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THE EFFECT OF LIPOCALIN-2 IN PERIODONTAL DISEASES

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Abstract
Current evidence suggests that Lipocalin-2 is a protein secreted from bone tissue and is elevated in the presence of periodontal disease. This systematic review will allow us to assess the concentration of LCN-2 in patients with periodontal disease, identify the most appropriate biological fluids for its detection, identify the form of periodontal disease in which this protein is most highly expressed, as well as to study the relationship of LCN-2 with other inflammatory markers and systemic diseases, and to monitor changes in its expression during treatment.

Keywords: Lipocalin-2, periodontal disease, inflammation, bone resorption, tissue dehydration, mediators, receptor, biological fluids.

Introduction

Lipocalin-2 (LCN-2), also known as neutrophil gelatinase-dependent lipocalin (NGAL), is synthesized mainly by neutrophils, osteoblasts, and adipocytes. Initially, LCN-2 was isolated from neutrophil granules as a 25 kDa glycoprotein and was found to participate in the body's resistance to infections by sequestering bacterial siderophores. In recent years, the role of LCN-2 in other physiological processes, such as appetite suppression and bone remodeling in response to mechanical stress, has been studied.

In addition, LCN-2 is also recognized as an inflammatory mediator, as its expression is activated by inflammatory cytokines such as IL-6, IFN-γ, and TNF-α in adipocytes, neutrophils, and macrophages, and it plays an important role in obesity and inflammatory diseases. LCN-2 is also associated with periodontal disease, one of the most common oral diseases, affecting approximately 19% of the world's population. Periodontitis is a clinical condition characterized by inflammation of the gums and alveolar bone, which, if left untreated, leads to tissue damage.

The mechanisms of soft and hard tissue loss depend on the interaction of innate and adaptive immune mediators, cytokines such as IL-1α, IL-1β, TNF-α, IL-6, IL-17, lipid mediators and chemokines. The formation of periodontal pockets and loss of alveolar bone are the main signs of periodontitis. This process causes excessive migration of neutrophils into the gingiva, but they cannot effectively fight the infection. Instead of neutrophils, macrophages, dendritic cells release cytotoxic substances and inflammatory cytokines, which further exacerbate inflammation. This microenvironment leads to increased expression of nuclear factor kB ligand (RANKL), which

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enhances the differentiation and activation of osteoclasts, leading to bone resorption. Although traditional methods, namely clinical and radiological indicators, are used to diagnose and treat periodontitis, they have limitations in assessing and predicting the degree of disease progression. The current periodontitis classification system is based on etiological factors, clinical history and indicators, and special importance is given to the use of biomarkers. At the same time, increased levels of LCN-2 in the blood or urine have also been found in systemic inflammatory conditions such as kidney disease, rheumatic diseases, obesity, diabetes and heart failure. However, the direct relationship of LCN-2 to periodontal inflammation has not yet been fully studied. So far, there is insufficient information on which body fluids are suitable for detecting LCN-2, how the increase in LCN-2 is related to the type of periodontal disease, and whether LCN-2 levels decrease as a result of periodontal treatment. Also, no clear conclusion has been drawn on the relationship between LCN-2 expression and periodontitis and systemic diseases. Therefore, the aim of this systematic review was to analyze the available clinical data to determine the association of LCN-2 with periodontal diseases.

Materials and Methods:

The study was conducted as a systematic review in accordance with Cochrane standards. In order to determine the consequences of LCN-2 expression in periodontal diseases, the following key questions were sought:

1. Is LCN-2 increased in periodontal diseases?
2. In which type of periodontal disease is LCN-2 more expressed?
3. In which body fluids is LCN-2 detected?
4. How do LCN-2 levels relate to other inflammatory biomarkers?
5. Do LCN-2 concentrations change as a result of periodontal disease treatment?
6. Are LCN-2 levels increased if periodontal disease is accompanied by systemic disease?

The criteria for this systematic review were determined based on key elements such as patient population, comparison groups, included studies, and outcomes.

Observations and Results:

There were significant differences in the definition and diagnostic criteria of periodontal disease. Complete data were provided on the basis of five key diagnostic parameters—bleeding point (BOP), pocket depth (PD), clinically relevant loss (CAL), plaque index (PI), and gingival index (GI). Five of the eleven studies included patients with gingivitis, and all eleven included patients with periodontitis. Most studies reported changes in LCN-2 concentrations.

Seven studies compared patients with periodontal disease with healthy controls and found increased LCN-2 levels in patients with periodontal disease. Although increased LCN-2 concentrations were also reported in patients with gingivitis, no significant difference was found between controls and patients with gingivitis. All seven studies showed a significant increase in LCN-2 levels in periodontitis, especially in stage III periodontitis. These results indicate that LCN-2 levels are directly proportional to the severity of periodontal disease. The biological fluids used to determine LCN-2 were also recorded in the studies. Specifically, gingival fluid (GCF) (n=4), saliva (n=4), urine (n=1), and tear (n=1) samples were used. LCN-2 levels were also assessed in

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subgingival tissues. GCF and saliva were the most frequently analyzed fluids. Regarding the evaluation methods, seven studies used the ELISA method and three studies used the multiplex immunoassay method.

In addition, nine of the eleven studies assessed other inflammatory markers associated with periodontal disease. Three of them reported increased IL-1β levels, two reported increased MMP-9 levels, and one study reported increased LCN-2 levels along with increased TNF-α and Sema-3 levels. Markers of inflammation associated with systemic diseases were also examined, such as increased urinary β-macroglobulin levels (a marker of nephropathy), as well as high-sensitivity C-reactive protein (hs-CRP) and brain-derived natriuretic peptide (NT-proBNP), which are associated with cardiovascular disease. In contrast, adiponectin levels (a hormone that regulates insulin sensitivity) were significantly reduced in patients with periodontitis and diabetes, while LCN-2 levels were increased. These data suggest that LCN-2 is closely related not only to periodontitis but also to systemic inflammatory processes.

Discussion:

To our knowledge, this systematic review is the first to examine the relationship between LCN-2 concentrations and stages of periodontal disease, the types of biological fluids suitable for its detection, and the relationship of LCN-2 with inflammatory markers and general systemic diseases. In addition, this study also examines the response to treatment in patients with periodontal disease by comparing them with periodontally healthy individuals.

Due to variability between studies, a meta-analysis was not possible. However, this systematic review included observational and experimental studies to assess the impact of LCN-2 expression on the development of periodontal diseases.

The results of the analysis showed that LCN-2 levels were elevated in all cases of gingivitis and almost all stages of periodontitis, which makes it a promising biomarker for the detection of periodontal diseases. Despite the fact that the methods of detecting LCN-2, the diagnostic criteria for periodontitis, and the methods of grouping patients according to the stage of the disease vary in different studies, it was possible to determine that the level of LCN-2 increases proportionally with the severity of the disease.

Conclusion:

According to the results of this systematic review, LCN-2 may play an important role in the development of periodontal diseases, mainly through inflammatory processes. Since LCN-2 levels are clearly elevated in periodontal diseases, its levels vary depending on the type and severity of the disease. Gingival sulcus fluid (GCF) and saliva samples are widely used for the detection of LCN-2. In addition, periodontal treatment helps to reduce LCN-2 levels, thereby reducing inflammatory markers and improving oral health.

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