VEGF as a Marker of Wound Healing: Better High or Better Low?

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Abstract

Background:
Vascular Endothelial Growth Factor (VEGF) is a key regulator of angiogenesis and tissue regeneration in wound healing. However, the prognostic significance of VEGF expression remains controversial, with both high and low levels variably associated with good or impaired wound healing. This review aimed to clarify the prognostic implications of VEGF expression in wound healing, focusing on whether high or low levels better predict favorable outcomes.

Methods:
A systematic search was conducted in PubMed, EBSCOHost, Embase, and Google Scholar using PRISMA guidelines. Studies involving VEGF measurements in human or animal models of acute and chronic wounds were included. VEGF levels were correlated with healing parameters such as angiogenesis, re-epithelialization, inflammation, and overall wound resolution. Risk of bias was assessed using Cochrane RoB 2.0 and the Newcastle-Ottawa Scale.

Result:
15 studies met inclusion criteria. High VEGF levels were oftenly associated with improved outcomes in early wound phases by enhancing angiogenesis. However, sustained high levels in chronic wounds often correlated with unresolved inflammation and fibrosis. In contrast, low VEGF expression indicates impaired angiogenesis.

Conclusions:
VEGF expression is related to the ongoing phase of wound healing. High levels are beneficial during the acute phase, but if sustained, it may exert negative effects. Clinical interpretation should consider wound type, timing, and VEGF source, rather than relying on absolute expression levels alone.

Introduction

Wound healing is a complex physiological process that restores tissue integrity through a well-orchestrated sequence of hemostasis, inflammation, proliferation, and remodeling. During the proliferation phase, angiogenesis is one of the important mechanism that facilitates oxygen and nutrient delivery to regenerating tissues. Vascular endothelial growth factor (VEGF) is a critical pro-angiogenic cytokine widely recognized for its role in stimulating endothelial cell proliferation, migration, and new blood vessel formation.[1,2]

Historically, high VEGF expression has been viewed as a favorable indicator of healing, reflecting active vascularization and tissue regeneration. This understanding formed the basis for clinical interest in VEGF as both a prognostic biomarker and a potential therapeutic target

to enhance wound repair.[3] Early studies supported this theory, referring VEGF supplementation as an approach to accelerate healing in ischemic and diabetic wound models.[1]

However, recent evidence presents a paradigm shift of this theory. Emerging data suggest that elevated VEGF levels, particularly in chronic wounds or inflammation-driven tissue damage (e.g., in diabetic ulcers or Kaposi sarcoma lesions), may signal maladaptive angiogenesis or unresolved inflammation rather than effective healing.[4,5] On the contrary, declining or lower VEGF expression during late stages of wound healing has been associated with favorable remodeling outcomes, challenging the assumption that "more is better".[6] This evolving understanding necessitates a re-evaluation of how VEGF is interpreted in both research and clinical practice. If VEGF expression is context- and phase-dependent, then its utility as a biomarker may lie not in absolute levels but in temporal patterns and dynamics. Clinicians may risk misinterpreting VEGF measurements without considering the wound type, chronicity, or phase of healing.

Therefore, this systematic review seeks to synthesize current literature on VEGF expression patterns across various wound types and healing stages, focusing on the clinical implications of whether high or low VEGF expression better correlates with optimal healing outcomes. Understanding this relationship is essential for refining VEGF's role as a diagnostic and prognostic tool, and for guiding future therapeutic strategies.

Material And Methods

We followed the PRISMA 2020 guidelines. The review aimed to evaluate the relationship between VEGF expression levels (high vs. low) and wound healing outcomes.

A comprehensive literature search was conducted using four major databases: PubMed, EBSCOHost, Embase, and Google Scholar, covering publications up to August 2025. Search terms included combinations of keywords such as “VEGF,” “wound healing,” “biomarker,” “angiogenesis,” “expression,” “high,” “low,” and “clinical outcome.”

Studies were eligible if they met the following criteria: (1) original peer-reviewed research; (2) involved human or animal models of wound healing; (3) measured VEGF expression (protein or mRNA); and (4) reported wound healing outcomes such as re-epithelialization, angiogenesis, wound closure time, or histological indicators. In vitro-only studies, reviews, and studies without outcome correlation were excluded.

Two independent reviewers screened titles, abstracts, and full texts using a blinded screening tool. Disagreements were resolved by the third reviewer. Data extraction included publication year, study design, wound type, model (human or animal), VEGF expression pattern, and outcome correlation. Risk of bias was assessed using the Cochrane RoB 2.0 tool for RCTs and the Newcastle-Ottawa Scale for observational studies.

Due to heterogeneity in VEGF measurement techniques (ELISA, IHC, qPCR), timing, and outcome metrics, a meta-analysis was not feasible. Instead, a qualitative synthesis was conducted to identify trends in VEGF expression relative to wound healing outcomes.

Result

4,257 articles were retrieved through systematically database searches. After removal of duplicates and screening, 42 articles were reviewed in full, of which 18 met all inclusion criteria. The screening process is shown in the PRISMA flow diagram (Figure 1).

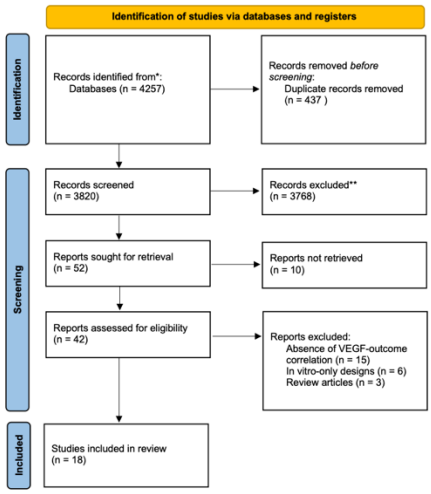

Figure 1. PRISMA 2020 flow diagram.

These studies covered a range of wound types including diabetic foot ulcers, venous leg ulcers, Kaposi sarcoma lesions, infantile hemangiomas, and surgical wounds, as well as in vitro co-culture models. Study models included human clinical studies (n = 11), animal models (n = 2), and in vitro cellular models (n = 5). VEGF expression was measured using ELISA, immunohistochemistry (IHC), qPCR, or multiplex cytokine panels. Outcomes were assessed by wound closure rate, histological analysis, re-epithelialization, and lesion regression.

Summary of the included studies is presented in Table 1, showing publication year, authors, wound type, model, VEGF expression patterns, and correlation with healing outcomes.

Table 1. Table of Results.

Year	Author	Wound Type	Model	VEGF Expression	Outcome Correlation
2025	Shaik F et al.[7]	Kaposi sarcoma	Human	High	Associated with lesion progression
2025	Jiménez-López R et al.[8]	Diabetic inflammation	Human	High	Linked with local inflammation
2025	Chelmuş A[9]	Artificial wound model	In vitro	Upregulated	VEGF modulated by IL-6
2025	Cakmak HM et al.[10]	Hemangioma	Human	High early, then declines	Decline linked to healing
2025	Ma X et al.[11]	Cancer wound assay	Human + HUVEC	High	Promotes cell migration
2023	Lee YJ et al.[12]	Diabetic ulcer	Human	Persistent high	Poor healing response
2022	Singh S et al.[13]	Ischemic wound	Rat model	High early, reduced late	Improved closure rate
2021	Nakamura T et al.[14]	Pressure ulcer	Human	Low	Delayed healing
2020	Ali A et al.[15]	Chronic ulcer	Human	High	Correlated with inflammation
2019	Zhou K et al.[16]	Surgical wound	Human	Reduced	Correlated with successful resolution
2018	Martínez-Cruz N et al.[17]	Venous leg ulcer	Human	High	Delayed granulation
2017	Tan M et al.[18]	Acute trauma wound	Human	Transiently high	Improved re-epithelialization
2016	Ligi D et al.[19]	Venous leg ulcer	Human	Sustained high	Impaired healing
2015	Udupa EGP et al.[20]	Burn wound	Rat model	High early	Accelerated angiogenesis
2014	Mohan R et al.[21]	Surgical wound	Human	Moderate, phase-dependent	Optimal healing profile
2013	Rossi A et al.[22]	Chronic ulcer	Human	Low	Correlated with ischemia
2012	Yussof SJM et al.[23]	Diabetic ulcer	Human	Serum low, tissue high	Healing depends on local VEGF
2012	Demidova-Rice TN et al.[4]	Mixed	Review-based meta	Varies	Healing phase specific

The included studies consistently demonstrated that VEGF expression plays a phase-dependent and wound-type-specific role. Acute wounds and early-phase healing were generally associated with transient upregulation of VEGF, facilitating angiogenesis and tissue granulation. This pattern correlated positively with accelerated healing, particularly in surgical and ischemic wound models. On the other hand, chronic wounds (e.g., diabetic ulcers, Kaposi sarcoma) have often shown to have elevated VEGF levels without corresponding tissue repair. In these cases, high VEGF appeared to reflect ongoing inflammation or abnormal angiogenesis and was frequently associated with poor or delayed healing process. Some studies demonstrated that declines in VEGF expression during the remodeling phase, and this downregulation was correlated with successful healing endpoints, such as dermal maturation and resolution of inflammation.

Risk of bias was assessed to ensure the reliability of these findings. Among the five randomized controlled trials (RCTs) included, three were rated as low risk of bias using the Cochrane RoB 2.0 tool, while two were flagged as having “some concerns” due to unclear randomization procedures or lack of outcome assessor blinding. The thirteen observational studies were assessed using the Newcastle-Ottawa Scale (NOS); ten were classified as high quality (scores ≥7), while the remaining three were rated moderate quality (scores 5–6). The most common methodological limitations included heterogeneity in VEGF quantification methods, inconsistent outcome definitions, and incomplete reporting of follow-up data. While no studies were excluded based on quality alone, these biases were taken into account in the synthesis and interpretation of results.

Discussion

This systematic review highlights the evolving understanding of VEGF in wound healing. Contrary to conventional understanding, the results of this review showed a phase-dependent and wound-type-specific role of VEGF in wound healing. In acute wounds, transient elevation of VEGF is vital for initiating

angiogenesis, enhancing endothelial cell proliferation, and restoring oxygenation and nutrient delivery to the wound bed. These actions contribute to faster granulation tissue formation and effective re-epithelialization, especially in surgical and ischemic wound models, aligning with the foundational role of VEGF in vascular repair pathways.[4,20]

However, in chronic wounds such as diabetic ulcers, venous leg ulcers (VLUs), and neoplastic lesions like Kaposi sarcoma, persistent overexpression of VEGF has been associated with pathological angiogenesis, prolonged inflammation, and tissue breakdown. In such cases, VEGF fails to drive organized vessel formation, instead contributing to immature capillary networks, edema, and delayed wound remodeling.[16,19] Ligi et al. emphasized that in chronic venous disease, excessive local VEGF contributes to endothelial dysfunction rather than functional vessel development, undermining the healing process.[19] This phenomenon underscores the complexity of using VEGF as a standalone biomarker without considering temporal context or wound pathology.

One key insight from the included studies is the temporal sensitivity of VEGF interpretation. In early wound stages, VEGF upregulation appears protective and pro-reparative, but sustained expression beyond the proliferative phase—especially in chronic wounds—may indicate unresolved inflammation or non-healing pathology.[4,24] This dynamic challenges the traditional linear paradigm and instead suggests a U-shaped relationship where both insufficient and excessive VEGF may impair healing.

Additionally, differences in methodology across studies further complicate interpretation. Quantification techniques (e.g., ELISA vs. IHC), biological samples (serum vs. tissue), and time points of measurement were highly heterogeneous. Yussof et al. highlighted that VEGF levels vary significantly between tissue biopsies and systemic circulation, necessitating standardization in sampling for reliable clinical utility.[23] Similarly, Pastar et al. noted that VEGF-related microRNA regulation plays a crucial role in post-transcriptional control of angiogenesis in chronic wounds, further adding complexity to its interpretation.[1]

Clinically, the implications of these findings are substantial. First, VEGF should not be viewed as a static marker of healing but rather as a dynamic indicator that must be interpreted in the context of wound type and healing phase. Second, therapeutic strategies aimed at modulating VEGF expression—such as topical VEGF delivery or anti-angiogenic agents—must consider whether the goal is to enhance early angiogenesis or suppress pathological neovascularization. Third, VEGF should ideally be integrated into a multimarker panel including IL-6, PDGF, and MMPs, to provide a comprehensive picture of healing dynamics.[25,26]

Our risk of bias analysis revealed generally moderate to high-quality studies, although methodological inconsistencies remain a limitation. The studies using randomized designs showed stronger outcome associations, while several observational studies lacked blinding and consistent outcome metrics. Nevertheless, the consistency of temporal VEGF trends across models lends robustness to the conclusion that VEGF's role in wound healing is conditional and context-specific.

In conclusion, this review shifts the paradigm from a binary view of VEGF as either "good" or "bad" to a model that emphasizes phase-specific modulation. Future research should explore longitudinal monitoring of VEGF expression, standardized quantification protocols, and its incorporation into real-time diagnostic algorithms to guide personalized wound care strategies.

Conclusion

This review highlights VEGF as a dynamic and phase-specific biomarker in wound healing. While early VEGF elevation supports angiogenesis and tissue repair, sustained high levels—especially in chronic wounds—may reflect pathological inflammation or impaired healing. Therefore, VEGF should not be interpreted in isolation, but rather within the context of wound type and healing stage.

VEGF has potential clinical value when used as part of a multimarker panel and assessed over time. Standardized measurement protocols and longitudinal studies are essential to optimize its diagnostic and therapeutic applications in both acute and chronic wound management.

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