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(REVIEW ARTICLE)

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Increase of alveolar bone damage in patients with chronic periodontitis due to obesity

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Abstract

Background: Obese patients have a body weight that exceeds normal, then there are disorders of the liver, consumption of a high- fat diet, and there are inflammatory factors that can trigger alveolar bone damageand cause periodontitis**.**

Objective: To explain the mechanism by which obesity can cause alveolar bone damage in patients with chronic periodontitis.

Research Methods: literature sources used in the preparation of articles through several databases (Pubmed, Embase, Scopus, Scient Direct, and CINAHL) with descriptions related to alveolar bone damage in patients with chronic periodontitisdue to obesity.

Results: Inflammatory cytokines in obese patients are associated with high C-reactive protein (CRP) levels and will induce prostaglandin E2 (PGE2) and matrix metalloproteinase (MMP) which can trigger osteoclastactivity. PGE2 will induce osteoblasts to produce receptor activator of nuclear factor kβ -ligand (RANKL). RANKL and receptor activator of nuclear factor kappa (RANK) will activate osteoclastogenesis. The regulation of RANKL with RANK by osteoprotegerin (OPG) will affect the activation and differentiation of osteoclasts and the damage of the periodontal ligament that cause alveolar bone destruction.

Conclusion: Alveolar bone damage in patients with chronic periodontitis due to obesity that occurs due to disorders of the liver and a high-fat diet that affects bone metabolism and causes a local inflammatory response. This obesity condition can eventually exacerbate the occurrence of alveolar bone damage by increasing CRP levels which stimulate MMP production. This review is corresponding to the Sustainable Development Goal No. 3, ensuring healthy life and improve the welfare of all populations of all ages.

Keywords: Chronic Periodontitis; Metabolic Syndrome; Obesity; Alveolar Bone Damage; Public Health

1. Introduction

Damage to the alveolar bone is one of the characteristics of a person experiencing chronic periodontitis. Under normal circumstances, there is a balance in the alveolar bone, namely by the process of remodeling. When alveolar bone damage occurs, infection occurs so that the process of destruction of alveolar bone is faster than the process of bone formation, so that this condition makes the bones appear damaged [1]. There are two factors that affect bone damage, namely bacteria and the host. The presence of bacterial plaque will cause the differentiation of bone progenitor cells to become osteoclasts, then the gingival cells will be stimulated to release mediators that will inhibit the work of osteoblasts and

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reduce the number of osteoblast cells and result in the remodeling process being inhibited and resorption activity increasing [2].

Various studies have proven a close relationship between periodontitis and obesity. Some research results show that obese people have a higher prevalence of periodontitis than non-obese people. Conversely, obesity can also exacerbate periodontitis through diabetes mellitus [3]. Obese sufferers have a high fat and glucose content which can cause infection due to an imbalance in cytokine production, resulting in an increase in cytokines which can trigger periodontitis [4]. Based on the description above, in this study, verification was carried out through analysis of journal reviews to determine whether there is damage to the alveolar bone in patients with chronic periodontitis due to obesity.

2. Methods

Inclusion criteria are papers comprised studies on periodontitis, alveolar bone degeneration, and obesity; they were written in English; they appeared in journals that were accredited both nationally and globally; they had to be published in the last ten years; and they could be read in full. The sources of information used are online journal databases at Google Scholar, Science Direct, NCBI, and PUBMED. Online searches on the Google Scholar database use the keywords: "Obesity and Periodontitis", "Relationship between Obesity and Periodontitis", "Periodontitis and Alveolar Bone Loss" [5].

Screening through reading journals related to the title of the literature review. Selection of journals based on: title, abstract, and relevant conclusions. Then the selection of articles based on inclusion and exclusion criteria. After the study selection was carried out, data extraction was based on predetermined inclusion criteria. The data extraction included in the review includes:

- Author and year of publication
- Research title
- Research conclusions [6]

3. Results

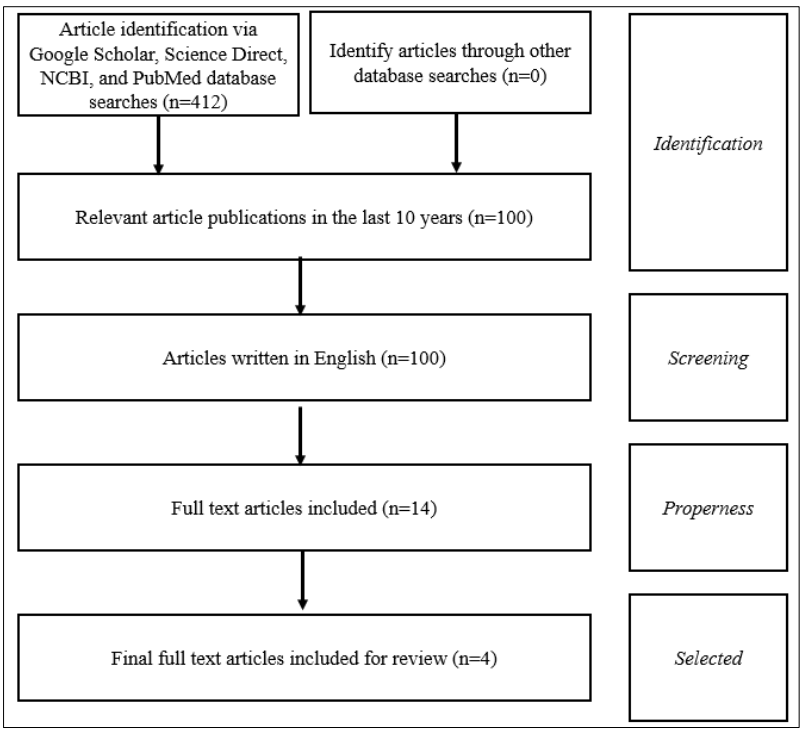

Figure 1 The Flow chart of article selection [5]

The authors searched articles using predefined keywords. Furthermore, a screening was carried out on the titles and abstracts of the selected articles and obtained several research articles that were relevant to the topic of the review.

Next, a selection of full text articles was carried out based on inclusion and exclusion criteria. The results of the selection of full text articles obtained 14 journals that match the research objectives. The final extraction results obtained 4 articles that could be included and analyzed. The selected articles are very relevant to the topic of the review which discusses alveolar bone damage in patients with periodontitis due to obesity. The whole process of article selection can be seen in the Figure 1.

4. Discussion

In the process of periodontitis, lipopolysaccharide (LPS) from gram-negative bacteria can trigger the emergence of acute phase inflammation (API). This inflammation can affect the periodontal tissue and other organs including the liver. Furthermore, the API will trigger the liver to produce C-reactive protein (CRP). Obesity is associated with high CRP levels due to the increased secretion of pro-inflammatory cytokines in obese individuals. CRP also affects leptin levels in obese patients thereby exacerbating alveolar bone damage in periodontitis sufferers through increased CRP which will facilitate replacement of the extracellular matrix in adipose tissue by increasing stimulate matrix metalloproteinase (MMP) production, where MMP itself if increased will stimulate the destruction of the gingival cellular matrix and result in alveolar bone damage [1,7].

Alveolar bone damage in patients with chronic periodontitis can be caused by obesity. Research conducted by Verzeletti et al [8] found being overweight can induce increased blood glucose levels and insulin resistance which can lead to severe alveolar bone damage. Obesity disorder has the potential to be affected by other diseases such as hypertension, heart disease, diabetes mellitus, and cancer. Studies show that obesity is associated with changes in immunocompetence such as a lower-than-normal number of lymphocytes and an altered amount of cytokine production. Obesity was also found to be associated with impaired osteoblast insulin signaling, reduced osteoblast cells, and decreased bone formation. Obesity can affect bone metabolism by increasing bone resorption and reducing bone formation. Obesity induced by a high-fat diet can lead to alveolar bone loss and exacerbate the severity of periodontitis. This is also supported by Khan [9] who stated that obese people cannot adapt and maintain homeostasis under sustainable energy and nutrition. Oxidative stress which is involved in various pathological conditions such as obesity can cause inflammatory responses and organ dysfunction. Inflammatory diseases such as periodontitis induce the production of proinflammatory cytokines.

Intra-abdominal fat and abdominal subcutaneous fat are important compared to subcutaneous fat in the lower extremities. This may be related to the fact that intra-abdominal fat is more lipolytically active than the others. Research conducted by Flier [10], at the University of Birmingham, England proved that fat cells around the waist are excess active cells that can disrupt insulin stability and increase blood pressure and cholesterol in the blood. Fat cells can produce cytokines that have effects similar to endocrine organs. Some of them are: leptin, adiponectin, interleukin-6 (IL-6), resistin, and tumor necrosis factor (TNF-α). In addition, IL-6 will also induce the production of inflammatory proteins from the liver such as CRP [1]. IL-6 is a cytokine produced by fat cells. The increase in IL-6 levels is affected by the size of the fat cells. The pro-inflammatory effect of IL-6 can be linked to insulin resistance. In obesity, adipocytes will secrete TNFα which will stimulate preadipocytes. Then the preadipocytes will secrete monocyte chemoattractant protein–1 (MCP–1) resulting in an increase in macrophages in adipose tissue. When macrophages in adipose tissue become active, they produce various cytokines, including leptin, IL-6, plasminogen activator inhibitor-1 (PAI-1), and angiotensinogen. Elevated cytokines in a person with high fat levels are associated with high CRP levels. Increased CRP will affect leptin levels and exacerbate alveolar bone damage in patients with periodontitis. Leptin levels in serum are related to leptin mRNA expression in fat cells and triglyceride levels in these cells [11].

The hypothalamus is an important site for leptin's work as a regulator of energy intake and expenditure and has a role in several neuroendocrine axes. Leptin can reduce fat and triglyceride synthesis and increase fatty acid oxidation so that insulin sensitivity can increase. According to Cavagni et al [12] the consistency of diet and bed can affect alveolar bone loss due to friction and damage to the periodontal tissue. Medium or long-term diabetic patients with multi-organ complications are prone to periodontitis. Fat-enriched diets can increase pathogens in the oral cavity of diabetic patients. Gram-negative bacteria produce LPS which enters the blood directly to exacerbate systemic inflammation and disease. Elevated plasma LPS levels have been shown to be the initiator of metabolic disease through increased systemic inflammation. Therefore, increased systemic inflammation in diabetic patients may be associated with systemic disease. Thus, inflammation could be the key to periodontitis by increasing CRP levels and exacerbating alveolar bone destruction [13].

In previous studies, it was stated that systemic inflammation exacerbated by obesity with increased production of pro-inflammatory cytokines and tumor necrosis factor alpha by adipocytes could increase osteoclast cell activity through the ratio of receptor activator of nuclear factor kβ -ligand and osteoprotegerin (RANKL/OPG) [12]. The timing of obesity

induction must be considered because different stages of obesity can lead to varying degrees of systemic inflammation. This study also shows that the regulation of bone metabolism may be affected by obesity when it is associated with periodontal disease.

The effect of periodontitis on biochemical serum parameters of metabolic diseases found in diet-induced obesity (DIO). This study used male rats which were divided into two groups, namely the group of rats that were given a normal diet and a high-fat diet (DIO). Based on the results of these studies it is known that metabolic dysregulation in the liver can increase due to periodontitis induced by ligature placement and Porphyromonas gingivalis infection. Oxidative stress is defined as an imbalance between reactive oxygen species (ROS) and antioxidant mechanisms caused by an increase in fatty acids. The accumulation of fat in the liver can increase the occurrence of damage caused by ROS. This then causes mitochondrial dysfunction, inflammation, and reduced antioxidant production by hepatocytes. According to Alazawi et al., 2017 [14] environmental factors such as diet influence bacterial metabolism in the oral cavity which increases certain sugar levels and insulin resistance. CRP is an acute phase reactant produced by the liver in response to various inflammatory stimuli. However, not all studies report an association between periodontal disease and CRP. These reports reflect the differences in the severity of periodontal disease in the different study populations. As many as 80% to 85% of patients who have acute bacterial infections have a CRP value of >100mg/L while a CRP value that is considered normal is <10mg/L. The increase in CRP is influenced by various factors such as high blood pressure, alcohol use, smoking, low level of physical activity, chronic fatigue, coffee consumption with high triglycerides, insulin resistance diabetes, estrogen consumption, eating high protein foods, and people with sleep disorders. accompanied by depression [15].

Obesity is associated with systemic diseases such as diabetes, hyperlipidemia, and non-alcoholic steatohepatitis. If a person is obese then there is an excess intake of fat in the body. This excess fat intake will then lead to fat accumulation in hypertrophic adipocytes. This will trigger the secretion of inflammatory cytokines such as type 2 diabetes, asthma, cancer, and osteoarthritis [14].

Based on recent epidemiological studies, periodontal disease contributes to the development of metabolic disorders associated with obesity. The relationship between obesity and periodontal disease will increase the risk of diabetes in a person. Obesity is related to genetic and environmental factors, especially diet. Generally, the diet used in obesity research is the high-fat diet (HFD) because it can lead to excess weight and rapidly increasing fat accumulation. HFD can also induce increased insulin levels and insulin resistance. Based on the observations made in this study, body weight, serum insulin level, and insulin resistance or homeostatic model assessment for insulin resistance (HOMA-IR) were much higher in the DIO group compared to the normal group [15].

The level of alanine aminotransferase (ALT) is an enzyme that occurs when liver damage occurs. ALT increased significantly in the ligature-induced rat group along with the application of P. gingivalis bacteria compared to the control group. These results indicate that there is a relationship between liver damage and P. gingivalis infection in damaged periodontal tissues. As anaerobic Gram-negative bacteria, endotoxin and fimbriae of P. gingivalis bacteria can stimulate acute inflammation not only in the periodontal area, but also in other organs such as the liver. If there is inflammation in the liver organ, it is associated with a high CRP level, where this condition will affect leptin levels and exacerbate alveolar bone damage in periodontitis patients. Uric-acid levels in patients with periodontitis are higher than healthy people and there is a significant correlation between biomarkers of salivary tissue damage and uric acid levels (Banu et al., 2015). Uric-acid may serve as a blood biomarker of the host inflammatory response in patients with periodontitis. Given these facts, ligature-induced periodontitis significantly increases uric-acid levels in the serum of DIO mice [16].

Research conducted by Muluke et al [17] regarding diet-induced obesity and its impact on bone destruction in the periodontal tissue aims to determine the impact of increased levels of fatty acids (FA) on alveolar bone damage carried out through a periodontal disease model. which has been induced by P. gingivalis bacteria in order to analyze the underlying cellular mechanisms of osteoclasts in absorbing bone and osteoblasts in bone formation. Based on these studies, obesity has the main characteristic of increasing circulating free fatty acids due to excess food intake that enters the body. The researchers chose palmitic acid (PA) and oleic acid (OA) as research materials in order to determine the inflammatory response of osteoblast cells as bone formation and osteoclast cells in bone resorption against P. gingivalis bacteria. Researchers investigated the induction of TNF-α, IL-6, and other proinflammatory cytokines involved in bone loss associated with periodontitis [18].

In the results of a study conducted by Muluke et al [17] showed that the presence of P. gingivalis bacteria could significantly increase TNF-α gene expression in osteoclasts. P. gingivalis bacteria induced IL-6 expression in all conditions, and the most visible was in osteoclasts cultured with PA. OA appears at the level of hyperlipidemic disease, but does not weaken the osteoclast cell inflammatory response to PG bacterial infection. The Toll-Like Receptor 2

(TLR2) and Toll-Like Receptor 4 (TLR4) genes produce proteins involved in the innate immune response that participate in identifying pathogens for destruction.

LPS activates TLR4 which can be found on the cell membrane of gram-negative bacteria such as PG. Analysis of the TLR4 gene showed an increase in expression in response to PG bacteria in all conditions, with PA producing the highest response, and TLR2 being involved in the recognition process for gram-positive bacteria. Researchers found an increase in the concentration of TNF-α secreted into the culture media by osteoclast cells with the addition of PG bacteria. The OA culture showed lower TNF-α secretion results compared to the PA culture in the presence of PG bacteria. meanwhile, IL-6 secretion increased in all conditions in response to bacterial inoculation but not much different from OA and PA [17].

RANKL and OPG have roles in osteoclast regulation. The investigators found a non-significant increase in RANKL and a decrease in OPG gene expression in osteoblasts cultured with PA and P. gingivalis. IL-6 gene expression showed a tendency to be higher in all cultures exposed to P. gingivalis and high-fat conditions. However, no difference was found between OA and PA and there was no trend in TNF-α gene expression. These results are in accordance with previous studies conducted by researchers, where the main effect of PA on bone homeostasis is through the influence of PA on osteoclasts. Inflammatory cytokines such as TNF-α are involved in the host inflammatory response to bacterial infection. Recent studies have shown that concurrent exposure of macrophages to LPS and PA can trigger an increase in inflammatory cytokine production via a nuclear factor-κB-mediated (NFKB) pathway [19].

PA is known to exacerbate inflammation while OA has anti-inflammatory properties. Therefore, the pro-inflammatory nature of PA may explain its adverse impact on bone health by increasing osteoclast differentiation through increased TNF-α. This is consistent with the results of this study where osteoclasts exposed to P. gingivalis bacteria showed a significant increase in TNF-α expression when cultured with PA levels of hyperlipidemia [17].

PA is a saturated fatty acid found in meat and milk. It increases TNF-a and then increases the inflammatory response of macrophages against P. gingivalis. Then P. gingivalis bacteria colonize with epithelial cells and result in an increase in CRP which will cause periodontitis and alveolar bone damage [19].

5. Conclusion

Alveolar bone damage in patients with chronic periodontitis due to obesity which occurs due to liver disorders and a high-fat diet which affects bone metabolism and causes a local inflammatory response. This obesity condition can eventually exacerbate alveolar bone damage by increasing CRP levels which stimulate MMP production. However, there have been many studies that support that decreasing CRP can improve the condition of the oral cavity.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare there is no conflict of interest in this study.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans' subjects by any of the authors.

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