing weakening of the arterial wall and tendency of aneurysm formation (49-51). Also, coronary vasculitis can lead to coronary occlusion by causing intimal fibrous thickening (21). Kariyanna *et al*. found that coronary stenosis and coronary aneurysm were the most common findings in coronary angiography in BS patients associated with ACS (52). Mouedder *et al*. reported a case of BS with myocardial infarction diagnosed resulting from thrombosis of the right coronary artery (53). In BS, two mechanisms may explain thrombosis: hypercoagulable state and vasculitis. Meta-analysis shows BS patients have higher levels of factor 8, von Willebrand factor, and factor V Leiden mutations (36). Vasculitis remains the main mechanism of thrombosis (54). Some scholars have also hypothesised that BS might lead to coronary microvascular dysfunction, therefore impairing coronary flow reserve (55).

Considering BS-associated inflammatory conditions are directly involved in the development of IHD, immunosuppressive therapy would be helpful. Chen *et al*. reported that of the 19 patients with BS associated with coronary involvement that received glucocorticoid and immunosuppressants, 15 (78.9%) patients achieved clinical remission (6). Whether immunosuppressants are beneficial or not requires further exploration.

We were unable to systematically study whether BS vasculitis activity or specific medications used to suppress inflammation modify the risk of IHD due to lack of reporting in individual studies included in meta-analysis. Besides, most of the included studies provide limited clinical information about traditional cardiovascular risk factors for BS patients and controls. Thus, we could not determine the potential contribution of each pathway.

Several limitations existed in this study. The first relates to the meta-analysis principle that associates different studies with different patients and other parameters. Although the sample sizes and designs of these studies are different, which may have an impact on the interpretation of the results, the heterogeneity of literatures we included is low after analysis. Second, the number of the studies included in the meta-analysis is small. The lack of related data mainly because of the low incidence of coronary involvement in the patients of BS, and few scholars pay attention to the relationship of IHD and BS. Third, in considering of enrolled studies are primarily of retrospective design, we only show a correlation rather than establishing causality. Therefore, we cannot conclude that BS itself or unknown confounding factors were responsible for the increased risk of IHD.

Conclusion

In summary, our meta-analysis indicated the increased risk of IHD among patients with BS. The reason for this finding remains unclear but could possibly be owing to accelerated subclinical atherosclerosis, coronary vasculitis, endothelial dysfunction and the higher baseline cardiovascular risk in BS. More researches, prospective researches in particular, are needed to verify our findings.

References

1. HATEMI G, CHRISTENSEN R, BANG D *et al*.: 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis* 2018; 77: 808-18.
2. GRECO A, DE VIRGILIO A, RALLI M *et al*.: Behçet's disease: New insights into pathophysiology, clinical features and treatment options. *Autoimmun Rev* 2018; 17: 567-75.
3. PINETON DE CHAMBRUN M, WECHSLER B, GERI G *et al*.: New insights into the pathogenesis of Behçet's disease. *Autoimmun Rev* 2012; 11: 687-98.
4. DESBOIS AC, WECHSLER B, CLUZEL P *et al*.: Cardiovascular involvement in Behçet's disease. *Rev Med Interne* 2014; 35: 103-11.
5. GULLU BH, BENEKLI M, MUDERRISOGLU H *et al*.: Silent myocardial ischemia in Behcet's disease. *J Rheumatol* 1996; 23: 323-7.
6. CHEN H, ZHANG Y, LI C *et al*.: Coronary involvement in patients with Behçet's disease. *Clin Rheumatol* 2019; 38: 2835-41.
7. GERI G, WECHSLER B, THI HUONG DL *et al*.: Spectrum of cardiac lesions in Behçet disease: A series of 52 patients and review of the literature. *Medicine* 2012; 91: 25-34.
8. HANSSON GK: Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; 352: 1685-95.
9. STEYERS III CM, MILLER JR FJ: Endothelial dysfunction in chronic inflammatory diseases. *Int J Mol Sci* 2014; 15: 11324-49.
10. LIN C-Y, CHEN H-A, WU C-H *et al*.: Is Behçet's syndrome associated with an increased risk of ischemic heart disease? A real-world evidence in Taiwan. *Arthritis Res Ther* 2021; 23: 161.
11. AHN HS, LEE D, LEE SY *et al*.: Increased cardiovascular risk and all-cause death in patients with behcet disease: A korean nationwide population-based dynamic cohort study. *J Rheumatol* 2020; 47: 903-8.
12. WELLS G, SHEA B, O'CONNELL J: The Newcastle-Ottawa Scale (NOS) for Assessing The Quality of Nonrandomised Studies in Meta-analyses. *Ottawa Health Research Institute Web site* 2014; 7.
13. DERSIMONIAN R, LAIRD N: Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177-88.
14. HIGGINS JPT, THOMPSON SG, DEEKS JJ *et al*.: Measuring inconsistency in meta-analyses. *Br Med J* 2003; 327: 557-60.
15. THOMAS T, CHANDAN JS, SUBRAMANIAN A *et al*.: Epidemiology, morbidity and mortality in Behçet's disease: a cohort study using The Health Improvement Network (THIN). *Rheumatology* (Oxford) 2020; 59: 2785-95.
16. YAVNE Y, TIOSANO S, WATAD A *et al*.: Investigating the link between ischemic heart disease and Behçet's disease: A cross-sectional analysis. *Int J Cardiol* 2017; 241: 41-5.
17. ÖZTüRK MA, ÜNVERDI S, OKTAR SO *et al*.: Vascular endothelial growth factor and carotid intima-media thickness in patients with Behçet's disease. *Clin Rheumatol* 2008; 27: 961.
18. OZGEN M, KOCA SS, DAGLI N *et al*.: Serum adiponectin and vaspin levels in rheumatoid arthritis. *Arch Med Res* 2010; 41: 457-63.
19. UPALA S, YONG WC, SANGUANKEO A: Increased arterial stiffness in Behçet's disease: A systematic review and meta-analysis. *Korean Circ J* 2017; 47: 477-82.
20. AGUS HZ, YILDIZ BS, KAHRAMAN S *et al*.: Increased Arterial Stiffness Measured by Carotid Femoral (Aortic) Pulse Wave Velocity in Patients with Inactive Behçet's Disease. *Kardiologiya* 2020; 60: 123-7.
21. SEYAHI E, UGURLU S, CUMALI R *et al*.: Atherosclerosis in Behçet's Syndrome. *Semin Arthritis Rheum* 2008; 38: 1-12.
22. LIBBY P, OKAMOTO Y, ROCHA VZ *et al*.: Inflammation in atherosclerosis: Transition

from theory to practice. *Circ J* 2010; 74: 213-20.
23. VITA JA, KEANEY JR JF: Endothelial function: A barometer for cardiovascular risk? *Circulation* 2002; 106: 640-2.
24. MONTECUCCO F, MACH F: Common inflammatory mediators orchestrate pathophysiological processes in rheumatoid arthritis and atherosclerosis. *Rheumatology* 2009; 48: 11-22.
25. RHO YH, CHUNG CP, OESER A *et al*.: Interaction between oxidative stress and high-density lipoprotein cholesterol is associated with severity of coronary artery calcification in rheumatoid arthritis. *Arthritis Care Res* 2010; 62: 1473-80.
26. NIESSNER A, SATO K, CHAIKOF EL *et al*.: Pathogen-sensing plasmacytoid dendritic cells stimulate cytotoxic T-cell function in the atherosclerotic plaque through interferon-α. *Circulation* 2006; 114: 2482-9.
27. TONG B, LIU X, XIAO J *et al*.: Immunopathogenesis of Behçet's disease. *Front Immunol* 2019; 10: 665.
28. PERAZZIO SF, ANDRADE LEC, DE SOUZA AWS: Understanding Behçet's disease in the context of innate immunity activation. *Front Immunol* 2020; 11: 586558.
29. KOBAYASHI M, ITO M, NAKAGAWA A *et al*.: Neutrophil and endothelial cell activation in the vasa vasorum in vasculo-Behcet disease. *Histopathology* 2000; 36: 362-71.
30. OZYAZGAN S, ANDICAN G, ERMAN H *et al*.: Relation of protein oxidation parameters and disease activity in patients with Behçet's disease. *Clin Lab* 2013; 59: 819-25.
31. PRASAD M, HERMANN J, GABRIEL SE *et al*.: Cardiorheumatology: Cardiac involvement in systemic rheumatic disease. *Nat Rev Cardiol* 2015; 12: 168-76.
32. OZUGUZ P, KARABULUT AA, TULMAC *et al*.: Markers of endothelial dysfunction and evaluation of vascular reactivity tests in Behçet disease. *Angiology* 2013; 65: 937-43.
33. ULUSOY RE, KARABUDAK O, KILICASLAN F *et al*.: Noninvasive assessment of impaired endothelial dysfunction in mucocutaneous Behçet's disease. *Rheumatol Int* 2008; 28: 617-21.
34. PROTOGEROU AD, LEKAKIS J, IKONOMIDIS I *et al*.: Pressure wave reflections, central blood pressure, and aortic stiffness in patients with adamantiades-Behçet's disease: a cross-sectional case-control study underlining the role of chronic corticosteroid treatment. *Am J Hypertens* 2006; 19: 660-6.
35. OZDEMIR R, BARUTCU I, SEZGIN AT *et al*.: Vascular endothelial function and plasma homocysteine levels in Behçet's disease. *Am J Cardiol* 2004; 94: 522-5.
36. MERASHLI M, STER IC, AMES PRJ: Subclinical atherosclerosis in Behçet's disease: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2016; 45: 502-10.
37. LA REGINA M, ORLANDINI F, PRISCO D *et al*.: Homocysteine in vascular behçet disease: A meta-analysis. *Arterioscler Thromb Vasc Biol* 2010; 30: 2067-74.
38. EL-NAJJAR AR, ELSAMMAK AA: Association between serum homocysteine and arterial stiffness in patients with Behçet's disease. *Egypt Rheumatol* 2020; 42: 129-33.
39. HARPEL PC, ZHANG X, BORTH W: Homocysteine and hemostasis: pathogenetic mechanisms predisposing to thrombosis. *J Nutr* 1996; 126: 1285S-9S.
40. WELCH GN, LOSCALZO J: Homocysteine and Atherothrombosis. *N Engl J Med* 1998; 338: 1042-50.
41. WALKER BR: Glucocorticoids and cardiovascular disease. *Eur J Endocrinol* 2007; 157: 545-59.
42. WEI L, MACDONALD TM, WALKER BR: Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* 2004; 141: 764-70.
43. HAFEZI-MOGHADAM A, SIMONCINI T, YANG Z *et al*.: Acute cardiovascular protective effects of corticosteroids are mediated by nontranscriptional activation of endothelial nitric oxide synthase. *Nat Med* 2002; 8: 473-9.
44. VALEN G, KAWAKAMI T, TAHEPOLD P *et al*.: Glucocorticoid pretreatment protects cardiac function and induces cardiac heat shock protein 72. *Am J Physiol-Heart Circul Physiol* 2000; 279: H836-H43.
45. PANDEY A, GARG J, KRISHNAMOORTHY P *et al*.: Predictors of coronary artery disease in patients with Behçet's disease. *Cardiology* (Switzerland) 2014; 129: 203-6.
46. UZUN N, TARAKCI E, ARMAN N *et al*.: Investigation of physical activity levels of patients with Behçet's disease. *Ann Rheum Dis* 2019; 78: 1062.
47. RIBEIRO F, ALVES AJ, DUARTE JA *et al*.: Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *Int J Cardiol* 2010; 141: 214-21.
48. TÜRKÖLMEZ Ş, GÖKÇORA N, ALKAN M *et al*.: Evaluation of myocardial perfusion in patients with Behçet's disease. *Ann Nucl Med* 2005; 19: 201-6.
49. HARRISON A, ABOLHODA A, AHSAN C: Cardiovascular complications in Behçet syndrome acute myocardial infarction with late stent thrombosis and coronary, ventricular, and femoral pseudoaneurysms. *Tex Heart Inst J* 2009; 36: 498-500.
50. MATSUMOTO T, UEKUSA T, FUKUDA Y: Vasculo-Behçet's disease – a pathological study of 8 cases. *Hum Pathol* 1991; 22: 45-51.
51. OZEREN M, DOGAN OV, DOGAN S *et al*.: True and pseudo aneurysms of coronary arteries in a patient with Behçet's disease. *Eur J Cardiothorac Surg* 2004; 25: 465-7.
52. KARIYANNA PT, SHAH P, JAYARANGAIAH A *et al*.: Acute coronary syndrome in Behçet's syndrome: A systematic review. *Eur J Rheumatol* 2021; 8: 31-5.
53. MOUEDDER F, BENBOUCHTA K, ISMAILI N *et al*.: Serious right coronary artery thrombosis revealing Behçet's disease in a female patient: a case report. *CUREUS* 2020; 12.
54. KO GY, BYUN JY, CHOI BG *et al*.: The vascular manifestations of Behçet's disease: angiographic and CT findings. *Br J Radiol* 2000; 73: 1270-4.
55. GULLU H, CALISKAN M, ERDOGAN D *et al*.: Impaired coronary microvascular functions in patients with Behçet disease. *J Am Coll Cardiol* 2006; 48: 586-7.