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REVIEW ARTICLE

Impact of vascular endothelial growth factor on the regeneration and healing of periodontal tissues

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ABSTRACT

Introduction: periodontitis is a chronic inflammatory disease that affects dental supporting structures and represents one of the main causes of tooth loss.
Objective: to analyze the role of vascular endothelial growth factor in periodontal regeneration and healing.
Methods: a systematic review of the scientific literature was conducted across various databases. The search was performed using an algorithm with keywords and boolean operators, allowing the identification of relevant sources. Selected studies, after applying inclusion and exclusion criteria, were critically analyzed considering timeliness, methodological quality, and thematic relevance, and were integrated into the final synthesis of the review.
Development: findings show that vascular endothelial growth factor promotes angiogenesis, cell migration and proliferation, and modulates the inflammatory response. Experimental studies demonstrate that fibroblasts and mesenchymal stem cells release vascular endothelial growth factors, attracting osteoblasts and promoting bone regeneration. Recent trials with gene-activated matrices and cellular overexpression confirm its therapeutic potential in wound healing and periodontal repair. However, challenges remain in controlled administration, evaluation of side effects, and standardization of clinical protocols.
Conclusions: vascular endothelial growth factor emerges as a promising tool in regenerative dentistry. Large-scale clinical studies are required to validate its efficacy and safety in advanced periodontitis.

Keywords: Wound Healing; Periodontal Diseases; Periodontium; Guided Tissue Regeneration, Periodontal.

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INTRODUCTION

Periodontal disease—particularly periodontitis—is a chronic inflammatory condition affecting the supporting structures of the teeth, including the gingiva, periodontal ligament, cementum, and alveolar bone. It is characterized by gingival inflammation and bleeding, and in advanced stages, by destruction of periodontal tissues and alveolar bone, leading to tooth loss. Periodontal disease represents a major public health problem, with an estimated global prevalence of 45 % among adults over 30 years of age.[1] In this concerning context, the search for more effective periodontal therapies becomes crucial. Within this framework, Vascular Endothelial Growth Factor (VEGF) emerges as a promising tool with significant potential to transform periodontal healing. VEGF—a key protein in angiogenesis, the process of new blood vessel formation—opens a new chapter in regenerative dentistry.[2]

In the context of periodontal healing, VEGF performs multiple biological functions that make it essential for tissue repair. Its primary effects include angiogenesis, which promotes new blood vessel formation in injured areas, optimizing oxygen and nutrient supply and accelerating tissue recovery.[3] Additionally, VEGF stimulates the migration and proliferation of progenitor cells such as osteoblasts and fibroblasts, which are fundamental for bone and periodontal tissue regeneration.[4] Finally, it contributes to modulation of the inflammatory response, reducing excessive inflammation that can damage tissues and creating a more favorable environment for healing.

VEGF, recognized as a key protein in angiogenesis, represents a significant advance in regenerative dentistry. Its therapeutic potential has generated growing interest in scientific research, offering new possibilities to improve clinical outcomes in patients with advanced periodontitis.[5,6] Given these considerations, this review was conducted to analyze the role of vascular endothelial growth factor in periodontal regeneration and healing.

METHODS

A systematic review of the scientific literature was carried out following PRISMA guidelines to evaluate the role of Vascular Endothelial Growth Factor (VEGF) in periodontal regeneration. The search period spanned from 2018 to 2024, encompassing recent clinical and experimental studies.

Databases consulted included PubMed, Scopus, and Web of Science, supplemented with secondary references from relevant articles. Search algorithms combined keywords and Boolean operators: ("VEGF" OR "vascular endothelial growth factor") AND ("periodontitis" OR "bone regeneration" OR "angiogenesis"). Publications in English, Spanish, and Portuguese were included.

Inclusion criteria were original, peer-reviewed studies reporting outcomes on periodontal healing and bone regeneration. Duplicates, articles without full access, and narrative reviews lacking experimental data were excluded. The selection process occurred in several stages: title identification, abstract screening, and full-text reading. Initially, 120 records were identified; 35 studies met eligibility criteria. The selection flow was documented using a PRISMA diagram.

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Data extraction included information on methodological design, type of intervention, study population, and clinical outcomes. A qualitative synthesis was performed, and where possible, an exploratory meta-analysis was conducted to assess the association between VEGF expression and periodontal healing.

DEVELOPMENT

Reviewed studies confirm the central role of vascular endothelial growth factor (VEGF) in periodontal healing and regeneration. First, VEGF demonstrates its capacity to promote angiogenesis—an indispensable process for oxygen and nutrient delivery to injured tissues—thereby accelerating recovery and fostering a biologically favorable environment for repair. Additionally, VEGF stimulates cell migration and proliferation, attracting osteoblasts and activating fibroblasts, which are essential for bone and periodontal tissue regeneration. Furthermore, it modulates the inflammatory response, regulating processes that, if uncontrolled, can exacerbate tissue damage. Collectively, these effects position VEGF as a key mediator in regenerative dentistry. Table 1 summarizes key findings reported in the literature.

Table 1. Key findings reported in the literature

Source	Title	Intervention	Outcome
Ren B et al.,[6]	VEGF as a potential molecular target in periodontitis: a meta-analysis and microarray data validation	Investigated VEGF expression in periodontitis patients vs. healthy controls via meta-analysis and microarray validation.	Significant association between VEGF expression and periodontitis (P=0.023). VEGF is predominantly involved in blood vessel development, cellular response to growth factors, proliferation, and adhesion.
Proksch S et al.,[7]	VEGF release from hMSCs triggers chemotaxis of alveolar osteoblasts	Used human mesenchymal stem cells (hMSCs) to assess their ability to attract alveolar osteoblasts for bone regeneration strategies.	hMSCs attract alveolar osteoblasts via VEGF release, potentially aiding alveolar bone regeneration. OPG, despite notable release, showed no chemotactic effect.
Ohshima M et al.,[8]	VEGF receptor 1 expression in fibroblasts as a molecular target in periodontitis	Compared gene expression profiles in periodontitis-associated fibroblasts (PAFs) vs. normal gingival fibroblasts using microarrays and 3D in vitro models.	42 genes upregulated and 5 downregulated in PAFs. VEGF receptor Flt-1 showed high activation linked to severe periodontitis. Its inhibition reduced collagen degradation and increased TIMP production.
Wang Y et al.,[9]	Enhanced VEGF-A expression and angiogenic differentiation in human gingival fibroblasts via TNF-α stimulation in vitro	Investigated how TNF-α-stimulated gingival fibroblasts influence angiogenic/osteogenic differentiation via VEGF-A.	TNF-α stimulation increased VEGF-A expression in human gingival fibroblasts (HGFs), promoting cell migration and angiogenic differentiation while inhibiting osteogenic differentiation—mediated by ERK1/2 phosphorylation in the MAPK pathway.

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Hwang J et al., [10]	Collagen-based gene-activated matrices encoding VEGF promote blood vessel formation and enhance wound repair	Used collagen-mimetic peptides (CMPs) to control VEGF-A gene delivery in fibroblasts, developing a hyaluronic acid-collagen gene-activated matrix (GAHCM).	CMP-modified GAHCM enabled tunable VEGF-A gene delivery, inducing persistent endothelial cell (EC) growth/migration for ≥7 days. High CMP modification (50%) yielded elevated CD31 expression and significantly larger, thicker EC networks.
Shams F et al., [11]	VEGF overexpression in dermal fibroblasts accelerates angiogenesis and wound healing function: in vitro and in vivo studies	Genetically modified fibroblasts to overexpress VEGF165; confirmed via qRT-PCR and Western blotting.	VEGF165-overexpressing cells enhanced angiogenesis and significantly reduced wound area in early postoperative days, suggesting therapeutic potential for impaired wound healing.
Lungu C et al.,[12]	Molecular motifs in vascular morphogenesis: VEGF-A as the main promoter of angiogenesis	Investigated VEGF-A angiogenic signaling and interactions with VEGFR2 and ADAMTS1 in peripheral arterial disease (PAD), using computational modeling.	VEGF-A interactions with VEGFR2 and ADAMTS1 are crucial in angiogenesis. Proposed development of novel vasodilatory and angiogenic molecules targeting tyrosine kinase pathways to improve PAD patient outcomes.

Findings by Ren B et al.,[6] reinforce this view by demonstrating a significant association between VEGF overexpression and periodontitis, suggesting its direct involvement in disease progression. Complementarily, Proksch et al.,[7] showed that human mesenchymal stem cells release VEGF, attracting alveolar osteoblasts and contributing to bone regeneration—highlighting VEGF-mediated cellular mechanisms in periodontal repair.

Ohshima et al.,[8] identified overexpression of VEGF receptor 1 (Flt-1) in periodontitis-associated fibroblasts, implicating it in extracellular matrix degradation. Receptor inhibition reduced collagen breakdown, opening therapeutic avenues to modulate VEGF activity in pathological contexts. Similarly, Wang et al.,[9] observed that TNF-α stimulation of gingival fibroblasts increases VEGF-A expression, promoting cell migration and angiogenic differentiation—though inhibiting osteogenic differentiation—underscoring the complexity of inflammatory mechanisms in periodontitis progression.

Recent advances point toward innovative therapeutic applications. Hwang et al.,[10] developed gene-activated collagen matrices enabling controlled VEGF-A release, achieving more efficient blood vessel formation and enhanced wound repair. Likewise, Shams et al.,[11] demonstrated that VEGF overexpression in dermal fibroblasts accelerates angiogenesis and healing in vitro and in vivo, confirming its clinical potential in patients with impaired healing. Finally, Lungu et al.,[12] elucidated molecular mechanisms of vascular morphogenesis, emphasizing VEGF-A interactions with specific receptors and proposing novel angiogenic molecules as therapeutic strategies.

In summary, available evidence shows that VEGF not only enhances periodontal regeneration but also opens avenues for advanced therapies based on genetic engineering and biomaterials. However, challenges persist regarding controlled delivery, long-term side effect evaluation, and clinical protocol standardization. Future research must focus on validating these findings in large-scale clinical trials to establish VEGF as a safe and effective tool for treating advanced periodontitis.[8,13]

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CONCLUSIONS

VEGF has the potential to significantly improve periodontal healing, bone regeneration, and inflammation reduction in patients with periodontal disease. Further research is needed to optimize VEGF delivery, evaluate long-term side effects, and establish standardized clinical protocols. Ongoing investigation into VEGF and periodontal disease offers exciting prospects for effective management of this condition and global improvement of oral health.

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