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Original Article

Circulating VEGF levels and genetic polymorphisms in Behçet's disease: a meta-analysis

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Objective: This study aimed to explore the relationship between circulating vascular endothelial growth factor (VEGF) levels and Behçet's disease (BD), as well as to examine the association between VEGF gene polymorphisms and BD.

Methods: We conducted a comprehensive search of the MEDLINE, Embase, and Web of Science databases to identify relevant research articles. A meta-analysis was performed to compare serum or plasma VEGF levels in BD patients with those in control groups. Additionally, we evaluated the potential associations between BD susceptibility and specific VEGF polymorphisms, namely –634 C/G, +936 C/T, and the 18 bp insertion/deletion (I/D) at –2549.

Results: The analysis included 15 studies with a total of 1,020 BD patients and 1,031 controls. BD patients exhibited significantly higher circulating VEGF levels compared to controls (standardized mean difference [SMD]=1.726, 95% confidence interval [CI]=1.030~2.421, p<0.001). Elevated VEGF levels were noted among BD patients from European and Arab populations. Subgroup analysis further confirmed the increase in VEGF levels across different data types and sample sizes. Patients with active BD had higher VEGF levels than those with inactive BD (SMD=0.635, 95% CI=0.092~1.177, p=0.022). However, no significant association was found between BD and the VEGF –634 C allele (odds ratio=1.023, 95% CI=0.707~1.481, p=0.904). Similarly, no association was detected between BD and the VEGF +936 C/T or 18 bp I/D at –2549 polymorphisms.

Conclusion: Our meta-analysis showed a strong association between elevated circulating VEGF levels and BD. However, the VEGF polymorphisms examined in this study do not appear to be associated with susceptibility to BD.

Keywords: Behçet's disease, Vascular endothelial growth factor, Polymorphism, Meta-analysis

INTRODUCTION

Behçet's disease (BD) is a complex, multisystem disorder marked by a wide range of clinical symptoms, including recurrent oral and genital ulcers, uveitis, skin lesions, and vascular complications [1]. Although substantial progress has been achieved in understanding its clinical characteristics and diagnostic criteria, the exact pathogenic mechanisms are still not well understood.

A key factor in BD pathogenesis is its association with vascular dysfunction, which frequently results in vascular lesions and thrombosis. Recent studies indicate that vascular endothelial growth factor (VEGF), a powerful angiogenic factor, plays a crucial role in BD's pathophysiology [2]. VEGF is vital for angiogenesis and vascular permeability, making it a central regulator of blood vessel formation and maintenance [3,4]. This led to growing interest in exploring the relationship between VEGF levels and VEGF gene polymorphisms in BD, as these may shed light on the disease's etiology and progression.

Previous researches have shown elevated VEGF levels in BD patients, but the consistency and extent of this association across different populations and disease stages remain debated [5-19].

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Additionally, the genetic basis of BD susceptibility is complex and involves multiple factors, with several immune-related genes implicated in its development. Among these, VEGF gene polymorphisms have been studied for their potential link to BD susceptibility, though findings have been inconsistent. This meta-analysis sought to consolidate existing evidence on the association between circulating VEGF levels and BD, while also investigating the potential connection between VEGF gene polymorphisms and BD susceptibility. The aim of our meta-analysis was to systematically examine the existing evidence on serum/plasma VEGF levels in patients with BD compared to controls, and to explore the relationship between VEGF polymorphism and the susceptibility to BD.

MATERIALS AND METHODS

Study selection and data retrieval

We conducted a comprehensive literature search to identify studies that examined VEGF levels in the circulation (serum or plasma) of patients with BD compared to healthy controls, as well as studies exploring the association between VEGF gene polymorphisms and BD. The search covered the MEDLINE, Embase, and Cochrane databases and included articles from the inception of these databases up to July 2024. Our search strategy involved keywords such as "vascular endothelial growth factor" "serum OR plasma OR circulating," "polymorphism," and "Behçet's disease." Additionally, we reviewed the references in the identified articles to find any relevant studies that may not have been captured in the database search. Eligible studies met the following criteria: (1) case-control, cohort, or cross-sectional design; (2) provided data on circulating VEGF levels in both BD patients and control groups; and (3) examined VEGF gene polymorphisms in both BD and control groups. Studies were excluded if they had overlapping or insufficient data, or if they were review articles or case reports. Two independent reviewers extracted information on the methods and results from the original studies, resolving any discrepancies by consensus. Extracted data included details such as the primary author, year of publication, country, ethnicity, adjustments for age and sex, number of participants, mean and standard deviation (SD) of VEGF levels, and allele and genotype frequencies of VEGF gene polymorphisms. Data were reported as mean and SD, or as median and interquartile range, using established formulae [20,21]. The definitions of active versus inactive BD varied across the studies: Arica et al. [6]: Patients with at least one mucocutaneous lesion or active organ involvement were classified as having "active disease," while those without any mucocutaneous lesions or systemic complaints at the time of blood collection were defined as having "inactive disease." Gheita et al. [7]: Active disease was defined as a Behçet's Disease Current Activity Form score of 2 or higher. Yalçındağ et al. [11]: Ocular involvement was considered an indication of active disease. Ibrahim et al. [12]: Patients with at least two of the following were classified as having active disease: aphthous stomatitis, genital ulceration, positive pathergy test, skin lesions, anterior iridocyclitis, panuveitis or posterior vasculitis, arthritis, vascular lesions, or manifestations affecting the pulmonary or central nervous systems. Kamoun et al. [14]: Ocular involvement was considered an indicator of active disease. Shaker et al. [15]: Active disease was defined by the presence of three out of five major findings on admission (skin lesions, positive pathergy test, uveitis, oral ulcers, and genital ulcers). Patients without any clinical or laboratory signs of BD for at least 1 month were classified as having inactive disease. Cekmen et al. [17]: The presence of three out of five major findings on admission (skin lesions, positive pathergy test, uveitis, oral aphthae, and genital ulcers) was considered to indicate active disease. The quality of each study was assessed using the Newcastle-Ottawa Scale [22]. The meta-analysis was conducted following the PRISMA guidelines [23].

Statistical analysis

We performed a meta-analysis to examine the relationship between VEGF levels and BD, as well as to assess the impact of minor alleles versus major alleles in various VEGF gene polymorphisms. Results were expressed as standardized mean differences (SMDs) with 95% confidence intervals (CIs) for continuous data, and odds ratios (ORs) with 95% CIs for dichotomous data. Cochran's Q test was used to assess within-study and between-study variations and to evaluate heterogeneity. A heterogeneity test determined whether the studies were evaluating the same effect. If the Q-statistic was significant ($p<0.10$), indicating heterogeneity, a random-effects model was applied; otherwise, a fixed-effects model was used, assuming all studies estimated the same underlying effect and considering within-study variations [24]. Heterogeneity was quantified using I^2, which measures inconsistency between studies, with I^2 values indicating low, moderate, or high levels of variation [25]. Statistical analyses were conducted using the Comprehensive Meta-

Analysis Program (BioStat, Englewood, NJ, USA).

Assessment of heterogeneity, sensitivity analysis, and publication bias

To identify potential sources of heterogeneity observed in the meta-analysis, we conducted a meta-regression analysis considering variables such as ethnicity, adjustments for age and/or sex, publication year, sample size, and data type. Sensitivity analysis was performed by systematically omitting each study to assess its influence on the overall effect size. Unlike funnel plots, which can be subjective and require studies of various types and sample sizes, Egger's linear regression test was used to assess publication bias, detecting funnel plot asymmetry by using a natural logarithm of the effect size [26].

RESULTS

Inclusion of studies in the meta-analysis

We identified a total of 128 studies through electronic and manual searches. Out of these, 19 were selected for a thorough review based on their titles and abstracts. Four studies were excluded due to either insufficient data or duplicate information. Consequently, 15 studies met the inclusion criteria which included data from 885 patients with BD and 875 control subjects (Tables 1, 2, and Figure 1) [5-19]. Two of these studies provided data on both VEGF levels and the VEGF gene polymorphisms of interest [5,14] and another two studies provided only data on the VEGF gene polymorphisms [18,19]. Thus, 13 investigated VEGF levels in both the affected and control groups, while four focused on VEGF gene polymorphisms in both BD and

Table 1. Circulating VEGF level analyzed in the meta-analysis

Author	Country	Ethnicity	Case (n)	Control (n)	SMD	Magnitude*	p-value
Sertoglu et al. [5]	Turkey	European	55	30	0.479	Small	0.037
Arica et al. [6]	Turkey	European	45	28	0.636	Medium	0.010
Gheita et al. [7]	Egypt	Arab	59	60	0.044	Small	0.811
Kul et al. [8]	Turkey	European	40	40	1.224	Large	<0.001
Eldin et al. [9]	Egypt	Arab	30	20	2.187	Large	<0.001
Ganeb et al. [10]	Egypt	Arab	70	70	3.708	Large	<0.001
Yalçındağ et al. [11]	Turkey	European	65	21	0.360	Small	0.154
Ibrahim et al. [12]	Egypt	Arab	40	40	3.117	Large	<0.001
Oztürk et al. [13]	Turkey	European	21	21	1.064	Large	0.001
Kamoun et al. [14]	Tunisia	Arab	135	157	2.582	Large	<0.001
Shaker et al. [15]	Egypt	Arab	30	15	4.156	Large	<0.001
Erdem et al. [16]	Turkey	European	33	20	1.076	Large	<0.001
Cekmen et al. [17]	Turkey	European	39	15	2.196	Large	<0.001

VEGF: vascular endothelial growth factor, SMD: standardized mean difference. *Magnitude of Cohen's d effect size: 0.2~0.5, small effect; 0.5~0.8, medium effect; and ≥0.8, large effect.

Table 2. VEGF polymorphisms analyzed in the meta-analysis

Author	Country	Ethnicity	Case (n)	Control (n)	VEGF polymorphism tested	Statistical findings (p-value)
Sertoglu et al. [5]	Turkey	European	55	30	VEGF −634 C/G, +936 C/T, −2758 A/C	NS
Kamoun et al. [14]	Tunisia	Arab	135	157	VEGF −634 C/G, +936 C/T, 18 bp I/D at −2549	NS
Nam et al. [19]	Korea	Asian	101	138	VEGF −634 C/G, +936 C/T	NS
Salvarani et al. [18]	Italy	European	122	200	VEGF −634 C/G, +936 C/T, 18 bp I/D at −2549	−634 C/G (p=0.020), +936 C/T (NS) and −2549 I/D (p=0.016)

VEGF: vascular endothelial growth factor, I/D: insertion/deletion, NS: not significant.

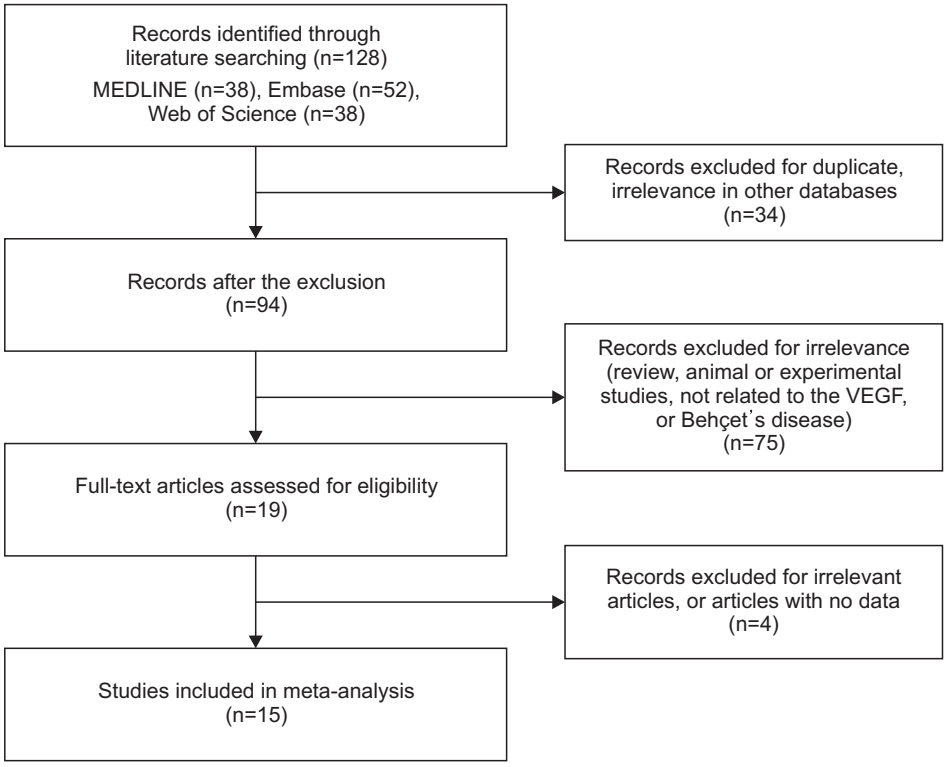


Figure 1. Flowchart depicting the process of study selection. VEGF: vascular endothelial growth factor.

Table 3. Meta-analysis of the association between circulating VEGF levels and Behçet's diseases

Group	Population	Study (n)	Subject		Test of association			Test of heterogeneity		
			Case (n)	Control (n)	SMD*	95% CI	p-value	Model	p-value	I^2
All	Overall	13	662	537	1.726	1.030~2.421	<0.001	R	<0.001	95.7
Ethnicity	European	7	298	175	0.963	0.558~1.367	<0.001	R	0.001	74.5
	Arab	6	364	362	2.605	1.317~3.893	<0.001	R	<0.001	97.3
Data type	Original	10	497	458	2.108	1.283~2.933	<0.001	R	<0.001	95.8
	Calculated	3	165	79	0.493	0.219~0.767	<0.001	F	0.734	0
Sample size (n)	≥100	3	264	287	2.104	0.070~4.139	0.043	R	<0.001	98.7
	<100	10	398	250	1.589	0.957~2.221	<0.001	R	<0.001	91.3
Disease activity	Active vs. inactive	7	267	183	0.635	0.092~1.177	0.022	R	<0.001	85.5

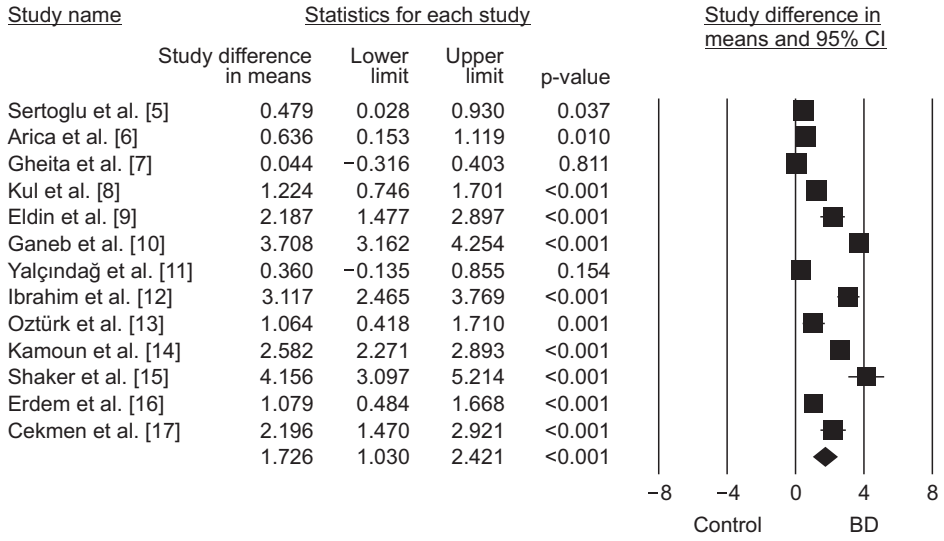
VEGF: vascular endothelial growth factor, SMD: standardized mean difference, CI: confidence interval, F: fixed effects model, R: random effects model. *Magnitude of Cohen's d effect size (SMD): 0.2~0.5, small effect; 0.5~0.8, medium effect; and ≥0.8, large effect.

control groups (Tables 1 and 2). Meta-analyses were conducted on VEGF polymorphisms where there were at least two comparisons. Due to the limited number of studies on candidate gene associations, three separate meta-analyses were performed, specifically analyzing VEGF polymorphisms –634 C/G, +936 C/T, and 18 bp insertion/deletion (I/D) at –2549. Each study was rated for quality on a scale of 5 to 7. Details regarding the characteristics of the included studies are provided in Tables 1 and 2.

Meta-analysis of circulating VEGF levels in BD patients vs. controls

The meta-analysis showed a significant difference in circulating VEGF levels between BD patients and controls (SMD=1.726, 95% CI=1.030~2.421, p<0.001) (Table 3 and Figure 2). Stratified by ethnicity, BD patients of European and Arab descent had higher VEGF levels compared to controls (Table 3). Subgroup analysis confirmed elevated VEGF levels in BD patients regardless of data type and sample size (Table 3). Furthermore,

A



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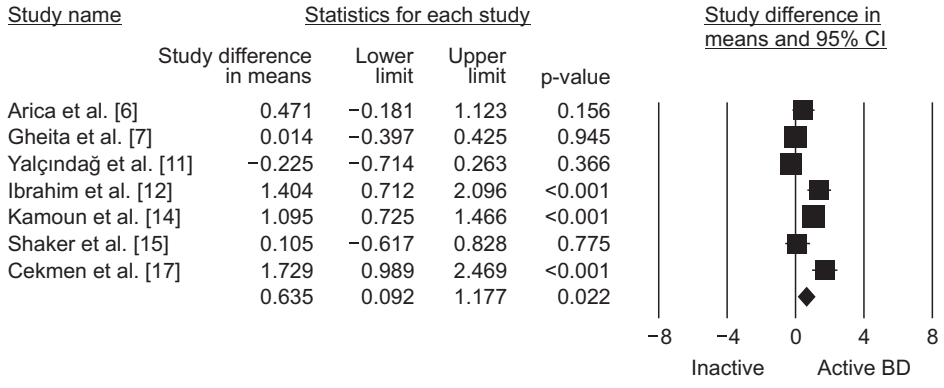

Figure 2. Meta-analysis examining (A) the relationship between BD and circulating VEGF levels, as well as (B) the comparison between active and inactive BD groups. BD: Behçet's disease, VEGF: vascular endothelial growth factor, CI: confidence interval.

VEGF levels were significantly higher in patients with active BD compared to those with inactive BD (SMD=0.635, 95% CI=0.092~1.177, p=0.022) (Table 3 and Figure 2).

Meta-analysis of VEGF polymorphisms −634 C/G, +936 C/T, and 18 bp I/D at −2549 and BD susceptibility

The meta-analysis revealed no significant association between BD and the VEGF −634 C allele when comparing pooled data from affected individuals and controls (OR=1.023, 95% CI=0.707~1.481, p=0.904) (Table 4 and Figure 3). Similarly, no significant association was found between BD and the VEGF +936 T allele (OR=1.072, 95% CI=0.811~1.417, p=0.628) (Table 4 and Figure 3). The analysis showed no significant association between BD and the VEGF 18 bp I/D polymorphism at −2549 (Table 4 and Figure 3).

Heterogeneity and assessment of publication bias

Heterogeneity was evident in most meta-analyses of VEGF levels in BD patients (Table 3). Meta-regression analysis indicated that data type, sample size, and publication year contributed to this heterogeneity. Sensitivity analysis showed that no single study had a disproportionate effect on the pooled SMD, supporting the robustness of the meta-analysis results. Heterogeneity was also present in meta-analyses of VEGF polymorphisms (Table 4). Although publication bias can arise from an imbalance of positive findings, our analysis found no evidence of such bias. Funnel plots did not show asymmetry, and Egger's regression test yielded p-values >0.05.

DISCUSSION

This meta-analysis revealed a significant increase in circulating VEGF levels in patients with BD compared to controls,

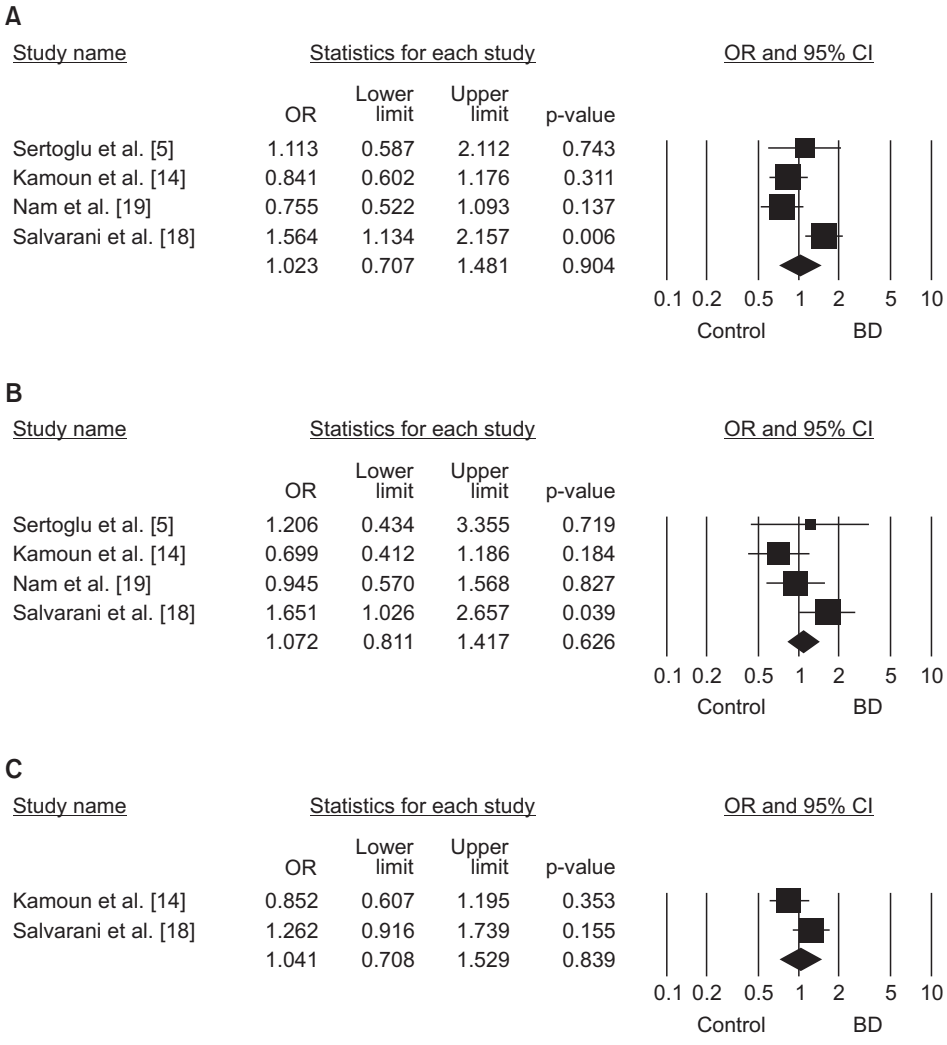

Figure 3. Meta-analysis of ORs with 95% CIs, showing results from individual studies and the combined data, focused on the allelic association between BD and VEGF polymorphisms (A) –634 C/G, (B) +936 C/T, and (C) 18 bp I/D at –2549. BD: Behçet's disease, VEGF: vascular endothelial growth factor, I/D: insertion/deletion, OR: odds ratio, CI: confidence interval.

Table 4. Meta-analysis of tests of association between polymorphisms in VEGF gene and Behçet's disease

Polymorphism	Population	Study (n)	Subject		Test of association			Test of heterogeneity		
			Case (n)	Control (n)	OR	95% CI	p-value	Model	p-value	I^2
VEGF –634 C vs. G	Pooled	4	413	525	1.023	0.707~1.481	0.904	R	0.014	71.8
VEGF +936 T vs. C	Pooled	4	413	524	1.072	0.811~1.417	0.628	F	0.113	49.7
VEGF –2549 I vs. D	Pooled	2	257	357	1.041	0.708~1.529	0.839	R	0.099	63.3

VEGF: vascular endothelial growth factor, I: insertion, D: deletion, OR: odds ratio, CI: confidence interval, R: random effect model, F: fixed effect model.

reinforcing the role of VEGF in the disease's pathogenesis. Our subgroup analysis demonstrated a consistent rise in VEGF levels among BD patients across various subgroups defined by data type and sample size, indicating that VEGF's involvement in BD is a stable finding, irrespective of differences in data collection methods and study sizes.

Significantly higher VEGF levels were observed in patients with active BD compared to those with inactive BD, highlighting VEGF's potential as a biomarker for disease activity. This increase in circulating VEGF levels in BD could be due to a complex mechanism involving innate and adaptive immune responses, leading to heightened angiogenesis and vascular permeability [27]. This suggests that VEGF might be useful in monitoring BD progression and tailoring treatment strategies.

We chose the specific VEGF polymorphisms (–634 C/G, +936 C/T, and 18 bp I/D at –2549) based on prior research suggesting their potential relevance to angiogenesis and immune regulation in BD. The –634 C/G polymorphism is located in the 5'-untranslated region (UTR) of the VEGF gene and has been associated with variations in VEGF protein expression [28]. The +936 C/T polymorphism is located in the 3'-UTR of the VEGF gene and influences plasma VEGF levels [29]. The 18 bp I/D polymorphism is located in the promoter region of the VEGF gene. This region is important for the regulation of VEGF expression [30]. Conversely, our analysis of VEGF polymorphisms, specifically –634 C/G, +936 C/T, and 18 bp I/D at –2549, did not show significant associations with BD susceptibility. This indicates that these specific genetic variations in the VEGF gene may not be associated with BD. However, it is important to acknowledge that genetic associations with complex diseases like BD are multifactorial, and other genetic variants not covered in this meta-analysis could still play a role.

The novelty of this meta-analysis lies in its dual focus: assessing both the role of VEGF polymorphisms and the direct association between VEGF elevation and disease activity in BD by confirming the association between elevated VEGF levels and active BD. The meta-analysis addresses inconsistencies in previous research regarding VEGF polymorphisms, demonstrating that these specific genetic variants are not significantly associated with increased BD risk. This finding shifts the focus away from these polymorphisms as risk markers, offering new insights into BD pathogenesis. However, further studies of basic or experimental study are needed.

While this meta-analysis provided valuable insights into the VEGF-BD relationship, it had limitations. Variability in study design, sample size, and data collection methods among the included studies could introduce heterogeneity and potential biases. Additionally, the analysis did not consider possible interactions between VEGF and other genetic or environmental factors that might contribute to BD development. Nonetheless, a key strength of this meta-analysis is the large number of included studies and patients, which provided a comprehensive and robust overview of the VEGF-BD association. This large sample size increased the statistical power of the analysis, enhancing the reliability of the results [31-33].

CONCLUSION

This meta-analysis confirms the association between elevated circulating VEGF levels and BD, emphasizing VEGF's potential role in the disease's pathogenesis and activity. However, the specific VEGF polymorphisms studied did not appear to be associated with BD susceptibility. Future research should focus on more extensive genetic studies and explore gene-gene and gene-environment interactions to better understand the complex etiology of BD and identify potential therapeutic targets.

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CONFLICT OF INTEREST

Y.H.L. has been an editorial board member since March 2010 but has no role in the decision to publish this article.

AUTHOR CONTRIBUTIONS

Y.H.L. and G.G.S. conceived and designed the study. Y.H.L. and G.G.S. were responsible for data acquisition, analysis, and interpretation. Y.H.L. drafted the manuscript. Y.H.L. and G.G.S. reviewed and revised the manuscript. All the authors approved the final version of the manuscript.

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REFERENCES

1. Nair JR, Moots RJ. Behcet's disease. Clin Med (Lond) 2017;17:71-7.
2. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004;25:581-611.
3. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J 1999;13:9-22.
4. Lee YH, Bae SC. Correlation between circulating VEGF levels and

disease activity in rheumatoid arthritis: a meta-analysis. Z Rheumatol 2018;77:240-8.
5. Sertoglu E, Yücel Ç, Omma A, Hayran Y, Colak S, Sandıkçı SC, et al. Determination of serum vascular endothelial growth factor (VEGF) and VEGF receptor levels with VEGF gene polymorphisms in patients with Behçet's uveitis. Adv Clin Exp Med 2022;31:231-40.
6. Arica DA, Akşan B, Örem A, Altinkaynak BA, Yayli S, Sönmez M. High levels of endothelial progenitor cells and circulating endothelial cells in patients with Behçet's disease and their relationship to disease activity. An Bras Dermatol 2019;94:320-6.
7. Gheita TA, Sakr BR, Rabea RE, Abd ElHamid SM. Value of hematological indices versus VEGF as biomarkers of activity in Behçet's disease. Clin Rheumatol 2019;38:2201-10.
8. Kul A, Ateş O, Alkan Melikoğlu M, Uğur M, Öztürk N, Erkayhan G, et al. Endocan measurement for active Behçet disease. Arch Rheumatol 2017;32:197-202.
9. Eldin AB, Ibrahim A. Assessment of the relationship between vascular endothelial growth factor and cardiovascular involvement in Egyptian patients with Behçet's disease. Egypt Rheumatol 2014;36:131-7.
10. Ganeb SS, Sabry HH, El-Assal MM, Kamal HM, Fayed AA, El-Shazly IM. Vascular endothelial growth factor and subclinical atherosclerosis by carotid ultrasonography in Egyptian patients with Behçet's disease. Egypt Rheumatol 2013;35:87-94.
11. Yalçındağ A, Gedik-Oğuz Y, Yalçındağ FN. The relationship between serum levels of angiogenin, bFGF, VEGF, and ocular involvement in patients with Behçet's disease. Graefes Arch Clin Exp Ophthalmol 2013;251:1807-12.
12. Ibrahim SE, Elshishtawy HF, HelmySamy A, Galal ZA. Role of vascular endothelial growth factor and monocyte chemoattractant protein-1 in Behçet's disease. Indian J Rheumatol 2011;6:168-72.
13. Oztürk MA, Unverdi S, Oktar SO, Bukan N, Gülbahar O, Ureten K, et al. Vascular endothelial growth factor and carotid intima-media thickness in patients with Behçet's disease. Clin Rheumatol 2008;27:961-6.
14. Kamoun M, Houman MH, Hamzaoui A, Hamzaoui K. Vascular endothelial growth factor gene polymorphisms and serum levels in Behçet's disease. Tissue Antigens 2008;72:581-7.
15. Shaker O, Ay El-Deen MA, El Hadidi H, Grace BD, El Sherif H, Abdel Halim A. The role of heat shock protein 60, vascular endothelial growth factor and antiphospholipid antibodies in Behçet disease. Br J Dermatol 2007;156:32-7.
16. Erdem F, Gündoğdu M, Kiki I, Ali Sari R, Kiziltunç A. Vascular endothelial and basic fibroblast growth factor serum levels in patients with Behçet's disease. Rheumatol Int 2005;25:599-603.
17. Cekmen M, Evereklioglu C, Er H, Inalöz HS, Doganay S, Türköz Y, et al. Vascular endothelial growth factor levels are increased and associated with disease activity in patients with Behçet's syndrome. Int J Dermatol 2003;42:870-5.
18. Salvarani C, Boiardi L, Casali B, Olivieri I, Cantini F, Salvi F, et al. Vascular endothelial growth factor gene polymorphisms in Behçet's disease. J Rheumatol 2004;31:1785-9.
19. Nam EJ, Han SW, Kim SU, Cho JH, Sa KH, Lee WK, et al. Association of vascular endothelial growth factor gene polymorphisms with Behcet disease in a Korean population. Hum Immunol 2005;66:1068-73.
20. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
21. Ridout KK, Ridout SJ, Price LH, Sen S, Tyrka AR. Depression and telomere length: a meta-analysis. J Affect Disord 2016;191:237-47.
22. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa: The Ottawa Hospital Research Institute, c2011 [cited 2021 May 3]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
23. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
26. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
27. Nurden AT. Platelets, inflammation and tissue regeneration. Thromb Haemost 2011;105 Suppl 1:S13-33.
28. Watson CJ, Webb NJ, Bottomley MJ, Brenchley PE. Identification of polymorphisms within the vascular endothelial growth factor (VEGF) gene: correlation with variation in VEGF protein production. Cytokine 2000;12:1232-5.
29. Renner W, Kotschan S, Hoffmann C, Obermayer-Pietsch B, Pilger E. A common 936 C/T mutation in the gene for vascular endothelial growth factor is associated with vascular endothelial growth factor plasma levels. J Vasc Res 2000;37:443-8.
30. Awata T, Inoue K, Kurihara S, Ohkubo T, Watanabe M, Inukai K, et al. A common polymorphism in the 5'-untranslated region of the VEGF gene is associated with diabetic retinopathy in type 2 diabetes. Diabetes 2002;51:1635-9.
31. Lee YH, Song GG. Circulating leptin and its correlation with rheumatoid arthritis activity: a meta-analysis. J Rheum Dis 2023;30:116-25.
32. Lee YH. An overview of meta-analysis for clinicians. Korean J Intern Med 2018;33:277-83.
33. Lee YH, Bae SC. Circulating adiponectin and visfatin levels in rheumatoid arthritis and their correlation with disease activity: a meta-analysis. Int J Rheum Dis 2018;21:664-72.