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Zhu, JF¹; Zhang, SH²; Shi, J³; Ning, N⁴; Wei, Y⁵; Zhang, Y⁶.**Corresponding author:**

Junfei zhu

zhujunfei2@126.com

Author Affiliation:

China Japan friendship hospital.

ADMINISTRATIVE INFORMATION**Support** - No funding.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202380126**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 August 2023 and was last updated on 30 August 2023.**INTRODUCTION**

Review question / Objective The objective of the study was to compare the levels of visfatin in body fluids including serum, saliva, and gingival crevicular fluid (GCF) between periodontitis patients and healthy individuals, and to elucidate the alteration of visfatin levels after periodontal treatments.

Condition being studied Periodontitis is a common inflammatory disease induced by polymicrobial factors. The consequences of periodontal disease are frequently presented as gingival infection, alveolar bone destruction, as well as periodontal attachment loss. The status of periodontitis strongly affected the quality of life. The destructed periodontal tissues not only give an annoying smell but also leads to aesthetic compromise, which influenced social life. Additionally, the masticatory function declined, which brought difficulties in nutrition intake. Moreover, periodontitis has been reported to be associated with multiple systemic diseases, such

as diabetes, cardiovascular disease, and cancer. The etiology of periodontitis has been extensively studied. Although the inflammation of periodontal tissue is supposed to be initiated by bacteria, the disproportionate and unbalanced host response to the microbial film and the inability of the host to resolve the inflammatory process is considered to be responsible for the occurred periodontal damage.

Adipokines are a complex cohort of cytokines produced by adipocytes, including leptin, adiponectin, resistin, and visfatin. etc. It has been widely demonstrated that adipokines are involved in multiple internal events, such as energy metabolism, wound healing, as well as inflammatory reactions. Visfatin, also identified as the pre-B-cell colony-enhancing factor (PBEF), is a 52-kDa protein promoting pre-B cell colony release from lymphocytes and improving the maturation of B lymphocytes. As a pleiotropic cytokine, visfatin has roles in many processes, including insulin mechanisms, apoptosis, and inflammation regulation. The association between visfatin and the pathogenesis of several systemic

diseases, such as type 2 diabetes mellitus, polycystic ovary syndrome, and cardiovascular diseases has also been reported. Additionally, in the process of inflammation, visfatin induces pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF- α), interleukin (IL)-1, 6, and 8[11], which played a critical role in the initiation and development of systemic inflammation from neutrophils, lymphocytes, and macrophages. The relationship between adipokines and periodontitis has been reported. Previously, the present author published a meta-analysis regarding the association between periodontitis and serum levels of leptin and adiponectin, finding that elevated serum leptin and decreased serum adiponectin were related to periodontitis. Recent year studies have shown that visfatin also played roles in the development of periodontitis. Multiple studies have been published to discover the possible links between visfatin and periodontitis, However, an evidence-based summative study was needed to provide a more precise evaluation.

METHODS

Search strategy Pubmed: ("periodontal"[Title/Abstract] OR "periodontitis"[Title/Abstract]) AND ("visfatin"[Title/Abstract] OR "nicotinamide phosphoribosyltransferase"[Title/Abstract] OR "NAMPT"[Title/Abstract] OR "pre b cell colony enhancing factor"[Title/Abstract] OR "PBEF"[Title/Abstract])

Embase: (visfatin:ab,ti OR 'nicotinamide phosphoribosyltransferase':ab,ti OR nampt:ab,ti OR 'pre b cell colony enhancing factor':ab,ti OR pbef:ab,ti) AND (periodontitis:ab,ti OR periodontal:ab,ti)

Web of Science: (TS=(periodontal) OR TS=(periodontitis)) AND (TS=(Visfatin) OR TS=(nicotinamide phosphoribosyltransferase) OR TS=(NAMPT) OR TS=(pre b cell colony enhancing factor) OR TS=(PBEF))

Cochrane Library: ((periodontal):ti,ab,kw OR (periodontal disease):ti,ab,kw (Word variations have been searched))AND ((visfatin):ti,ab,kw OR (nicotinamide phosphoribosyltransferase):ti,ab,kw OR (NAMPT):ti,ab,kw OR (pre b cell colony enhancing factor):ti,ab,kw OR (PBEF):ti,ab,kw (Word variations have been searched)).

Participant or population Patients with periodontitis and health individuals for control.

Intervention Periodontal treatment.

Comparator We compared the Visfatin levels of patients before and after the periodontal treatments.

Study designs to be included Case-controlled studies and single-armed clinical trials.

Eligibility criteria The inclusion criteria for the included studies were as follows: (1) the observational studies comparing visfatin levels in serum, saliva, or GCF between periodontitis patients and periodontally healthy individuals; (2) Clinical trials comparing visfatin levels in serum, saliva, or GCF before and after periodontal treatments; (3) Studies with sufficient data for the statistical analyses; and (4) Studies in English or Chinese. The exclusion criteria were as follows: (1) Conference abstracts; (2) Trial registry records; and (3) those with repeated data.

Information sources Pubmed, Embase, Web of Science and Cochrane Library.

Main outcome(s) The levels of visfatin in body fluids including serum, saliva, and gingival crevicular fluid(GCF).

Data management Stata.

Quality assessment / Risk of bias analysis The methodological qualities of the included case-controlled studies were assessed according to the Newcastle–Ottawa scale (NOS). Three dimensions including selection, comparability, and exposure were considered. In the section on comparability, the most important factor was identified to be BMI. Eight items were graded, with a score range of 0–9 points. Overall, studies with final scores of 1–3, 4–6, and 7–9 were considered to be of low, moderate, and high qualities. Additionally, the Methodological Index for Nonrandomized Studies (MINORS) was applied for assessing the qualities of the included clinical trials. A total of 12 items were considered, and 0–2 points could be graded for each item. As in the present study we only evaluated the quality of single-arm designs, the first 8 items were employed. The final scores ranged from 0 to 16 points. Studies with scores 0–5, 6–10, and 11–16 were considered to be of low, moderate, and high qualities.

Strategy of data synthesis The data of visfatin levels were presented as mean (M) \pm standard deviation (SD). The results in the form of median (minimum – maximum) were shifted to $M \pm SD$ according to the estimation method reported by Hozo et al. The standard mean difference (SMD) and corresponding 95% confidence interval (CI) were calculated. Heterogeneity was estimated by chi-square and I². Random-effects model was used when the P value \geq 50%. Sensitivity analyses were performed to test the robustness. The

statistical analyses were processed using STATA 15.0.

Subgroup analysis The subgroup analysis was not conducted..

Sensitivity analysis The sensitivity analyses were proceeded by removing a single study each time and observing the influence of each study on the result. According to the sensitivity analyses, the robustness of the results was confirmed.

Country(ies) involved China.

Keywords Visfatin; Periodontitis; Periodontal treatment; Gingival crevicular fluid; Meta-analysis.

Contributions of each author

Author 1 - Junfei Zhu.

Email: zhujunfei2@126.com

Author 2 - Suhan Zhang.

Email: 455179304@qq.com

Author 3 - Jing Shi.

Author 4 - Ning Ning.

Author 5 - Ying Wei.

Author 6 - Ye Zhang.

Email: 327052665@qq.com