**SUBCINICIAL ATHEROSCLEROSIS IN BEHCET’S DISEASE AND ITS INVERSE RELATION TO AZATHIOPRINE USE: AN UPDATED META-ANALYSIS**

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**ABSTRACT**

**Objectives.** To evaluate the intima media thickness of carotid arteries (IMT) and its clinical, laboratory and treatment correlates in Behcet’s disease (BD). **Methods**. Systematic search of EMBASE and PubMed databases from January 2016 to October 2022; we employed random effect meta-analyses for continuous outcomes and Peto’s odds ratio for rare events**.** **Results.** The meta-analysis included 36 case control studies: the IMT was greater in BD (n=1103) than in controls (n=832) (p<0.0001) with wide heterogeneity (I*2*=86.9%); a sensitivity analysis that included mean age of BD participants, gender, disease duration and activity, atherogenic index of plasma, blood pressure, C-reactive protein, ethnicity, smoking status, anti-inflammatory and immune suppressive agents, revealed that male gender, mean age of participants and azathioprine use (the latter two in inverse fashion) partly explained the heterogeneity variance (p=0.02, p=0.005, and p=0.01). The IMT was greater in vascular (n=114) than in non-vascular BD (n=214) (p=0.006). BD patients (n=782) had a greater pooled prevalence of carotid plaques than controls (n=537) (13.1% vs 2.97%, p<0.0001). **Conclusion.** Subclinical carotid artery atherosclerosis represents a vascular feature of BD, independently of the traditional risk factors but for male gender; the inverse relations with age and azathioprine use suggest that carotid arteries are thicker at disease onset but do not progress over time, eventually dampened by immune suppressive treatment: this assumption needs verification on adequately designed clinical trials.

**Key words:** Behcet’s disease, intima media thickness, atherosclerosis, azathioprine

**INTRODUCTION**

Behcet’s disease (BD) is an autoinflammatory disease with protean clinical manifestations affecting mucous membranes, eyes, bowels, lungs, heart, brain and joints; from the vascular point of view, recurrent thrombophlebitis, thromboembolism involving upper and lower limbs, superior and inferior vena cava, splanchnic and cerebral veins are frequent [1]. Moreover, vasculitis of the *vasa vasorum* induces medial destruction and fibrosis, leading to the formation of aneurysms, stenoses and occlusions, mostly in the aorta and in the pulmonary vessels. This vascular involvement is responsible for severe morbidity and long-term mortality [2]. The inflammatory nature of BD lead to the evaluation of premature atherosclerosis via functional assessments such as flow mediated and endothelial mediated vasodilation that rely on the biological activity of endogenous and exogenous nitric oxide respectively, and morphological assessment that rely on ultrasound measurement of the intima media thickness (IMT) of the carotid arteries. An earlier metanalysis suggested impaired flow mediated vasodilatation and subclinical atherosclerosis of carotid arteries in BD, offset however by wide heterogeneity, unexplained by the sensitivity analysis [3]. Given that endothelial dysfunction, detected as impaired pulse wave velocity, was confirmed by a later meta-analysis [4], we performed an updated systematic review and meta-analysis to reassess subclinical atherosclerosis by IMT of carotid arteries and to identify explanatory variables that were not detected in the previous meta-analysis possibly due to the limited number of studies available at the time.

**MATERIAL AND METHODS**

**Research hypothesis and outcome measures**

To assess the presence of subclinical atherosclerosis in BD and in its different subsets we calculated the standardized mean IMT differences and the pooled prevalence of carotid plaques between BD patients and healthy controls and between BD subgroups without or with certain clinical features and these represented our outcome measures.

**Search strategy**

Because our previous meta-analysis was performed on articles deriving from a systematic search that was carried out from inception to January 2016 [3], on this occasion the Medline database was screened from January 2016 to October 2022 using the Medical Subject Headings (“Behcet’s disease” [All fields] AND (“atherosclerosis”) [All fields] AND (“intima media thickness”) [All fields]; likewise the EMBASE database was screened between the same dates with “Behcet’s disease” OR “atherosclerosis” AND “intima media thickness”. The searches were done on the 17th of October 2022. To reduce the effect of possible publication bias, we used the same search terms in natural language to screen the Grey Literature via theDANS EASY Data Archive, as well as Google, looking for additional citations. We finally hand searched the reference list of all papers subsequently included in the systematic review to ensure we had not missed any relevant articles.

**Inclusion criteria:** 1) IMT measured by validated and published methods; 2) retrospective, cross-sectional and prospective case-control or cohort studies addressing the difference in mean plasma IMT between BD patients and controls (CTR) or between patients with and without different clinical manifestations BD; 3) articles written in any language.

**Exclusion criteria**: 1) IMT not measured with validated methods; 2) case studies, prevalence studies and reviews; 3) articles not comparing BD patients with healthy CTR. Two investigators (PRJA and AA) checked independently the resulting citations for relevancy and removed duplicates (via EndNote); AA and MM screened all titles and abstracts, excluded the irrelevant ones and applied the eligibility criteria to the relevant ones in order to include the appropriate studies. PRJA resolved any disagreements developing at this stage. PRJA and FG also screened the reference list of retrieved papers for papers that could have been missed. Eventual articles not written in English were translated.

**Data extraction/protocol**

AA and MM independently extracted data from the articles that considered: year of publication, study design, sample size, demographic data, disease duration, clinical features of BD, inflammatory markers, outcome means and corresponding dispersion measures (standard deviations or confidence intervals). In addition, and where study allowed, we calculated and charted the male/female ratio, the cardiovascular and cerebrovascular histories, the atherogenic index of plasma, the diastolic and systolic blood pressures, the use of anti-inflammatory and immune suppressive medication (expressed as the ratio of users/non-users) and the smoking status, that were all used for the sensitivity analysis. The 2020 PRISMA guideline was followed to ensure transparency of identification, selection, appraisal and synthesis of the studies included in the systematic review and meta-analysis (5). We did not subscribe the systematic review to a registry because our data derive from case-control and observational studies with no intervention, with data extracted as described above. The electronic sheets with collected data will be available on request.

### **Evaluation of the quality of the studies**

The quality of the studies included in the meta-analysis [6] was determined by the Newcastle Ottawa Quality Assessment Scale for observational case-control studies; two investigators, MM and FG, scored the studies independently and PRJA resolved any discrepancies. The inter-rater agreement between the two assessors was high (Cohen kappa 0.7412, 95% CI 0.589, 0.921).

### **Statistical analysis**

The statistical analysis was carried out via Comprehensive Meta-analysis (Version 3, Englewood, NJ 2013, USA). Random effect meta-analysis for continuous outcomes was employed because our estimates derived from cross-sectional observational studies and not from clinical trials [7]. Peto’s odds ratio for rare events was used to compare pooled frequencies between groups [8]. The heterogeneity across study results was assessed by the I2 statistics: a value of 0% indicated no heterogeneity; values less than 25% indicated low, between 25% and 50% moderate and over 50% high heterogeneity [9]. A [Funnel plot](https://www.sciencedirect.com/topics/medicine-and-dentistry/funnel-plot) (Supplementary Figure 1) was employed for publication bias [10,11]. Sensitivity analyses were performed by meta-regression and by subgroup according to results, clinical plausibility and judgement.

**RESULTS**

**Study Number**

The database search between January 2016 and October 2022 yielded 38 records; following the screening and exclusion processes indicated in Figure 1 we evaluated 21 new cross-sectional case-control studies, that were added to the 15 articles used in our previous meta-analysis [3], for a total of 36 articles that examined the relationship between BD and atherosclerosis [12-47] ([Table 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8020102/table/table1-10760296211002914/)).

**Reporting and calculation of disease activity**

The studies varied in their disease activity scoring systems: twelve studies [24, 26, 28, 31, 35, 36, 40, 41, 42, 44-46] adopted the Behçet`s Disease Current Activity Form [48]; three studies [33, 42, 47] adopted the Behcet’s Syndrome Activity Score [49]; six studies adopted [16, 18, 19, 20, 21, 34] earlier scoring systems [50, 51]; thirteen studies calculated and reported disease activity [18, 20, 24, 26, 28, 30, 31, 33, 36, 40, 41, 44, 46], 5 studies included patients with variable degrees of disease activity without calculating it [21-23, 30, 34, 45, 47] and the remaining 12 studies never quoted disease activity.

**Varied characteristics of the studies**

One study did not report the male to female ratio [37] and four did not report the disease duration [12, 14, 23, 37]; vascular involvement was an exclusion criterion in seven studies [19, 21, 25, 30, 34, 37, 38] while it affected variable numbers of BD patients in the remaining studies; a history of cardiovascular disease (myocardial infarction, ischemic stroke) and chronic kidney disease was an exclusion criterion for twenty six studies [12,13, 15-20, 22, 24, 25, 27-30, 34-36, 38-40, 41, 43, 44, 46, 47], it was not in six studies [14, 21, 23, 31, 32, 37] and was not defined in the remaining studies; three studies differentiated muco-cutaneous disease from disease with major organ involvement [20, 30, 39] and one differentiated active versus inactive lesions [29] and we analysed the data from these four studies together. Steroid treatment was an exclusion criterion in eight studies [19, 28-31, 36, 38, 39], it was reported in fourteen studies [13, 19, 21, 23, 24, 26, 27, 33, 40, 41, 44-47] but not quoted in the remaining studies; only five studies reported plasma homocysteine [13, 17, 18, 22, 38, 41]. Smoking status was reported in sixteen studies [13-16, 18-20, 22, 23, 30, 33, 38, 41, 42-44], it was an exclusion criterion in seven studies [17, 25, 27, 28, 31, 34, 35] and it was not reported in the remaining studies. As one paper reported the atherogenic index of plasma [31] we calculated this parameter according to the formula “log (triglycerides/high density lipoprotein)” [30] for all the articles that contained the required variables and used it in our analyses. C-reactive protein (CRP) was reported in twenty-two studies, ten of which expressed the results in milligrams per litre [19-22, 29, 34, 38-40, 42, 43] that were transformed into milligrams per decilitre to harmonize the results for the sensitivity analysis (Table 1).

**Intima media thickness of carotid arteries in Behcet’s disease and normal controls**

Pooled data from 33 case-control studies comprised 1103 patients with BD and 832 controls: the effect size favoured BD (p<0.0001) with wide heterogeneity (I*2*=86.9%, p<0.0001) (Figure 2). A sensitivity analysis by meta-regression evaluated article quality, mean age of BD participants, male to female ratio, disease duration and activity, atherogenic index, diastolic and systolic blood pressure, C-reactive protein (CRP), colchicine, cyclosporin A and azathioprine as moderator variables: part of the heterogeneity variance was positively explained by gender and negatively by age and by azathioprine use (Table 2A). In the control group age and IMT were positively correlated (n=36, r=0.376, 95% CI 0.054 to 0.627, p=0.02), even more so after excluding participants younger than 35 years of age (n=28, r=0.589, 95% CI 0.277 to 0.789, p=0.001). A sensitivity analysis by subgroups assessing ethnicity (Mediterranean versus non-Mediterranean), disease activity, smoking status, vascular involvement and immune suppressive agents failed to explain any heterogeneity variance but for a slight effect of ethnicity (Table 2B).

**Prevalence of carotid plaques in Behcet’s disease**

Twelve studies investigated the presence of carotid plaques but one found plaques neither in BD nor in controls so the data from 11 case–control studies comprising 782 BD patients and 537 controls were pooled for this effect size: the prevalence of carotid plaques was higher in BD patients than in controls (13.1% vs 2.97%, p<0.0001) with no heterogeneity (Figure 3). Plaque prevalence was similar in male and females (13% vs 12.8%).

**Intima media thickness of carotid arteries in Bechet’s disease and disease controls**

Pooled data from four studies employing disease controls, one with systemic lupus erythematosus [13] and three rheumatoid arthritis [20, 21, 33] comprised 430 patients with BD and 266 with disease controls: the effect size favoured disease controls (p<0.0001) with no heterogeneity (Figure 4).

**Intima media thickness of carotid arteries by vascular involvement**

Six studies explored the relation between vascular involvement and IMT: these comprised 114 BD patients with vascular involvement and 214 patients without such involvement; the effect size favoured vascular involvement (p=0.006) with no heterogeneity (Figure 5).

**Intima media thickness of carotid arteries by systemic/mucocutaneous involvement**

Four studies compared IMT in patients with systemic versus mucocutaneous involvement: we pooled their data comprising 216 BD participants with systemic involvement and 117 with muco-cutaneous involvement: the effect size was neutral (p=0.74) with no heterogeneity (Figure 6).

**DISCUSSION**

**Intima media thickness and its explanatory variables in Behcet’s disease**

Our meta-analysis reveals that subclinical atherosclerosis of the carotid arteries is a vascular feature of BD, in that the effect size of IMT favoured BD, though offset by high heterogeneity that was extensively investigated: the traditional atherogenic risk factors such as blood pressure, lipid profile, smoking and inflammatory status (expressed as CRP) as well as a history of cardiovascular or cerebrovascular disease failed to explain any of the heterogeneity variance. That said, the studies included in the meta-analysis were carried out on BD patients too young to develop essential hypertension (52) and premature cardiovascular disease (53) and whose lipid profiles were mostly normal.

Instead, the meta-regression revealed an inverse correlation between age of BD participants and IMT: the risk of either venous or arterial thrombosis is higher in the early stages of BD [54] and decreases with immune suppressive treatment in subsequent years [55, 56]. Given that 64.5% of the studies included in the metanalysis investigated patients with a disease duration ranging between 5 and 10 years and 19.3% investigated patients with a disease duration greater than 10 years, it is possible that ongoing immune suppressive treatments attenuated or reduced the risk of atherosclerosis in later years from diagnosis. Indeed, the inverse and significant relation between azathioprine and IMT and the non-significant but inverse trends for disease duration, colchicine and cyclosporin A would be in keeping with these concepts.

The meta-regression also revealed an association between male gender and IMT: it is known that vascular disease is more likely to occur in male BD patients [57] and males are more at risk of carotid atherosclerosis in the general population [58]. Furthermore, pooled studies performed on BD patients outside the Mediterranean basin showed a slightly lower heterogeneity, suggesting that certain ethnic backgrounds with inherent dietary and lifestyle patterns [59-61] coupled with the genetic variability of atherosclerosis [62] may influence the IMT.

**Intima media thickness in subsets of Behcet’s disease**

 Of relevance, IMT was greater in BD with vascular disease than without, in agreement with the notion that venous thromboembolism may associate with atherosclerosis [63, 64] and its complications [65], notion indirectly confirmed by the observation that IMT was similar in studies comparing BD patients with muco-cutaneous and systemic manifestations (of which only 4 patients had a vessel involvement). On the other hand, IMT was lower in BD than in rheumatoid arthritis and systemic lupus erythematosus patients: this means that the atherogenic potential of an relapsing/remitting auto-inflammatory disease like BD is inferior to that of two chronic systemic inflammatory diseases, though the ages and the disease durations of the lupus and rheumatoid arthritis patients were greater than those of BD (13, 20, 21, 33). Anyhow, the strong effect size for carotid plaques suggests that atherosclerosis may develop in BD, though IMT progression and plaque formation/growth follow different biological pathways [66].

**Limitations of the study**

The current meta-analysis has several limitations: 1) all studies were cross-sectional and not prospective; 2) the lack of reporting disease activity and/or of the different disease activity scoring systems, as this would have given a better understanding of the relation between disease activity and IMT; 3) the lack of reporting number and length of inflammatory flares since diagnosis, as this would have better informed the relation with IMT; 4) owing to the involvement of plasma HC in BD [67], the relation with the IMT could not be adequately assessed as HC was reported in five studies only; 5) only four studies reported the use of anti-tumour necrosis factor agents [29, 40, 42, 46] precluding an appreciation of their effect on the IMT; 6) the inverse relation between azathioprine use and IMT derived from 19 studies, half of those included in the meta-analysis; 7) the use of an empirical graphical method to evaluate publication bias can be misleading [10,11] and inappropriate for observational studies [5].

**CONCLUSION**

**Relevant points**

The results of our meta-analysis indicate that: 1) subclinical atherosclerosis is a vascular feature of BD; 2) age (in an inverse fashion) and male gender relate to IMT; 3) azathioprine use associates with a lower IMT. This unreported observation is not unexpected: monocytes are involved in the pathogenesis of BD (68) and atherosclerosis (69) and 6-mercaptopurine (the pro-drug of azathioprine) induces monocyte apoptosis (70) whereas colchicine is believed to provide cardiovascular protection (71).

**Prospects for future research**

The hazard ratios for ischemic heart disease and mortality in BD are 3.09 and 1.40 respectively [72]: further research is required to identify other auto-inflammatory markers, possibly related to free radical overproduction [73], inflammasome activation [74] and inhibitory RNA modulation [75] that may be more relevant [76] to vascular damage in BD; equally, randomized clinical trials are needed to better define whether immune suppressive or anti-inflammatory agents (such as colchicine) may reduce the vascular risk of BD.

**Statements and Declarations**

None of the authors has any financial or non-financial competing interest to declare.

**REFERENCES**

1) Bettiol A, Alibaz-Oner F, Direskeneli H et al. Vascular Behçet syndrome: from pathogenesis to treatment. Nat Rev Rheumatol 2023; 19: 111-126

2) Seyahi E. Behçet's disease: How to diagnose and treat vascular involvement. Best Pract Res Clin Rheumatol 2016; 30: 279-295

3) Merashli M, Ster IC, Ames PRJ. Subclinical atherosclerosis in Behcet's disease: A systematic review and meta-analysis. Semin Arthritis Rheum 2016; 45: 502-510

4) Upala S, Yong WC, Sanguankeo A. Increased Arterial Stiffness in Behçet's Disease: A Systematic Review and Meta-Analysis. Korean Circ J 2017; 47: 477-482

5) Rethlefsen ML, Kirtley S, Waffenschmidt S et al; PRISMA-S Group. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021; 10: 39

6) Wells GA, Shea B, O’Connell D et al. Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available from: URL*: www.ohri.ca/programs/clinical\_epidemiology / oxford.htm*

7) Borenstein M, Hedges LV, Higgins JP, Rothstein HA. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010; 1: 97-111

8) Brockhaus AC, Grouven U, Bender R. Performance of the Peto odds ratio compared to the usual odds ratio estimator in the case of rare events. Biom J 2016; 58: 1428-1444

9) Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003; 327: 557-560

10) Tang JL, Liu JL. Misleading funnel plot for the detection of bias in meta-analysis. Clin Epidemiol 2000; 253: 477-484

11) Lau J, Ioannidis JPA, Terrin N et al. The case of the misleading funnel plot. BrMed J 2006; 333: 597-600

12) Sait A, Ulgen MS, Akdeniz S et al. Intima-media thickness and arterial distensibility in Behçet’s disease. Angiology 2004; 55: 413–419

13) Keser G, Aksu K, Tamsel S et al. Increased thickness of the carotid artery intima-media assessed by ultrasonography in Behçet’s disease. Clin Exp Rheumatol 2005; 23(4 Suppl. 38): S71–S76.

14) Oflaz H, Mercanoglu F, Karaman O et al. Impaired endothelium-dependent flow-mediated dilation in Behçet’s disease: more prominent endothelial dysfunction in patients with vascular involvement. Int J Clin Pract 2005; 59: 777

15) Oztürk MA, Oktar SO, Unverdi S et al. Morphologic evidence of subclinical atherosclerosis obtained by carotid ultrasonography in patients with Behcet’s disease. Rheumatol Int 2006;26: 867–872

16) Rhee MY, Chang HK, Kim SK. Intima-media thickness and arterial stiffness of carotid artery in Korean patients with Behçet’s disease. J Korean Med Sci 2007; 22: 387–392

17) Caliskan M, Gullu H, Yilmaz S et al. Cardiovascular prognostic value of vascular involvement in Behcet’s disease. Int J Cardiol 2008; 125: 428–430

18) Hong SN, Park JC, Yoon NS et al. Carotid artery intima-media thickness in Behcet’s disease patients without significant cardiovascular involvement. Korean J Intern Med 2008; 23: 87–89

19) Oztürk MA, Unverdi S, Oktar SO et al. Vascular endothelial growth factor and carotid intima-media thickness in patients with Behçet’s disease. Clin Rheumatol 2008; 27: 961–966

20) Seyahi E, Ugurlu S, Cumali R et al. Atherosclerosis in Behçet’s Syndrome. Semin Arthritis Rheum 2008; 38: 1–12.

21) Ozgen M, Koca SS, Dagli N et al. Serum adiponectin and vaspin levels in rheumatoid arthritis. Arch Med Res 2010; 41: 457–463.

22) Messedi M, Frigui M, Ben Mahfoudh K et al. Intima-media thickness of carotid artery in patients with Behçet’s disease. Arch Med Res 2011; 42: 398–404

23) Can M, Gunes M, Haliloglu OA et al. Effect of vitamin D deficiency and replacement on endothelial functions in Behçet’s disease. Clin Exp Rheumatol 2012; 30(3 Suppl. 72): S57–61.

24) Hassan S, Gheita T, Ghoneim S, Nasr L. Subclinical atherosclerosis in Behçet’s disease. Turk J Rheumatol 2012; 27: 109–114

25) Yurdakul S, Erdemir VA, Yıldırımtürk O, Gürel MS, Aytekin S. Evaluation of endothelial functions in patients with Behcet’s disease without overt vascular involvement. Turk Kardiyol Dern Ars 2012; 40: 518–522

26) Caldas CA, Borba EF, Bortolotto LA et al. Increased arterial stiffness assessed by pulse wave velocity in Behçet’s disease and its association with the lipid profile. J Eur Acad Dermatol Venereol 2013; 27: 454–459

27) Uyar B, Solak A, Genç B et al. Evaluation of Arterial Stiffness in Patients with Behçet's Disease by Using Noninvasive Radiological Methods such as Intima-Media Thickness of the Carotid, Ankle-Brachial Pressure Index, Coronary Artery Calcium Scoring, and Their Relation to Serum Fetuin-A Levels: A Case-Control Study. Ann Dermatol 2015; 27: 702-708

28) Icli A, Cure E, Cumhur Cure M et al. Novel myokine: irisin may be an independent predictor for subclinic atherosclerosis in Behçet's disease. J Investig Med 2016; 64: 875-881

29) Sereflican B, Kizildag B, Halicioglu S et al. Extra-medial thickness of carotid artery in patients with Behçet's disease: evaluation of atherosclerotic vessel wall changes with a novel carotid artery ultrasound index. Int J Dermatol 2016; 55: 1124-1130

30) Yıldırım A, Karakaş MS, Kılınç AY, Altekin RE, Yalçınkaya AS. Evaluation of arterial stiffness and subclinical atherosclerosis in patients with Behçet's disease without cardiovascular involvement. Turk Kardiyol Dern Ars 2016; 44: 575-581

31) Cure E, Icli A, Ugur Uslu A et al. Atherogenic index of plasma may be strong predictor of subclinical atherosclerosis in patients with Behçet disease. Z Rheumatol 2017; 76: 259-266

32) El-Gazzar I, El-Dakrony AH, Sayed S et al. Clinical significance of metabolic syndrome and carotid intima-media thickness in Behҫet’s disease patients: Relation to disease activity. Egypt Rheumatol 2017; 39: 171-174

33) Yolbaş S, Gözel N, Dağlı MN, Koca SS, Dönder E. Carotid artery stiffness in Behçet's disease. Eur J Rheumatol 2017; 4: 122-126

34) Alis D, Durmaz ESM, Civcik C et al. Assessment of the common carotid artery wall stiffness by Shear Wave Elastography in Behcet's disease. Med Ultrason 2018; 20: 446-452

35) Elden MS, Hmmad G, Farouk H, Fawzy RM, Abdelwhaba B*.* Neutrophil-to-lymphocyte ratio: relation to disease activity and carotid intima-media thickness in Behçet’s disease. Egypt Rheumatol Rehabil 2018; **45:** 133–139

36) Icli A, Cure MC, Cure E et al. Soluble Tumor Necrosis Factor (TNF)-Like Weak Inducer of Apoptosis (Tweak) Independently Predicts Subclinical Atherosclerosis in Behcet's Disease. Acta Medica 2018; 61: 86-92

37) Kankilic N, Aslan A, Karahan O et al. Investigation of the arterial intima-media thickness in Behcet's disease patients without vascular complaints. Vascular 2018; 26: 356-361

38) Ozdemir R, Yagmur J, Acikgoz N et al. Relationship between serum homocysteine levels and structural-functional carotid arterial abnormalities in inactive Behçet's disease. Kardiol Pol 2018; 76: 413-417

39) Ozisler C, Kaplanoglu H. Evaluation of subclinical atherosclerosis by ultrasound radiofrequency data technology in patients with Behçet's disease. Int J Rheum Dis 2019; 22: 781-788

40) Hassan WA, Behiry EG, Abdelshafy S, Salem T, Baraka EA. Assessment of Endocan Serum Level in Patients with Behçet Disease: Relation to Disease Activity and Carotid Intima Media Thickness. Egypt J Immunol 2020; 27: 129-139

41) El-Najjar AR, Alsammak AA. Association between serum homocysteine and arterial stiffness in patients with Behçet’s disease. Egypt Rheumatol 2020; 42: 129-133

42) Kaymaz S, Yılmaz H, Ufuk F et al. Ultrasonographic measurement of the vascular wall thickness and intima-media thickness in patients with Behçet’s disease with symptoms or signs of vascular involvement: A cross-sectional study. Arch Rheumatol 2021; 36: 258-266

43) Uslu Yurteri E, Üstüner E, Torgutalp M et al. Can Subclinical Atherosclerosis Be Assessed More Precisely in Behçet Syndrome Patients by Using a Particular Cutoff Value for Carotid Intima Media Thickness? J Clin Rheumatol 2021 Jul 28.

44) Rodrigues FM, Bacchiega AB, Bacchiega BC et al. Evaluation of endothelial function in patients with Behçet's disease in remission: A cross-sectional study. Eur J Rheumatol 2022; 9: 139-143.

45) Hussein MA, Ramadan MM, Moneam MAE, Halim HAE, Ghaffar NAE, Fawzy MW. Interleukin 37; a possible marker of arterial stiffness in Behçet's disease. Am J Med Sc 2022; 364: 425-432

46) Aydogan Baykara R, Yilmaz PD, Göktepe MH, Kadiyoran C, Ogul M, Kucuk A et al. Proprotein convertase subtilisin/kexin type 9 is associated with atherosclerosis in patients with Behcet's disease. Clin Exp Hypertens 2022; 44: 480-486

47) Ismail MA, Mounir O, Sedky A, Algahlan HA, Abda EA, Radwan AR et al. Exists a role for serum irisin in Egyptian Behcet's patients with subclinical atherosclerosis? Clin Rheumatol. 2022 Sep 16. doi: 10.1007/s10067-022-06368-9. Epub ahead of print. PMID: 36112245.

48) Bhakta BB, Brennan P, James TE, et al. Behcet’s disease: evaluation of a new instrument to measure clinical activity. Rheumatology (Oxford) 1999; 38:728–733

49) Forbees C, Swearingen C, Yazici Y. Behcet’s syndrome activity score (BSAS): a new disease activity assessment tool, composed of patient-derived measures only, is strongly correlated with the Behcet’s Disease Current Activity Form (BDCAF) Arthritis Rheum2008; 58(Suppl 9): S854–S855

50) Chang HK, Cheon KS. The clinical significance of a pathergy reaction in patients with Behcet’s disease. J Korean Med Sci 2002; 17: 371–374.

51) Krause I, Molad Y, Mitrani M, Weinberger A. Pathergy reaction in Behcet’s disease: lack of correlation with mucocutaneous manifestations and systemic disease expression. Clin Exp Rheumatol 2000; 18: 71-74

52) Suvila K, Langén V, Cheng S, Niiranen TJ. Age of Hypertension Onset: Overview of Research and How to Apply in Practice. Curr Hypertens Rep 2020; 22: 68

53) Sharifi M, Futema M, Nair D, Humphries SE. Polygenic Hypercholesterolemia and Cardiovascular Disease Risk. Curr Cardiol Rep 2019; 21: 43

54) Toledo-Samaniego N, Oblitas CM, Peñaloza-Martínez E et al. Arterial and venous involvement in Behçet's syndrome: a narrative review. J Thromb Thrombolysis 2022; 54: 162-171

55) Desbois AC, Wechsler B, Resche-Rigon M et al. Immunosuppressants reduce venous thrombosis relapse in Behçet’s disease. Arthritis Rheum 2012; 64: 2753-60.

56) Saadoun D, Asli B, Wechsler B et al. Long-term outcome of arterial lesions in Behçet disease: a series of 101 patients. Medicine 2012; 91: 18-24

57) Torgutalp M, Sahin Eroglu D, Sezer S, Yayla ME, Karatas G, Uslu Yurteri E et al. Analysis of vascular involvement in 460 patients with Behçet's syndrome: Clinical characteristics and associated factors. Joint Bone Spine 2022; 89: 105277

58) Gasbarrino K, Di Iorio D, Daskalopoulou SS. Importance of sex and gender in ischaemic stroke and carotid atherosclerotic disease. Eur Heart J 2022; 43: 460-473

59) Savey L, Resche-Rigon M, Wechsler B et al. Ethnicity and association with disease manifestations and mortality in Behçet's disease. Orphanet J Rare Dis 2014; 9:42

60) Rozenbaum M, Boulman N, Slobodin G et al. Behcet disease in adult Druzes in north Israel: the influence of ethnic origin on disease expression and severity. J Clin Rheumatol 2007; 13: 124–127

61) Seyahi E. Phenotypes in Behçet's syndrome. Intern Emerg Med 2019; 14: 677-689

62) Tada H, Takamura M, Kawashiri MA. What is the mechanism of genetic contributions to the development of atherosclerosis? Atherosclerosis 2020; 307: 72-74

63) Prandoni P, Bilora F, Marchiori A et al. An association between atherosclerosis and venous thrombosis. N Engl J Med 2003; 348: 1435–1441

64) Jezovnik MK, Fareed J, Poredos P. Subjects with a history of idiopathic deep venous thrombosis have long-term increased levels of inflammatory markers and markers of endothelial damage. Clin Appl Thromb Hemost 2017; 23: 124–131

65) Kaptoge S, Di Angelantonio E, Lowe G et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010; 375: 132–140.

66) Migdalski A, Jawien A. New insight into biology, molecular diagnostics and treatment options of unstable carotid atherosclerotic plaque: a narrative review. Ann Transl Med 2021; 9: 1207

67) Merashli M, Bucci T, Pastori D et al. Plasma Homocysteine in Behcet's Disease: A Systematic Review and Meta-Analysis. Thromb Haemost 2022 Jan 7. doi: 10.1055/s-0041-1740637. Epub ahead of print. PMID: 34996122.

68) Wu X, Wang Z, Shi J, Yu X, Li C, Liu J, Zhang F, Chen H, Zheng W. Macrophage polarization toward M1 phenotype through NF-κB signaling in patients with Behçet's disease. Arthritis Res Ther 2022; 24: 249.

69) Susser LI, Rayner KJ. Through the layers: how macrophages drive atherosclerosis across the vessel wall. J Clin Invest 2022; 132: e157011

70) Pols TW, Bonta PI, Pires NM, Otermin I, Vos M, de Vries MR et al. 6-mercaptopurine inhibits atherosclerosis in apolipoprotein e\*3-leiden transgenic mice through atheroprotective actions on monocytes and macrophages. Arterioscler Thromb Vasc Biol 2010; 30: 1591-1597

71) Casula M, Andreis A, Avondo S, Vaira MP, Imazio M. Colchicine for cardiovascular medicine: a systematic review and meta-analysis. Future Cardiol 2022; 18: 647-659.

72) 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 2020; 59: 2785-2795

73) Emmi G, Becatti M, Bettiol A et al. Behçet's syndrome as a model of thrombo-inflammation: the role of neutrophils. Front Immunol 2019; 10: 1085

74) Kim, E.H., Park, MJ., Park, S. et al. Increased expression of the NLRP3 inflammasome components in patients with Behçet’s disease. J Inflamm 2015; **12:** 41

75) Emmi G, Bagni G, Lastraioli E, Di Patti F, Bettiol A, Fiorillo C, Becatti M, Silvestri E, Urban ML, Emmi L, Prisco D, Arcangeli A. A unique circulating miRNA profile highlights thrombo-inflammation in Behçet's syndrome. Ann Rheum Dis 2022; 81: 386-397

76) Chekaoui A, Lahmar K, Belguendouz H et al. Increased IL-1β levels are associated with an imbalance of "oxidant/antioxidant" status during Behçet's disease. Eur Cytokine Netw 2018; 29: 95-102

**Legend to figures**

Figure 1. flowchart indicating the screening and exclusion of articles up to final inclusion in

qualitative and quantitative analysis

Figure 2: forest plot of studies comparing intima media thickness in Behcet’s disease and controls.

Figure 3: forest plot of studies comparing the pooled prevalence of carotid plaques in Behcet’s disease and controls

Figure 4: forest plot of studies comparing intima media thickness in Bechet’s disease and disease controls

Figure 5: forest plot of studies comparing intima media thickness in vascular versus non-vascular Behcet’s disease

Figure 6: forest plot of studies comparing intima media thickness in muco-cutaneous versus systemic Behcet’s disease

Table 1. Demographics, clinical and laboratory variables of control and Behcet’s disease participants

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref** | **Author** |  | **CTR** | **M/F** | **Age** | **IMT** | **BD** | **M/F** | **Age** | **IMT** | **DD** | **DA** | **CRP** | **NOS** |
| **No** | **Year**  |  | **No** |  | **years** | **mm** | **No** |  | **years** | **mm** | **years** |  | **mg/dl** |  |
|  |  | **Country** |  |  | ***x̅* ± *σ*** | ***x̅ ± σ*** |  |  | ***x̅ ± σ*** | ***x̅ ± σ*** | ***x̅ ± σ*** | ***x̅ ± σ*** | ***x̅ ± σ*** |  |
| 11 | Sait, 2004 | Turkey | 42 | 25/17 | 40±9 | 0.59±0.12 | 40 | 19/21 | 39.8±8 | 0.81±0.12 |  |  |  | 5 |
| 12 | Keser, 2005 | Turkey | 77 | 46/31 | 37±7.8 | 0.48±0.09 | 114 | 68/46 | 38±9.4 | 0.55±0.14 | 10±6.58 |  | 1.1 ± 2.0 | 6 |
| 13 | Oflaz, 2005 | Turkey | 46 | 37/9 | 36±9.3 | 0.55±0.14 | 50 | 41/9 | 38±9.3 | 0.69±0.15 |  |  |  | 6 |
| 14 | Ozturk 2006 | Turkey | 34 | 21/13 | 34±8.5 | 0.54±0.13 | 34 | 21/13 | 34±8.5 | 0.81±0.17 | 0.57±0.43 | 5.8±2.0. | 27.4±50 | 5 |
| 15 | Rhee, 2007 | Korea | 53 | 26/27 | 37±7.2 | 0.52±0.06 | 41 | 20/21 | 37±7.9 | 0.52±0.09 | 6.5±0.6 |  |  | 6 |
| 16 | Caliskan, 2008 | Turkey | 35 | 19/16 | 38±7.9 | 0.46±0.18 | 53 | 24/29 | 36±.3 | 0.51±0.01 | 4.13±4.5 |  | 3.91±5.1 | 4 |
| 17 | Hong, 2008 | Korea | 20 | 13/7 | 40±5.1 | 0.59±0.11 | 40 | 24/16 | 39±8.5 | 0.71±0.17 | 5.2±4 | 1.3±1.3 | 0.5±0.5 | 6 |
| 18 | Ozturk, 2008 | Turkey | 21 | 15/6 | 35±8 | 0.57±0.14 | 21 | 15/6 | 35±8.6 | 0.86±0.18 | 7.3±5.8 |  | 1.07±1.3 | 5 |
| 19 | Seyahi, 2008 | Turkey | 156 | 83/73 | 39±6.6 | 0.68±0.08 | 239 | 162/77 | 40±8.7 | 0.71±0.09 | 12 | 8.1± 4.0 | 3.4±4.0 | 7 |
| 20 | Ozgen, 2010 | Turkey | 29 | 6/23 | 38±10 | 0.54±0.04 | 37 | 18/19 | 35±10 | 0.67±0.07 | 3.9±4.7 |  | 2.8 ±3.6 | 5 |
| 21 | Messedi, 2011 | Tunisia | 50 | 35/15 | 46±7 | 0.58±0.08 | 50 | 35/15 | 48±6 | 0.65±0.11 | 12.8±8.7 |  | 0.22±0.1 | 6 |
| 22 | Can 2012 | Turkey | 51 | 23/28 | 34±7.2 | 0.39±.09 | 36 | 14/22 | 39±6.4 | 0.56±0.12 |  |  |  | 4 |
| 23 | Hassan, 2012 | Egypt | 20 | 10/10 | 34±4.2 | 0.4±0.1 | 30 | 25/5 | 35±8.7 | 0.72±0.04 | 8.7±5.9 | 2.2±1.5 |  | 5 |
| 24 | Yurdakul, 2012 | Turkey | 20 | 12/8 | 45±8.2 | 0.59±0.09 | 40 | 24/16 | 44±5.4 | 0.69±0.15 | 5.9 |  |  | 6 |
| 25 | Caldas, 2013 | Brazil | 23 | 11/12 | 35±4.6 | 0.56±0.13 | 23 | 11/12 | 35±7.6 | 0.59±0.13 | 8.9±5.6 | 5.7±5.5 | 7.5 ± 12 | 6 |
| 26 | Uyar 2015 | Turkey | 25 | 12/13 | 32±9.2 | 0.6±0.16 | 26 | 12/14 | 35±9 | 1.02±0.3 | 7±5 |  | 0.65 ±4.2 | 8 |
| 27 | Icli 2016 | Turkey | 50 | 29/21 | 36±12 | 0.41±0.23 | 48 | 31/17 | 36±11.5 | 0.68±0.26 | 7.8±6.2 | 3.5±1.7 | 12.1±12.2 | 6 |
| 28 | Sereflican 2016 | Turkey | 26 | 5/21 | 31±5.3 | 0.56±0.11 | 31 | 12/19 | 35±9 | 0.48±0.08 | 8.1±6.7 | 1.3±1.4 | 1.24±1.8 | 6 |
| 29 | Yildirim 2016 | Turkey | 30 | 18/12 | 37±12 | 0.62±0.06 | 30 | 17/13 | 39±12.3 | 0.64±0.07 | 9.2±9.4  |  |  | 8 |
| 30 | Cure 2017 | Turkey | 84 | 58/26 | 36±9.5 | 0.48±0.11 | 84 | 60/24 | 37±10.5 | 0.61±0.14 | 12.5±9.8 | 4±2.3 | 5.7 ± 8.5 | 6 |
| 31 | El-Gazzar 2017 | Egypt | 38 | 30/8 | 35±6.5 | 0.42±0.12 | 38 | 30/8 | 36±7.8 | 0.78±0.32 | 7.6±5.1 | 2.5 ± 1.4 |  | 7 |
| 32 | Yolbas 2017 | Turkey | 40 | 29/11 | 43±13 | 0.64±0.08 | 49 | 28/21 | 37±11 | 0.62±0.09 | 7.0±6.0 | 14.8±17.2 | 1.37±2.2 | 5 |
| 33 | Alis 2018 | Turkey | 28 | 15/13 | 36±8.2 | 0.41±0.07 | 34 | 18/16 | 40±10 | 0.5±0.12 | 9.2±9.8 |  | 0.93±0.2 | 6 |
| 34 | Elden 2018 | Egypt | 20 | 15/5 | 36±9.4 | 0.47±0.04 | 20 | 17/3 | 32±9.9 | 0.64±0.03 | 9.6 ±6.0 | 3.8±1.55 | 1.35±1.7 | 5 |
| 35 | Icli 2018 | Turkey | 30 | 24/6 | 38±12 | 0.43±0.09 | 48 | 32/16 | 37±11.2 | 0.62±0.13 | 8±6.3 | 2.75±2 | 3.9 ± 4.3 | 6 |
| 36 | Kancilic 2018 | Turkey | 16 |  | 39±7.7 | 0.47±0.11 | 24 |  | 38±11 | 0.49±0.16 |  |  |  | 5 |
| 37 | Ozdemir 2018 | Turkey | 40 | 25/15 | 41±8 | 0.59±0.1 | 68 | 42/26 | 42.1±9 | 0.7±0.07 | 11.8±3.9 |  | 0.77 ± 0.2 | 7 |
| 38 | Ozisler 2019 | Turkey | 33 | 14/19 | 40±8 | 0.52±0.11 | 33 | 14/19 | 40±8.8 | 0.52±0.10 | 11.3 ± 6.5 |  | 0.42 ± 0.3 | 6 |
| 39 | Hassan 2020 | Egypt | 42 | 23/19 | 37±8 | 0.64±0.17 | 42 | 25/17 | 35±7.8 | 0.85±0.3 | 3.5±1.18 | 2.7±0.6 | 2.6±0.7 | 6 |
| 40 | El-Najjari 2020 | Egypt | 50 | 32/18 | 32±8 | 0.57±0.32 | 50 | 37/13 | 35±8.5 | 0.75±0.71 | 6.8±3.8 | 2.37±1.5 |  | 0.19 |
| 41 | Kaymaz 2021 | Turkey | 30 | 14/16 | 40±11 | 0.47±0.07 | 63 | 41/22 | 41±14 | 0.56±0.11 | 9 ± 4.4 | 1.7±1.07 |  | 8 |
| 42 | Uslu-Y 2021 | Turkey | 30 | 12/18 | 41±12 | 0.69±0.13 | 100 | 38/62 | 46±12 | 0.78±0.21 |  |  | 0.70±1.4 | 5 |
| 43 | Rodrigues 2022 | Brasil | 12 | 3/9 | 50±8 | 0.74±0.08 | 12 | 5/7 | 46±5.9 | 0.73±0.10 | 15±4.4 |  | 5.15±4.4 | 6 |
| 44 | Hussein 2022 | Egypt | 30 | 23/30 | 31±11  | 0.6±0.1 | 40 | 35/5 | 30.9±9.2 | 0.8±0.1 | 5.35 ±4.8 |  | 0.05±0.22 | 5 |
| 45 | Baykara 2022 | Turkey | 58 | 30/28 | 37± 6 | 0.41±0.1 | 58 | 32/26 | 40±10 | 0.51±0.1 | 10.3±8.03 | 3.5±1.7 | 12.5±11.9 | 7 |
| 46 | Ismail 2022 | Egypt | 50 | 38/12 | 29±5 | 0.56±0.25 | 50 | 38/12 | 30±6 | 0.80±0.29 | 2.32±1.1 | 5.8±1.7 |  | 5 |

Abbreviations. Ref: reference CTR: control; M/F male/female; IMT: intima media thickness; BD: Behcet’s disease; DD: disease duration; DA: disease activity; CRP: C-reactive protein; NOS: Newcastle Ottawa Score; No: number; mm: millimetre; x̅ ± σ: mean±standard deviation.

Table 2. Sensitivity analysis in the Behcet’s disease/control comparison

|  |
| --- |
| 1. **Sensitivity analysis by meta-regression**
 |
|  |  |  |  |  |
|  | **Studies No** | **CC** | **95% CI** | **p-value** |
|  |  |  |  |  |
| NOQAS | 36 | -0.168 | -0.394, 0.058 | 0.14 |
|  |  |  |  |  |
| Mean age of BD  | 36 | -0.077 | -0.130, -0.023 | 0.004 |
|  |  |  |  |  |
| Male/female ratio | 35 | 0.198 | 0.041, 0.355 | 0.01 |
|  |  |  |  |  |
| Disease duration | 27 | -0.056 | -0.146, 0.034 | 0.22 |
|  |  |  |  |  |
| Disease activity | 17 | -0.053 | -0.121, 0.013 | 0.19 |
|  |  |  |  |  |
| Atherogenic index | 23 | -0.086 | -2.512, 2.343 | 0.94 |
|  |  |  |  |  |
| Diastolic blood pressure | 22 | -0.005 | -0.074, 0.063 | 0.87 |
|  |  |  |  |  |
| Systolic blood pressure  | 22 | 0.006 | -0.031, 0.044 | 0.74 |
|  |  |  |  |  |
| C-reactive protein | 23 | 0.024 | -0.023, 0.073 | 0.33 |
|  |  |  |  |  |
| Colchicine | 20 | -0.030 | -0.069, 0.086 | 0.12 |
|  |  |  |  |  |
| Cyclosporin A | 19 | -0.969 | -2.364, 0.895 | 0.33 |
|  |  |  |  |  |
| Azathioprine | 19 | -0.547 | -0.984, -0.110 | 0.01 |
| Azathioprine (minus outlier) | 18 | -1.176 | -2.049, -0.304 | 0.008 |
|  |  |  |  |  |
| 1. **Sensitivity analysis by subgroups**
 |
|  |  |  |  |
|  | **Studies**  | **Heterogeneity** | **Effect size** |
|  |  |  |  |  |
| **By ethnicity** | **No** | **%** | **p-value** | **p-value** |
| Turkey + Egypt +Tunisia | 31 | 87.7 | <0.0001 | <0.0001 |
| Brazil + Korea | 5 | 64.2 | 0.02 | 0.07 |
|  |  |  |  |  |
| **By disease activity** |  |  |  |  |
| Reported | 17 | 87.8 | <0.0001 | <0.0001 |
| Not Reported | 19 | 87.7 | <0.0001 | <0.0001 |
|  |  |  |  |  |
| **By smoking status** |  |  |  |  |
| Reported | 16 | 83.2 | <0.0001 | <0.0001 |
| Excluded | 7 | 76.7 | 0.001 | <0.0001 |
| Not reported | 13 | 82.1 | <0.0001 | <0.0001 |
|  |  |  |  |  |
| **By vascular involvement** |  |  |  |  |
| Reported | 28 | 85.3 | <0.0001 | <0.0001 |
| Not reported | 8 | 86.6 | <0.0001 | <0.0001 |
|  |  |  |  |  |
| **By MI, IS, CKD** |  |  |  |  |
| Reported | 8 | 92.0 | <0.0001 | <0.0001 |
| Excluded | 26 | 84.1 | <0.0001 | <0.0001 |
| Not reported | 2 | 33.4 | 0.2 | <0.0001 |
|  |  |  |  |  |
| **By steroid intake** |  |  |  |  |
| Reported | 14 | 89.5 | <0.0001 | <0.0001 |
| Excluded | 8 | 84.7 | <0.0001 | <0.0001 |
| Not reported | 14 | 81.1 |  0.0001 | <0.0001 |
|  |  |  |  |  |
| **By any immune suppression\*** |  |  |  |  |
| Reported | 20 | 86.3 | <0.0001 | <0.0001 |
| Not reported | 16 | 87.8 | <0.0001 | <0.0001 |
|  |  |  |  |  |

Abbreviations. C: correlation coefficient; CI: confidence interval; BD: Behcet’s disease; NOQAS: Newcastle Ottawa Quality Assessment Score; MI: myocardial infarction; IS: ischaemic stroke; CKD: chronic kidney disease;

\*includes colchicine, cyclosporin A, azathioprine and anti-tumor necrosis factor-α

**Identification of new studies via other methods**

**Identification of new studies via databases and registers**

**Previous studies**

Records identified from:

Websites n = 3

Organisations n = 0

Citation searching n = 2

Records removed *before screening*: 0

Duplicate records removed n=10

Records marked as ineligible by automation tools n = 0

Records removed for other reasons n = 0

Records identified from databases:

Medline n=12

Embase n=26

Registers n=0

Studies included in previous version of review n =15

Reports of studies included in previous version of review n = 0

**Identification**

Records excluded by a human n=1

Records screened n=28

Reports not retrieved

n = 0

Reports sought for retrieval

n = 5

Reports not retrieved n=0

Reports sought for retrieval n=27

**Screening**

Reports excluded:

Paper without extractable data n=1

Abstracts incomplete data n=6

Paper on femoral arteries n=1

Paper on paediatric Behcet’s n=1

Review paper n=1

Reports excluded:

Prevalence data n = 1

Reports assessed for eligibility n = 4

Reports assessed for eligibility n=27

New studies included in review

n = 17

**Included**

Figure 1

Total studies included in review

n = 36



Figure 2



Figure 3



Figure 4



Figure 5



Figure 6