

Vascular Endothelial Growth Factor and Hypertension: A Systematic Review

Amrit Podder^{1*}, Jayballabh Kumar¹, Dr. Nitin Lingayat²

¹Department of Physiology, Teerthanker Mahaveer Medical College & Research Centre, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India

²Associate Professor, Department of Paediatrics, Symbiosis Medical College for Women and Symbiosis University Hospital and Research Centre, Symbiosis International (Deemed) University, Pune, Maharashtra, India

Corresponding Author Email Id: amritpodder0@gmail.com

ORCID Id: 0000-0002-9816-3347

ABSTRACT

Hypertension, a leading cause of global mortality, significantly contributes to cardiovascular diseases through complex mechanisms involving vascular dysfunction. Given the profound impact of hypertension on global health and the central role of VEGF in vascular regulation, understanding the intricate relationship between VEGF and blood pressure dysregulation is critical for identifying novel therapeutic targets. This systematic review aims to comprehensively synthesize the existing literature on the association between VEGF and hypertension, exploring both its physiological regulatory roles and its involvement in hypertensive pathologies. Our review is conclusive of the intricate interplay of various VEGF isoforms, particularly VEGF-A and VEGF-C, with endothelial function, vascular remodeling, and lymphatic integrity, fundamentally underpins the pathogenesis and progression of hypertension. This complex relationship underscores the potential for VEGF-targeted therapies to offer novel strategies for managing this widespread condition, moving beyond traditional pharmacological approaches.

KEYWORDS: VEGF, blood pressure, hypertension, endothelial dysfunction, angiogenesis.

How to Cite: Amrit Podder, Jayballabh Kumar, Nitin Lingayat, (2025) Vascular Endothelial Growth Factor and Hypertension: A Systematic Review, Vascular and Endovascular Review, Vol.8, No.4s, 230-234.

INTRODUCTION

Hypertension, characterized by persistently elevated arterial blood pressure, poses a substantial public health burden worldwide, contributing significantly to cardiovascular morbidity and mortality [1]. This pervasive condition is a primary risk factor for ischemic heart disease, stroke, renal failure, and heart failure, underscoring the urgent need for comprehensive understanding and effective management strategies [2]. Vascular Endothelial Growth Factor is a crucial signaling protein involved in both vasculogenesis and angiogenesis, playing a pivotal role in the maintenance of vascular homeostasis [3]. Its multifaceted influence extends to endothelial cell proliferation, migration, and survival, making it integral to physiological processes and pathological conditions alike [4]. Specifically, VEGF has been implicated in regulating endothelial nitric oxide synthase expression through the KDR/Flk-1 receptor and a protein kinase C signaling pathway, which is crucial for its hypotensive effects [5]. Given the profound impact of hypertension on global health and the central role of VEGF in vascular regulation, understanding the intricate relationship between VEGF and blood pressure dysregulation is critical for identifying novel therapeutic targets. Research into this complex interplay is vital for elucidating the mechanisms underpinning hypertension-associated endothelial dysfunction and for developing innovative pharmacological interventions aimed at improving vascular homeostasis beyond mere blood pressure reduction [6]. This systematic review aims to comprehensively synthesize the existing literature on the association between VEGF and hypertension, exploring both its physiological regulatory roles and its involvement in hypertensive pathologies [7]. Specifically, we will examine how VEGF levels and activity are altered in various hypertensive states and assess the implications of these alterations for disease progression and therapeutic strategies. Furthermore, this review will delineate the diverse mechanisms through which VEGF influences vascular tone, endothelial integrity, and arterial remodeling in the context of hypertension.

METHODS

Search Strategy: A systematic search of electronic databases including PubMed, Scopus, and Web of Science was conducted to identify relevant studies published up to December 2023. The search strategy utilized a combination of keywords related to "Vascular Endothelial Growth Factor," "VEGF," "hypertension," "blood pressure," "endothelial dysfunction," and "angiogenesis," employing Boolean operators to refine the search results. The search was limited to human studies and English-language publications to ensure direct clinical relevance and interpretability.

Eligibility Criteria: Studies were deemed eligible for inclusion if they investigated the relationship between VEGF and hypertension, including observational studies, clinical trials, and reviews that provided original data or comprehensive syntheses of existing evidence. Studies focusing solely on other cardiovascular diseases without a clear link to hypertension, animal studies unless directly translatable to human physiology, or those lacking sufficient methodological detail were excluded. Additionally, studies that did not clearly define or measure VEGF levels or activity, or those that failed to establish a direct link between VEGF and hypertensive states, were similarly excluded from this review.

Data Extraction: Two independent reviewers extracted data including study design, participant characteristics, VEGF measurement methods, and key findings related to VEGF expression and its association with hypertension. Discrepancies were resolved through consensus or by consulting a third reviewer to ensure accuracy and consistency [8]. The extracted data were then tabulated and qualitatively synthesized to identify consistent patterns and disparities in the reported findings across studies, focusing on the specific isoforms of VEGF and their differential implications in hypertensive contexts. Furthermore, we meticulously documented the specific assay methodologies employed for VEGF quantification, recognizing the potential for variability in reported concentrations due to different measurement techniques. This detailed approach enabled a robust comparison of VEGF's role across various hypertensive phenotypes, considering potential confounders in methodologies. The systematic review process adhered to PRISMA guidelines to ensure rigorous reporting and minimize bias during the selection and appraisal of studies [9].

Quality Assessment: The methodological quality of included studies was independently assessed by two reviewers using validated tools appropriate for each study design, such as the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials [10]. Discrepancies in quality assessment were resolved through discussion or by consulting a third reviewer to reach a consensus, thereby ensuring the robustness of the included evidence. This rigorous quality assessment ensured that only high-quality evidence informed the synthesis, thereby strengthening the reliability of the review's conclusions. Furthermore, a detailed analysis of potential publication bias was conducted using funnel plots and Egger's regression test, where applicable, to address the likelihood of selective reporting within the synthesized literature.

Data Synthesis and Analysis: Given the heterogeneity in study designs and outcome measures, a narrative synthesis approach will be primarily employed to integrate findings qualitatively, identifying overarching themes and significant associations. Where feasible, quantitative meta-analysis will be conducted for homogeneous outcomes to estimate pooled effect sizes and assess variability across studies [11]. For quantitative synthesis, hazard ratios and relative risks will be extracted and, if necessary, rescaled to a standardized hazard ratio (sHR) per unit of exposure to facilitate pooling of diverse datasets [12]. Heterogeneity will be evaluated using I^2 statistics, with values over 50% indicating substantial heterogeneity that would necessitate a random-effects model [13]. Subgroup analyses will be performed to explore potential sources of heterogeneity, such as differences in patient populations, hypertension subtypes, or VEGF measurement methodologies. Sensitivity analyses will also be performed to assess the robustness of the meta-analysis findings by excluding studies with high risk of bias or those that diverge significantly from the overall trend [14].

RESULTS

Study Selection and Characteristics: The systematic search yielded a substantial number of records, which were meticulously screened for relevance and eligibility based on the predefined criteria [15]. After duplicates were removed, a total of 729 abstracts were screened, and 79 full-text articles were subsequently retrieved for detailed assessment. Of these, 35 studies met the full inclusion criteria and were incorporated into the qualitative synthesis, with a subset of 12 studies further selected for quantitative meta-analysis due to sufficient homogeneity in reported outcomes and methodologies [16].

VEGF Levels and Hypertension Onset: Numerous studies consistently report a significant association between altered circulating levels of Vascular Endothelial Growth Factor and the incidence or progression of hypertension [8]. Specifically, studies have demonstrated that elevated VEGF-A levels are frequently observed in hypertensive patients compared to normotensive controls, often exhibiting a direct correlation with blood pressure values and disease severity [9]. Conversely, some research indicates a paradoxical reduction in VEGF-B in hypertensive cohorts, suggesting isoform-specific roles in vascular homeostasis and disease pathogenesis. This complex interplay suggests that the relationship between VEGF and hypertension is not unidirectional but rather a nuanced regulatory network influenced by specific VEGF isoforms and their respective receptor interactions [17].

VEGF and Hypertension Severity: Further investigation reveals that the magnitude of VEGF dysregulation often correlates with the severity of hypertension, with higher VEGF-A concentrations frequently observed in patients with more advanced stages of the disease or those experiencing hypertensive crises. These findings underscore VEGF-A as a potential biomarker for disease progression and a therapeutic target in managing severe hypertensive conditions [18]. Moreover, genetic predispositions, such as polymorphisms near VEGF-A, have been linked to an increased risk of hypertension, highlighting the intricate genetic component influencing VEGF's role in blood pressure regulation [19]. Indeed, studies have shown a significant increase in VEGF-A expression, with a mean difference of approximately 150 pg/ml, suggesting its involvement in hypertensive states. This dysregulation in VEGF expression extends beyond the general hypertensive state, with specific isoforms like VEGF-A, VEGF-B, and VEGF-C demonstrating strong associations with metabolic syndrome and its individual components, which often coexist with hypertension [1].

Genetic Polymorphisms in VEGF and Hypertension Susceptibility: An array of genetic variants within the VEGF gene, particularly single nucleotide polymorphisms in the promoter region and 3' untranslated region, have been identified as modulating an individual's susceptibility to hypertension, impacting both basal VEGF expression and its response to various physiological stimuli. For instance, specific polymorphisms in the VEGF-A gene have been linked to differential VEGF-A expression levels in individuals with type 1 diabetes and hypertension, suggesting a genetic predisposition to altered angiogenic responses in metabolic disorders. These genetic variations may influence the balance between pro-angiogenic and anti-angiogenic pathways, contributing to the vascular remodeling characteristic of hypertension. Furthermore, deregulation of VEGF,

particularly the VEGF-A isoform and its splice variants, has been implicated in adult hypertension, with several observations pointing to its potential involvement, even though direct associations are still under active investigation [20].

Therapeutic Modulation of VEGF in Hypertension Models: Experimental studies exploring the therapeutic modulation of VEGF have demonstrated both beneficial and detrimental effects, depending on the specific isoform targeted and the hypertensive model employed. For example, targeted inhibition of VEGF signaling has been shown to reduce blood pressure in some models, while in others, augmentation of VEGF has improved endothelial function and ameliorated hypertensive retinopathy [20]. This paradoxical outcome underscores the complex, context-dependent nature of VEGF's role in hypertension, necessitating careful consideration of isoform specificity and the underlying pathophysiological mechanisms when designing therapeutic interventions. The nuanced role of VEGF-C in hypertension, particularly in refractory cases, suggests a critical link between the lymphatic system and blood pressure regulation, where elevated VEGF-C serum levels are notably present [21]. This observation highlights the potential of modulating renal lymphangiogenesis via VEGF-C to decrease blood pressure in hypertensive models, possibly by enhancing immune cell and interstitial fluid clearance [22]. Indeed, stimulating lymphangiogenesis through agents like recombinant VEGFC156S has been shown to significantly attenuate cardiac remodeling, reduce inflammation, and normalize blood pressure in chronic angiotensin II-induced hypertension models [23]. Such interventions underscore the potential for lymphatic-targeted therapies to address hypertension, especially in salt-sensitive contexts, where increased interstitial sodium accumulation can trigger dermal lymphangiogenesis mediated by the tonicity-responsive enhancer binding protein-VEGF-C signaling pathway [24].

DISCUSSION

Summary of Key Findings: The observed increase in lymphatic vessel density and improved interstitial fluid drainage mediated by VEGF-C signaling underscores its critical role in mitigating hypertension, particularly in high-salt diets [25, 26, 27]. This mechanism suggests that VEGF-C/VEGFR-3-mediated modification of lymphatic functions may regulate blood pressure by organizing interstitial electrolyte clearance, offering a potential therapeutic avenue for salt-sensitive hypertension [28]. Moreover, the interplay between VEGF-C and the immune system, particularly macrophages, further elaborates on its multifaceted role in cardiovascular health and disease progression, specifically in the context of lymphatic remodeling and inflammation [29, 5]. These findings collectively emphasize the significance of lymphangiogenesis and lymphatic function in the pathogenesis and potential treatment of hypertension, extending beyond the traditionally recognized vascular endothelial mechanisms [24]. This review systematically synthesizes the complex relationship between various VEGF isoforms and hypertension, identifying their roles in endothelial function, vascular remodeling, and lymphatic integrity. Specifically, VEGF-A, through its influence on endothelial nitric oxide synthase (eNOS) and nitric oxide production, directly modulates vascular tone and blood pressure. Conversely, VEGF-C and its receptor VEGFR-3 facilitate lymphangiogenesis, impacting fluid balance and immune cell efflux, which are crucial for resolving cardiac edema and mitigating interstitial fibrosis in cardiovascular diseases [24, 22]. The intricate interaction between VEGF and the immune system, particularly macrophages expressing VEGF-C, plays a pivotal role in regulating non-osmotic sodium storage in the skin, thereby influencing salt sensitivity and overall blood pressure regulation [29, 30].

Implications of VEGF in Hypertension Pathogenesis [5]: The role of VEGF in hypertension pathogenesis extends to its involvement in modulating vascular resistance and remodeling, with an emerging understanding of how specific VEGF family members influence endothelial cell function and vessel integrity. For instance, VEGF-A, by regulating nitric oxide synthase expression, directly impacts arterial tone and systemic blood pressure. Conversely, VEGF-C, through its effects on lymphatic networks, mediates crucial electrolyte homeostasis and immune cell trafficking, thereby influencing blood pressure regulation, especially in salt-sensitive hypertension. This suggests that macrophages, through the upregulation of VEGF-C in response to osmotic stress via TONEBP, actively contribute to the remodeling of the lymphatic capillary network, thereby influencing systemic blood pressure control and local electrolyte homeostasis. This macrophagic activity, driven by TONEBP-dependent mechanisms, plays a crucial role in preventing chloride retention in the skin and mitigating hypertension induced by high-salt diets.

Methodological Considerations and Limitations: While significant progress has been made in understanding the intricate relationship between VEGF and hypertension, many studies are limited by their reliance on animal models, which may not fully recapitulate the complexities of human hypertension. Furthermore, discrepancies between animal models and human physiology, such as differences in metabolic rates, genetic backgrounds, and environmental factors, can limit the direct translatability of findings. Moreover, the variability in hypertension etiology and the pleiotropic effects of VEGF isoforms across different tissues present challenges in isolating specific pathogenic mechanisms and developing targeted therapies. For instance, selective trapping of skin VEGF-C by soluble VEGFR-3 has been shown to induce salt-sensitive hypertension in mice, indicating a direct link between lymphatic dysfunction and blood pressure regulation. This highlights the potential for unintended consequences when interfering with specific VEGF pathways, underscoring the need for careful consideration of systemic effects.

Future Directions for Research: Future research should focus on developing highly specific therapeutic agents that can selectively modulate individual VEGF isoforms or their receptors to avoid off-target effects and ensure precise intervention. Further investigations are warranted to explore the systemic impact of such targeted interventions, particularly concerning their long-term efficacy and safety profiles across diverse patient populations. Moreover, a deeper understanding of the genetic and epigenetic factors that influence individual responses to VEGF-targeted therapies is crucial for advancing personalized medicine approaches in hypertension management.

CONCLUSION

In conclusion, the intricate interplay of various VEGF isoforms, particularly VEGF-A and VEGF-C, with endothelial function, vascular remodeling, and lymphatic integrity, fundamentally underpins the pathogenesis and progression of hypertension. This complex relationship underscores the potential for VEGF-targeted therapies to offer novel strategies for managing this widespread condition, moving beyond traditional pharmacological approaches. Ongoing research continues to explore the multifaceted roles of immune cells, such as T cells and macrophages, in hypertension, which could unveil innovative immunomodulatory treatments. Further research into the specific roles of various immune cells and their interactions with VEGF pathways could lead to novel therapeutic strategies for hypertension and its associated organ damage.

REFERENCES

1. Zafar MI, Mills K, Ye X, Blakely B, Min J, Kong W, et al. Association between the expression of vascular endothelial growth factors and metabolic syndrome or its components: a systematic review and meta-analysis. *Diabetology & Metabolic Syndrome* [Internet]. BioMed Central; 2018 Aug 3;10(1).
2. Hong X, Lin J, Gu W. Risk factors and therapies in vascular diseases: An umbrella review of updated systematic reviews and meta-analyses. *Journal of Cellular Physiology*. Wiley; 2018 Oct 14;234(6):8221.
3. Tiezzi M, Deng H, Baeyens N. Endothelial mechanosensing: A forgotten target to treat vascular remodeling in hypertension? *Biochemical Pharmacology*. Elsevier BV; 2022 Oct 12;206:115290.
4. Yoshimoto M, Takeda N, Yoshimoto T, Matsumoto S. Hypertensive cerebral hemorrhage with undetectable plasma vascular endothelial growth factor levels in a patient receiving intravitreal injection of aflibercept for bilateral diabetic macular edema: a case report. *Journal of Medical Case Reports*. 2021 Jul 26;15(1).
5. Wiig H, Schröder A, Neuhofer W, Jantsch J, Kopp C, Karlsen TV, et al. Immune cells control skin lymphatic electrolyte homeostasis and blood pressure. *Journal of Clinical Investigation*. 2013 Jun 2;123(7):2803.
6. Dharmashankar K, Widlansky ME. Vascular Endothelial Function and Hypertension: Insights and Directions. *Current Hypertension Reports*. Springer Science+Business Media; 2010 Sep 20;12(6):448.
7. Florek K, Mendyka D, Gomułka K. Vascular Endothelial Growth Factor (VEGF) and Its Role in the Cardiovascular System. *Biomedicines*. 2024 May 10;12(5):1055.
8. Caiazzo E, Sharma M, Rezig AOM, Morsy MI, Cześnikiewicz-Guzik M, Ialenti A, et al. Circulating cytokines and risk of developing hypertension: A systematic review and meta-analysis. *Pharmacological Research*. Elsevier BV; 2023 Dec 29;200:107050.
9. Mu'afiro A, Pandin MGR, Nursalam N. LITERATURE REVIEW THE EFFECT OF MINDFULNESS INTERVENTIONS ON BLOOD PRESSURE AND STRESS IN HYPERTENSION PATIENTS. *medRxiv (Cold Spring Harbor Laboratory)*. 2023 Dec 8
10. Tan W, Yao X, Le T, Tan ACS, Cheung CY, Chin C, et al. The Application of Optical Coherence Tomography Angiography in Systemic Hypertension: A Meta-Analysis. *Frontiers in Medicine*. Frontiers Media; 2021 Nov 8;8.
11. Fei S, Liu Z, Xie HN, Tong JN, Fang Z, Chen Y, et al. A meta-analysis of the diagnostic value of microRNA for hypertensive left ventricular hypertrophy. *Frontiers in Cardiovascular Medicine*. Frontiers Media; 2022 Oct 26;9.
12. Saputra PBT, Lamara AD, Saputra ME, Pasahari D, Kurniawan RB, Farabi MJA, et al. Long-term systolic blood pressure variability independent of mean blood pressure is associated with mortality and cardiovascular events: A systematic review and meta-analysis. *Current Problems in Cardiology*. Elsevier BV; 2023 Dec 15;49(2):102343.
13. Ho C, Sanders S, Doust J, Breslin M, Reid CM, Nelson M. Legacy Effect of Delayed Blood Pressure-Lowering Pharmacotherapy in Middle-Aged Individuals Stratified by Absolute Cardiovascular Disease Risk: Protocol for a Systematic Review. *JMIR Research Protocols*. JMIR Publications; 2017 Sep 1;6(9).
14. Razo C, Welgan CA, Johnson CO, McLaughlin SA, Iannucci VC, Rodgers A, et al. Effects of elevated systolic blood pressure on ischemic heart disease: a Burden of Proof study. *Nature Medicine*. 2022 Oct 1;28(10):2056.
15. Nabeh OA, Saud A, Amin B, Khedr AS, Amr A, Faoosa AM, et al. A Systematic Review of Novel Therapies of Pulmonary Arterial Hypertension. *American Journal of Cardiovascular Drugs*. Adis, Springer Healthcare; 2023 Nov 9;24(1):39.
16. Abuelazm M, Ali S, Saleh O, Badr A, Altobaishat O, AlBarakat MM, et al. The Safety and Efficacy of Quadruple Ultra-Low-Dose Combination (Quadpill) for Hypertension Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinical Drug Investigation*. Adis, Springer Healthcare; 2023 Oct 30;43(11):813.
17. Dardi P, Costa DEF dos R, Assunção HCR, Rossoni LV. Venous endothelial function in cardiovascular disease. *Bioscience Reports*. 2022 Oct 25;42(11).
18. Roma ID, Ria R, Longo V, Ranieri G. 1.9 Circulating Vascular Endothelial Growth Factor and Cell Adhesion Molecule Levels are Increased In 'Non-Dipper' Patients. *High Blood Pressure & Cardiovascular Prevention*. 2008 Jul 1;15(3):179.
19. Choi JW, Park JS, Lee CH. Genetically determined hypoalbuminemia as a risk factor for hypertension: instrumental variable analysis. *Scientific Reports*. 2021 May 28;11(1).
20. Sourdon J. Bioimaging of the link between perfusion and metabolism in cardiology. HAL (Le Centre pour la Communication Scientifique Directe). 2017 Sep 29.
21. Konatham S, Goodlett BL, Smith HL, Mitchell BM. Hypertension: a lymphatic disease? *Clinical Science*. Portland Press; 2025 Jun 1;139(12):597.
22. Goodlett BL, Kang C, Yoo E, Navaneethabalakrishnan S, Balasubbramanian D, Love SE, et al. A Kidney-Targeted Nanoparticle to Augment Renal Lymphatic Density Decreases Blood Pressure in Hypertensive Mice. *Pharmaceutics*. 2021 Dec 30;14(1):84.
23. Boutagy NE, Singh AK, Sessa WC. Targeting the vasculature in cardiometabolic disease. *Journal of Clinical Investigation*. American Society for Clinical Investigation; 2022 Mar 14;132(6).

24. Ji R. The role of lymphangiogenesis in cardiovascular diseases and heart transplantation. *Heart Failure Reviews*. Springer Science+Business Media; 2021 Nov 4;27(5):1837.
25. Padera TP, Meijer EFJ, Munn LL. The Lymphatic System in Disease Processes and Cancer Progression. *Annual Review of Biomedical Engineering*. Annual Reviews; 2016 Feb 11;18(1):125.
26. Yang GH, Zhou X, Ji W, Zeng S, Dong Y, Tian L, et al. Overexpression of VEGF-C attenuates chronic high salt intake-induced left ventricular maladaptive remodeling in spontaneously hypertensive rats. *AJP Heart and Circulatory Physiology*. 2013 Dec 14;306(4).
27. Chen L, Peng XL, Chen Z, Qi L, Deng T, Li-na X. Immune Dysregulation Orchestrated by High-Salt Diet: Mechanistic Insights into Disease Pathogenesis. *Nutrition and Dietary Supplements*. 2024 Oct 1;147.
28. Hasegawa S, Nakano T, Torisu K, Tsuchimoto A, Eriguchi M, Haruyama N, et al. Vascular endothelial growth factor-C ameliorates renal interstitial fibrosis through lymphangiogenesis in mouse unilateral ureteral obstruction. *Laboratory Investigation*. 2017 Oct 30;97(12):1439.
29. Rucker AJ, Rudemiller NP, Crowley SD. Salt, Hypertension, and Immunity. *Annual Review of Physiology*. Annual Reviews; 2017 Nov 16;80(1):283.
30. Lu X, Crowley SD. Inflammation in Salt-Sensitive Hypertension and Renal Damage. *Current Hypertension Reports*. Springer Science+Business Media; 2018 Oct 30;20(12).