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REVIEW

PROSPECTIVE ROLE OF VEGF IN THE ASSOCIATION BETWEEN PERIODONTITIS AND PSORIASIS: A SCOPING REVIEW

Papel prospectivo del VEGF en la asociación entre periodontitis y psoriasis: Revisión sistemática exploratoria

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ABSTRACT

Introduction: Increasing evidence suggests an association between periodontitis and psoriasis. Both diseases share immunoinflammatory mechanisms and involve angiogenesis mediated by vascular endothelial growth factors (VEGF). Therefore, it is plausible that VEGF plays a role in connecting both diseases. **Objetive:** To systematically summarize current evidence regarding the biological plausibility of VEGF's involvement in the association between periodontitis and psoriasis.

Materials and Methods: A Scoping Review was conducted following established guidelines. Ad-hoc keywords and inclusion criteria were developed for a comprehensive literature search in PubMed. Only human studies published in the last 7 years were included, excluding non-English or non-Spanish publications. Two independent reviewers performed title and abstract screening, followed by full-text analysis and data extraction.

Results: Twelve studies were included. Main focuses were the gingival crevicular fluid (GCF) levels of VEGF in patients with periodontitis (n=7), the blood serum levels of VEGF in patients with periodontitis (n=3), and the blood serum levels of VEGF in patients with psoriasis (n=3). No studies regarding the GCF levels of VEGF in patients with psoriasis were found. None of the included studies addressed individuals with concurrent periodontitis and psoriasis.

Conclusions: Existing evidence shows elevated levels of VEGF in GCF and serum samples of patients with periodontitis. Increased levels of VEGF were also observed in serum samples of individuals with psoriasis. There is a knowledge gap regarding the GCF levels of VEGF among this group. The exact role of VEGF in the interplay between periodontitis and psoriasis remains to be explored.

Keywords: Periodontitis; Psoriasis; Vascular Endothelial Growth Factor A; Gingival Crevicular Fluid; Serum.

RESUMEN

Introducción: Periodontitis y psoriasis se asocian en la literatura. La angiogénesis mediada por factores de crecimiento endotelial vascular (VEGF) es un mecanismo común a ambas patologías. Es posible que el VEGF participe en la asociación entre ambas enfermedades. **Objetivo:** Resumir sistemáticamente la evidencia disponible con respecto a la plausibilidad de la participación del VEGF en la asociación periodontitis/psoriasis.

Materiales y Métodos: Revisión sistemática exploratoria. Se seleccionaron palabras clave y criterios para una búsqueda comprensiva en PubMed. Solo se incluyeron estudios en humanos publicados en los últimos 7 años. Publicaciones en idiomas que no fuesen inglés/español fueron excluidas. Dos revisores independientes realizaron el cribado y la tabulación de datos.

Resultado: Se incluyeron doce estudios. Sus principales enfoques fueron: Niveles de VEGF en el fluido crevicular gingival (FCG) de pacientes con periodontitis (n=7), niveles de VEGF en el suero de pacientes con periodontitis (n=3) y niveles de VEGF en el suero de pacientes con psoriasis (n=3). No se encontraron estudios sobre los niveles de VEGF en el FCG de pacientes con psoriasis. Ningún estudio incluyó personas con periodontitis y psoriasis concurrentes.

Conclusión: La evidencia muestra niveles aumentados de VEGF en el FCG y suero de pacientes con periodontitis, y niveles aumentados de VEGF en el suero de sujetos con psoriasis. Si bien el VEGF participa de la patogénesis de ambas enfermedades, existe un vacío de conocimiento en relación con sus niveles en el FCG de pacientes psoriásicos. Los mecanismos exactos y rol del VEGF en la asociación periodontitis/psoriasis son desconocidos.

Palabras Clave: Periodontitis; Psoriasis; Factor A de Crecimiento Endotelial Vascular; Fluido Crevicular Gingival; Suero.

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INTRODUCTION

Psoriasis is a chronic immune-inflammatory disease characterized by persistent skin lesions that predominantly affect genetically susceptible individuals with poor lifestyle choices.[1] Typically presenting as painful red plaques covered with silvery scales, psoriasis primarily targets the skin on extensor surfaces such as elbows, knees, scalp, and lower back, but can manifest on any other skin area of the body.[2] In Chile, the reported incidence of psoriasis in 2017 was 22.7 (21.8-23.6) cases per 100.000 individuals,[1] but there is currently no available information on the prevalence and comorbidity risk.[3]

Beyond its physical symptoms, psoriasis can lead to profound psychosocial distress and societal stigma, causing a significant impact on patients' quality of life, social wellbeing and lifespan.[2] Psoriasis has been previously associated with an increase of the systemic inflammatory burden of affected patients, which in turn heightens their risk of developing other immunoinflammatory conditions including cardiovascular diseases and periodontitis among others.[4,5]

Periodontitis is a complex multifactorial, host-mediated inflammatory disease, associated with dysbiotic changes in the oral microbiome.[6] The condition precipitates a hyperresponsive and excessively destructive inflammatory response, which in turn culminates in the degeneration and loss of the periodontal attachment apparatus.[6]

Periodontitis not only leads to oral health decline, but similarly to psoriasis, increases the risk of developing other immunoinflammatory comorbidities such as diabetes and cardiovas--cular disease.[7] A recent systematic review reported that patients with periodontitis present a significantly higher risk of developing psoriasis than periodontally healthy controls.[8]

Moreover, psoriasis patients often exhibit worst periodontal health compared to non-psoriatic healthy controls, as evidenced by pronounced gingival inflammation, higher rates of alveolar bone loss, and an increased incidence of tooth loss.[9] These findings suggest a potential bidirectional relationship between both diseases; however, the exact underlying mechanisms driving these associations remain poorly understood.

It is theorized that periodontitis impacts psoriasis through the systemic translocation of periodontal pathogens and their virulence factors, as well as imbalances in the IL-23/Th17/IL-17 systemic immune response.[10] A recent study revealed variations in the relative abundance of bacterial species in the saliva between individuals with psoriasis and non-psoriatic subjects with and without periodontitis, indicating that the abundance of periodontal pathogens could play a significant role in the pathogenesis of psoriasis.[11] Furthermore, it is conceivable that psoriasis influences periodontitis by the systemic dissemination of molecules from psoriatic skin lesions into the bloodstream, subsequently reaching distant sites such as the periodontal tissues.[12] Supporting this notion, elevated levels of S100A8 and IL-18 have been reported in the gingival crevicular fluid (GCF) of psoriasis patients compared to systemically healthy controls.[12,13]

Angiogenesis refers to the formation of new blood vessels from preexisting ones and is regulated by growth factors and cytokines which are also involved in the pathogenesis of periodontitis and psoriasis.[14,15] Vascular Endothelial Growth Factor (VEGF) is considered a key proangiogenic factor as it induces endothelial cell proliferation, differentiation, and increases vascular permeability and monocyte chemotaxis.[16] Consequently, VEGF exhibits both proangiogenic and proinflammatory properties, which are fundamental in the development of periodo-titis and psoriasis. Fibroblasts, keratinocytes, smooth muscle cells, and endothelial cells, among others, synthesize VEGF.

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The VEGF family consists of VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor. Among these, VEGF-A holds a particular significance as one of the key drivers of the angiogenesis process.[16] Experimental periodontitis show that periodontitis leads to an upregulation of VEGF-at a systemic level,[17] and mice models of psoriasis have also demonstrated increased VEGF-A levels in the skin.[18] Accordingly, these findings highlight the central role of inflammatory and angiogenic processes in periodontitis and psoriasis.[16] The known functions of VEGF in both psoriasis and periodontitis[16,19-23] are summarized in Table 1.

Emerging evidence indicates that systemic diseases, such as diabetes, can influence the expression of VEGF in periodontal tissues. This factor may partly contribute to the association between periodontitis and diabetes.[16,24] Therefore, it is possible that VEGF also plays a significant role in the pathogenic mechanisms that associate periodontitis with psoriasis. However, this hypothesis remains to be explored. Therefore, this Scoping Review aims to systematically explore and summarize current evidence regarding the biological plausibility of VEGF's involvement in the association between periodontitis and psoriasis. The idea was to determine the current understanding of the role of VEGF as a potential underlying mechanism linking periodontitis and psoriasis.

MATERIALS AND METHODS

Protocol and registration

The original research proposal for this scoping review received approval from the ethical-scientific committee of the Faculty of Dentistry of Universidad Andres Bello, Santiago, Chile (#PROPRGFO_2021_30).

The protocol was registered on the Open Science Framework (OSF) platform to ensure accessibility and transparency. The manuscript was structured following the theoretical-conceptual framework for conducting scoping reviews proposed by Arskey and O'Malley,[25] along with its subsequent extensions.[26,27] In addition, the study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) guideline to ensure comprehensive reporting.[28]

Research question and eligibility criteria

The study was articulated using the population/concept/context (PCC) framework recommended by the Joanna Briggs Institute (JBI) to identify the key concepts in primary research questions and guide the search strategy in scoping reviews. The primary research question of this review was: "What is the current evidence regarding the biological plausibility of VEGF's involvement in the association between periodontitis and psoriasis in adult human populations, based on quantitative studies."

The following inclusion criteria were used to comprehensively select studies:

(i) Population: Original primary studies involving human participants with periodontitis and/or psoriasis, published in Indexed scientific journals within the past 7 years, available in either Spanish or English, and accessible electronically through the digital library resources of Universidad Andres Bello;

(ii) Concept: Focus on investigating the biological plausibility of VEGF's involvement as an underlying mechanism linking periodontitis and psoriasis in adult human populations, and;

(iii) Context: No restrictions based on gender, race, geographic location and clinical setting.

Exclusion criteria were as follows:

(a) Case reports and case series;

(b) Secondary studies, including narrative

reviews, systematic-reviews and other types of reviews;
(b) Original primary studies conducted in non-human models (*i.e.* animal or *in vitro* models);
(c) Studies published in non-indexed scientific journals;
(d) Studies published in other languages besides Spanish or English;
e) Studies without clear relevance to the research question (*i.e.* studies that do not examine the relationship between the main variables: VEGF, periodontitis and/or psoriasis).

Information sources and literature search

An extensive electronic literature search was conducted using the PubMed database between March 2021 and December 2022. The purpose of the search was to identify and retrieve relevant manuscripts pertaining to the research question published within the past 7 years. Six different search strategies were employed using recognized MESH/DeCS keywords: [*"VEGF"* AND *"gingival crevicular fluid"* AND *"periodontitis"* AND *"psoriasis"*], ["VEGF" AND *"gingival crevicular fluid"* AND *"periodontitis"*], [*"VEGF"* AND *"gingival crevicular fluid"* AND *"psoriasis"*], [*"VEGF"* AND "serum" AND *"periodontitis"* AND *"psoriasis"*], [*"VEGF"* AND *"serum"* AND *"periodontitis"*], AND [*"VEGF"* AND *"serum"* AND *"psoriasis"*].

All searches were filtered using the "human species" filter and a custom publication date range from 2017 to 2022. Further cross-referencing was performed to identify any additional studies. The included articles were compiled using the systematic literature review software tool Rayyan, accessible at *https://www.rayyan.ai/#.*

Selection and screening of studies

Two independent reviewers (C.S and C.P) used the "blind reviewer" mode in the Rayyan software to screen and select articles based on their title and abstract. The software's integrated duplicate assessment tool was utilized to promptly identify and remove any duplicate studies. Subsequently, the remaining articles were retrieved and subjected to a comprehensive evaluation by reading their full texts. Pre-defined inclusion and exclusion criteria were applied to assess the relevance of each article to the research objective, resulting in the exclusion of studies deemed irrelevant. Any discrepancies or disagreements between reviewers were resolved through discussion and consensus with the senior reviewers (A.F and C.J).

Data charting process

Two independent reviewers (C.S and C.P) conducted the data charting process. Any discrepancies or disagreements were resolved through consultation with the senior reviewers (A.F and C.J). All relevant data from studies were extracted and organized in a predefined excel form, including author, title, year, journal, country, language, study objective, study design, population, comparison (control), GCF levels of VEGF, serum levels of VEGF, VEGF measurement method, main outcomes, outcome significance based on p-value, and conclusions. The primary outcome of interest was to determine the current understanding of the role of VEGF as a potential underlying mechanism linking periodontitis and psoriasis.

Synthesis of results

All included studies underwent careful analysis and were integrated into the synthesis of results. The collected data were comprehensively summarized and presented in both narrative and tabular formats. Additionally, we explored the possibility of utilizing graphics, such as graphs or figures, to enhance the understanding of descriptive data.

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RESULTS

The initial electronic search yielded 53 articles. After removing duplicates, 48 studies underwent screening. Among them, 36 publications were excluded as they did not meet the predefined inclusion criteria based on title, abstract, and content. Ultimately, 11 articles qualified for this review (Figure 1).

Studies included in this work ranged from 2017 to 2023, with 2019 being the most prolific year, yielding three papers.[29,31] Subsequent years saw variable contributions with 2017[32,33] and 2021,[14,34] each having two studies, while 2018,[35] 2020,[30] 2022.[36] and 2023,[37] contributed with one publication each. Geographically, Turkey ranked highest in the number of research articles on the subject (n=6),[14,29,30,32,33,38] followed by Italy,[35] Brazil,[37] Poland,[34] England,[36] and Japan,[37] each contributing one article to the body of research. Regarding methodology, cross-sectional designs were the predominant approach (n=5),[14,29,30,34,37] followed by two longitudinal cohort studies,[35,38] two case-control studies,[33,36] one controlled clinical trial,[32] and one cohort study.[31]

Conversely, the distribution of investigations among journals showed a concentration of studies within the *"Journal of Periodontology"* (n=4),[29,31,38] *"Clinical Oral Investigations"* (n=2),[14,35] and *"The journal of Dermatology"* (n=1).[37] Single articles appeared in *"Archives of Dermatologic Therapy"*,[33] *"Journal of Applied Oral Science"*,[31] and *"Dermatologic Therapy"*.[34]

In general, VEGF was quantified in two forms: levels and concentrations. Levels typically refer to the total amount of VEGF per sample, measured in units of weight such as picograms (pg) or nanograms (ng). Concentrations, on the other hand, were expressed as a ratio of weight to volume, such as picograms per milliliter (pg/mL). Main methods used for quantification of VEGF on the GCF, or serum of affected patients were ELISA and Multiplex bead immunoassays.

To present the results in an organized manner, the articles were categorized based on the characteristics of the study population (patients with periodontitis or psoriasis) and the biological fluid (GCF or blood plasma) from which VEGF was sourced. Consequently, publications were classified into the following groups:

(1) Studies focusing on the GCF levels of VEGF in patients with periodontitis (Table 2).[2]

(2) Studies investigating the blood serum levels of VEGF in patients with periodontitis (Table 3), and;

(3) Studies examining the blood serum levels of VEGF in patients with psoriasis (Table 4).

Since no studies were found concerning the GCF levels of VEGF in patients with psoriasis, no results are presented in that regard. Interestingly,

Table 1. Summary of plausible functions of VEGF in psoriasis and periodontitis.

Role of VEGF in Psoriasis	Role of VEGF in Periodontitis
Keratinocyte proliferation.	Stimulation of alveolar bone resorption.
Keratinocytes mitotic activity.	Induction of osteoclast differentiation.
Upregulation of the VEGFR-1 and VEGFR-2 expression in keratinocytes and endothelial cells.	Inhibition of apoptosis in endothelial cells.
Increases vascular permeability.	Leukocytes' extravasation.
Increases cell adhesion molecules in endothelial cells.	Aberrant vascularization.
Facilitates the migration of leukocytes to the skin.	
Perpetuation of angiogenesis and inflammation.	

Table 2. Summary of studies on vascular endothelial growth factor levels in the gingival crevicular fluid of periodontitis patients.

Author, year	Aim	Study	Population design	Comparison (control)	VEGF measurement method	VEGF Outcomes	*p*-value
Türer et al.,32 2017	To evaluate correlation between GCF endocan levels, VEGFA, and TNF-a levels with periodontal probing depth (PD).	Controlled Clinical Trial	P (n=20)	PH (n= 20)	ELISA (before and 6 weeks after therapy)	Total GCF levels of VEGF-A -were higher in P compared to PH controls (mean ± SD: 12.05±3.65 and 4.66±3.20 pg respectively). No difference was found in the total concentration of VEGF-A between P (15.60+ 4.62 pg/mL) and controls (15.20+10.52pg/mL). A significant reduction of VEGF-A levels and concentrations in the GCF after periodontal treatment (3.15+2.87 pg and 6.35 + 5.89 pg/mL, respectively).	$p<0.05$, $p>0.05$ and $p<0.001$, respectively
Romano *et al.*,[35] 2018	To assess the effects of non-surgical periodontal treatment on gingival crevicular fluid (GCF) cytokines in patients with generalized aggressive periodontitis (GAgP), in relation to clinical parameters.	Longitudinal cohort	AP (n= 16)	PH (n= 15)	Multiplex bead immunoassay (at baseline and at 3- and 6-months post-treatment)	At baseline, VEGF levels and concentrations in moderate and severe periodontal pockets of AP patients were significantly higher than those of PH controls. At baseline, the VEGF levels were positively correlated with the probing depth and gingival inflammation in AP patients. After 3- and 6- months of treatment, VEGF levels decreased significantly compared to baseline, however continued to be significantly higher than those of HP controls. After periodontal treatment, the GCF levels of VEGF continued to correlate positively with gingival inflammation.	$p<0.05$, $p<0.001$ and $p<0.05$, respectively.
Afacan *et al.*,[30] 2019	To investigate the gingival crevicular fluid (GCF) and salivary HIF-1α VEGF, and TNF-α levels in periodontal health and disease.	Cross-sectional	P (n= 20) AP (n= 20) G (n= 26)	PH (n= 21)	ELISA (at baseline and at 3-6-months post-treatment)	Both periodontitis groups presented significantly higher VEGF total amounts (ng/2 samples) compared to gingivitis and periodontally healthy controls. No significant intergroup differences in the GCF total amounts of VEGF (ng/2 samples) were found between P and AP groups. GCF concentrations of VEGF (pg/mL) were significantly higher in controls than in AP, P and G. No significant differences were found in the GCF concentrations of VEGF (pg/mL) between P, AP and G groups. GCF levels of VEGF correlated positively with site-specific periodontal clinical parameters and with TNF-a GCF levels.	$p<0.05$, $p>0.05$, $p<0.05$, $p>0.05$, and $p<0.05$, respectively.

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Author, year	Aim	Study	Population design	Comparison (control)	VEGF measurement method	VEGF Outcomes	*p*-value
Mahmure *et al.*,[29] 2019	To determine levels of ADAMTS-1 in gingival crevicular fluid (GCF) in patients with advanced periodontal diseases and identify their asso-ciation with hypoxia-inducible factor-1alpha (HIF-1α), vascular endothelial growth factor (VEGF-A), and clinical parameters of periodontitis.	Cross-sectional	P (n=21) AP (n=20)	PH (n=20)	ELISA	The total levels of VEGF-A were significantly higher in the AP group compared to the P and PH group (mean and SD: 216.82±185.68 versus 87.27±77.97 and 54.02±42.76 pg/site, respectively). There was no significant differences in the total levels of VEGF-A between patients with P and PH controls (mean + SD: 87.27±77.97 and 54.02±42.76 pg/site, respectively). Concentration of VEGF-A were significantly higher in PH controls (mean + SD: 55.05 + 46.84 pg/uL) versus P and AP patients (mean + SD: 35.87 + 31.85 and 17.33 + 18.04 pg/uL, respectively), with no statistically significant differences between the P and AP. GCF levels of VEGF-A significantly correlated with the examined periodontal clinical parameters and the GCF levels of HIF-1a and ADAMTS-1.	$p<0.05$, $p<0.05$ and $p<0.05$, respectively.
Borges *et al.*,[31] 2019	To monitor early periodontal disease progression and to investigate clinical and molecular profile of inflamed sites by means of crevicular fluid and gingival biopsy analysis.	Cohort	P (n=18)	PH (n=9)	Multiplex Cytokine Profiling Assay (baseline, 15 days and 2 months post treatment).	Total amounts of VEGF were consistently and significantly higher at inflamed sites throughout the study, as compared to healthy controls. No significant differences were observed in the VEGF levels (pg) and expression (mRNA) before and after treatment.	$p<0.05$ and $p>0.05$
Afacan *et al.*,[38] 2020	To assess the effect of non-surgical periodontal treatment on gingival crevicular fluid (GCF) HIF-1α, VEGF, and TNF-αevels in generalized aggressive periodontitis (G-AgP).	Longitudinal cohort	AP (n=20)	PH (n= 20)	ELISA (baseline, 1- and 3-months post treatment)	At baseline, VEGF levels (pg/sample) were significantly higher in AP patients compared to PH controls. After treatment, VEGF levels (pg/sample) in the AP group remained unchanged and continued to be significantly higher than those of PH group. A significant and positive correlation was observed between HIF-1a and VEGF at both baseline and 3 months after treatment.	$p<0.05$, $p<0.05$ and $p<0.05$.
Koidou *et al.*,[36] 2022	To profile, for the first time, the gingival crevicular fluid (GCF) of intrabony defects against a wide array of inflammatory and regenerative markers.	Clinical Trial, Split-Mouth	Intrabony defects (n=21) within systemically healthyperiodontitis patients.	Periodontally healthy sites (n=21) within systemically healthy periodontitis patients.	Multiplex bead immunoassay	Intrabony sites presented significantly higher GCF volumes (uL) compared to controls (mean: 0.85 and 0.45 uL, respectively). Intrabony sites presented significantly higher GCF volumes (uL) compared to controls (mean: 0.85 and 0.45 uL, respectively). GCF concentrations (pg/ml) of VEGF were significantly higher at intrabony sites compared to controls (median and interquartile ranges: 150.48 [102.68 – 210.19] and 64.65 [43.72 – 96.85] pg/ml, respectively. Significance was achieved after adjustment using Bonferroni correction).	$p=0.0007$ and $p=0.0002$

SD: Standard Deviation. **VEGF:** Vascular Endothelial Growth Factor. **GCF:** Gingival crevicular fluid. **P:** Periodontitis. **CP:** Generalized chronic periodontitis. **AP:** Aggressive periodontitis. **G:** Gingivitis. **HI:** Healthy individuals. **PH:** Periodontally healthy controls.

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Table 3. Summary of studies on vascular endothelial growth factor levels in the blood serum of periodontitis patients.

Author, year	Aim	Study	Population design	Comparison (control)	VEGF measurement method	VEGF Outcomes	*p*-value
Türer *et al.,*[32] 2017	To evaluate correlation between GCF endocan levels, VEGFA, and I TNF-a levels with periodontal probing depth (PD).	Controlled Clinical Trial	P (n=20)	PH (n= 20)	ELISA (before and 6 weeks	Serum concentrations of VEGF-A were significantly higher in P compared to PH controls (mean and SD: 735.65±532.67 and 149.76±79.94 pg/ml, respectively).A significant reduction in the serum VEGF-A concentrations was observed after periodontal treatment (mean and SD: 253.12±306.18 pg/ml).	$p<0.01$, $p>0.05$
Mahmure *et al.*[29] 2019	To determine levels of ADAMTS-1 in gingival crevicular fluid (GCF) in patients with advanced periodontal dise-ases and identify their asso-ciation with hypoxia-in-ducible factor-1alpha (HIF-1α), vascular endo-thelial growth factor (VEGF-A), and clinical parameters of periodon-titis.	Cross-sectional	P (n=21) AP (n=20)	PH (n=20)	ELISA	There were no significant diffe rences in the serum VEGF-A levels among groups (mean ± SD: P: 8.81 ± 14.61, AP: 5.88 ± 6.17 and PH: 7.87 ± 7.10 pg/mL).	$p<0.05$,
Çiğdem *et al.,*[14] 2022	To examine the salivary and serum concentrations of angiogenesis related proteins in relation to smo-smoking and periodontitis.	Cross-sectional	P (n=20) AP (n=20)	PH (n=18) PHS (n=20)	Luminex® -xMAP™	Serum concentrations (pg/mL) of VEGF were significantly higher in periodontitis patients *versus* co-ntrol (median and minimum - maximum ranges: 1.9 [1 – 17.6] and 1.3 [0.8-20] pg/ml, respec-pectively). Smoker patients sho-wed a non-significant increase in the serum concentrations of VEGF compared to non-smoker subjects (median and minimum - maximum ranges: 1.8 [0.8 – 20] and 1.5 [0.8-8.9] pg/ml respec-tively).	$p=0.014$a $p>0.256$, respecti-vely.

VEGF: Vascular Endothelial Growth Factor. **P:** Periodontitis. **AP:** Aggressive periodontitis. **PS:** Periodontitis smoker. **PHS:** Periodontally Healthy Smoker. **PH:** Periodontally healthy controls.

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Table 4. Summary of studies on vascular endothelial growth factor levels in the blood serum of psoriasis patients.

Author, year	Aim	Study design	Population	Comparison (control)	VEGF measure-ment method	VEGF Outcomes	*p*-value
Capkin *et al.*,[33] 2017	To investigate the levels of signal peptide CUB-RGF family domainning protein (SCUBE) 1 and 3 and assess possible relation of SCUBE 1 and 3 with disease activity in conjunction with VEGF levels as an established marker of angio-genesis.	Case – control	Ps (n= 48)	HC (n= 48)	ELISA	Higher levels of serum VEGF-A in the Ps gro-up compared to HC group (mean + SD: 346.74 +213 ng/mL and 243.8 +118 ng/mL, respectively).	*p*=0.004
Socha *et al.*,[34] 2021	To determine the serum concentrations of selected pro- and anti-angiogenic factors and their inter-relation ships in patients with plaque psoriasis	Cross-sectional	Ps (n= 41)	HC (n= 38)	ELISA	No differences in the serum VEGF-A concentrations (pg/ml) between Ps and HC groups (104.31 + 24.3 and 92 + 24.1, respectively). Among Ps, the C-reactive protein concentration correlated moderately with VEGF-A concentrations (pg/ml). VEGF-A levels correlated posi tively with psoriasis severity measured in terms of PASI and BSA.	*p*= 0.25, *p*= 0.2 and *p*= 0.0009
Watanabe *et al.*,[37] 2023	To explore the serum levels of angiogenesis-related factors in patients with psoriasis and investigated their association with clinical severity and laboratory data.	Cross-sectional GPP (n=13)	PsV (n=18)l HC (n=10)	PsA (n=24) plexTM	LEGEND	Higher serum VEGF concentrations (pg/mL) in the GPP group compared to the HC group. Serum VEGF concentrations (pg/mL) in the GPP group decreased significantly after systemic therapy, reaching similar levels to those of HC. Among patients with GPP, serum concentrations of VEGF were positively correlated with the serum concentrations of CRP.	*p*= 0.032, *p*= 0.0117 and *p*= 0.0003

VEGF: Vascular Endothelial Growth Factor. **P:** Periodontitis. **AP:** Aggressive periodontitis. **PS:** Periodontitis smoker. **PHS:** Periodontally Healthy Smoker. **PH:** Periodontally healthy controls.

no studies were found that explored the levels of VEGF in both GCF and/or blood serum samples of patients with concurrent periodontitis and psoriasis.

Overall, none of the studies included in this review directly addressed our research question regarding the prospective association of periodontitis and psoriasis by means of VEGF. Instead, investigations focused on the recurring theme of exploring VEGF as a prospective inflammatory/angiogenic-related biomarker for monitoring disease severity, progression, and treatment response in either periodontitis or psoriasis independently. In periodontitis, studies observed that the levels of VEGF were consistently elevated in the GCF and serum of patients with periodontal disease compared to healthy controls (Table 2 and Table 3).

The levels of VEGF in the GCF were also found to positively correlate with the severity of periodontal disease, as evidenced by periodontal clinical parameters and HIF1a protein levels. Although treatment of periodontal disease generally led to significant reductions in the GCF and serum VEGF levels, findings from one of the longitudinal cohorts studies[35] indicated that even after 3 and 6 months, VEGF levels in the GCF did not fully revert to those observed in periodontally healthy individuals (Table 2). This persistent elevation suggests that there might be other systemic or non-periodontal sources contributing to the GCF levels of the growth factor in these patients.

In psoriasis, research showed that the serum levels of VEGF were usually higher in psoriasis patients compared to systemically healthy controls (Table 3). The levels of VEGF in the serum were also found to be positively correlated with psoriasis severity and systemic inflammation, as evidenced by the PASI and BSA indexes and the C-reactive protein. Finally, psoriasis treatment resulted in a reduction of the serum VEGF levels in psoriasis patients (Table 3).

DISCUSSION

Several epidemiological studies have demonstrated an association between periodontitis and psoriasis.[4,23] In fact, some studies have explored the bacterial composition in saliva and the levels of biomarkers in oral fluids and blood serum to explain the potential mechanisms underlying the association between both conditions.[11–13,39] However, the biological mechanisms have not been fully elucidated. In this scoping review, we found that levels of VEGF-A are elevated in both GCF and serum of patients with periodontal diseases, as well as in the serum of psoriatic patients. However, to date, there are no studies that evaluate this growth factor considering both conditions, indicating a significant gap in the existing literature on the topic.

Regarding periodontitis, there are several reasons as to why the GCF levels of VEGF may be upregulated. One of these derives from the differences in the GCF volumes between periodontally healthy patients and those with periodontal disease since GCF volume increases in the presence of inflammation.[40] Therefore, it is expected that patients with periodontitis would have higher GCF volumes, and consequently, higher GCF levels of VEGF. Despite this, the decrease in VEGF-A levels in the GCF after conventional periodontal treatment reinforces the involvement of VEGF-A in the pathogenesis of periodontal disease.[35]

Moreover, and in line with this, VEGF-A levels increase in the serum of individuals with periodontitis compared to healthy controls, and they also decrease after periodontal treatment.[32] Therefore, it is plausible that VEGF-A has a key role in the modulation of angiogenesis in the inflammatory and regenerative processes involved in periodontal disease.

Hypoxic conditions associated with periodontal disease may be another potential pathway

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that explains the rise in VEGF-A levels in the GCF.[41] Hypoxia-inducible factor 1 (HIF-1) is a heterodimeric transcription factor composed of two subunits: HIF-1α and HIF-1β. HIF-1α is found in the cytosol and is frequently regulated by cellular oxygen tension. Under normoxic conditions, prolyl hydroxylases (PHD) or asparagine hydroxylases hydroxylate HIF-1α, initiating its proteasomal degradation. In contrast, HIF-1β is constitutively expressed and localized in the nucleus. Under hypoxic conditions, PHDs are inhibited, leading to the stabilization of HIF-1β. Consequently, HIF-1α translocate to the nucleus, dimerizes with HIF-1β, and initiates the transcription of various target genes, such as VEGF.[42,43] The influence of hypoxia on the increase in VEGF-A levels in periodontitis can be supported by a clinical study that observed a positive correlation between HIF-1α and VEGF-A levels in the GCF and saliva of patients with periodontitis.[29,38]

When it comes to psoriasis, it has been observed that VEGF-A is overexpressed in both keratinocytes and fibroblasts from psoriatic skin lesions, in comparison to cell samples from normal, healthy skin. This observation suggests that VEGF-A could have a significant role in the development and formation of psoriasis plaques.[44] Based on this, our hypothesis proposes that VEGF-A might disseminate from psoriatic skin lesions into the systemic circulation of patients with psoriasis. Several studies have shown higher levels of VEGF-A in the blood serum of psoriatic patients compared to non-psoriatic healthy controls,[33,37] and these levels tend to decrease following psoriasis treatment,[37] indicating that systemic VEGF-A levels are influenced by psoriasis activity. Therefore, it is plausible to consider that the regulation of VEGF-A in subjects with psoriasis is dependent on TNF-α.[45,46] This is supported by evidence showing that treatment with TNF-α blockade leads to downregulation of VEGF-A expression and a decrease in the blood vessel area in the skin of patients with psoriasis.[46] This illustrates the dependence on VEGF-A in inflammatory diseases. Therefore, it is plausible to assume that the systemic inflammation associated with both periodontitis and psoriasis,[47,48] can contribute to the increased systemic levels of VEGF-A, affecting both the skin and periodontal tissues, thereby promoting the progression of both diseases.

Regarding the limitations observed in the articles included in this review, there are several points to consider. Firstly, no studies were found that comprehensively analyzed or proposed the molecular mechanisms behind the association between periodontitis and psoriasis. This lack of in-depth investigation into the molecular pathways involved in both diseases limits our understanding of the specific role of VEGF in connecting these two diseases. Secondly, the sample sizes in the studies were generally small, which may limit the representativeness and generalizability of their results in larger populations. In addition, many of these articles did not have a long-term follow-up period, with some extending to up to six months. The limited duration of follow-up restricts our ability to assess the long-term effects and outcomes related to VEGF in the context of periodontitis, psoriasis and the connection of both. While there is a significant body of literature dedicated to the investigation of biomarkers in psoriasis, the number of articles particularly focused on VEGF is limited. This scarcity of studies hampers our comprehensive understanding of its specific role and contribution to the pathogenesis of the dermatosis. Lastly, one of the articles only included male patients as participants This gender bias limits the generalizability of the findings and highlights the need for more inclusive studies that encompass diverse populations.

In terms of future directions, as a research group, we propose conducting studies on the VEGF levels in the GCF of patients with psoriasis with and without periodontitis. This would provide

insights into the role of VEGF in the pathogenesis of psoriasis and its potential connection to periodontitis. To enhance the robustness of future studies, it is crucial to include larger sample sizes. This will increase the representativeness of the findings and allow for more reliable conclusions. Additionally, extending the follow-up period in these studies would provide valuable information on the long-term effects and outcomes associated with VEGF in the context of periodontitis and psoriasis.

CONCLUSION

Based on the literature analyzed in this scoping review, it is possible to conclude that there is a significant increase in the VEGF levels in both GCF and serum among subjects with periodontitis compared to periodontally healthy controls. Similarly, patients with psoriasis also exhibit increased levels of serum VEGF compared to dermatologically healthy controls. These findings suggest that VEGF might be involved in the pathogenesis of both diseases. However, more studies are needed to fully elucidate the exact mechanisms by which both diseases might be connected, and the precise role of VEGF in this association.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS APPROVAL

This study was approved by the ethical-scientific committee of the Faculty of Dentistry, Universidad Andres Bello, Santiago (#PROPRGFO_2021_30).

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