

Potential of alveolar bone damage in periodontitis patients with dyslipidemia

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World Journal of Advanced Research and Reviews, 2023, 19(02), 152–161

Publication history: Received on 17 June 2023; revised on 29 July 2023; accepted on 31 July 2023

Article DOI: <https://doi.org/10.30574/wjarr.2023.19.2.1498>

Abstract

Background: Severe periodontitis is the sixth most prevalent disease across the globe. Periodontitis is highly associated with decreased HDL, increased LDL concentrations, and triglycerides. The increase of serum lipid levels beyond the physiological range will change immune cell function by increasing the production of pro-inflammatory cytokines which will interfere with tissue response and affect wound healing thereby increasing susceptibility to periodontitis.

Purpose: To explain the mechanism of increased alveolar bone destruction in patients with periodontitis accompanied by dyslipidemia.

Methods: This study uses a narrative review

Results: Several mechanisms of alveolar bone destruction in periodontitis accompanied by dyslipidemia are through the severity of the metabolic syndrome, serum Lp-PLA2, CRP, chemerin, plasma secretion of TNF- α , IL1 β , IL-6, PGE2, IL-2, interferon gamma, matrix metalloproteinases, systemic inflammatory burden, serum triglyceride levels, increased HDL and LDL levels, and decreased serum cholesterol.

Conclusions: Alveolar bone damage in periodontitis accompanied by dyslipidemia can occur through several mechanisms. This study complies with and supports the Sustainable Development Goal No. 3, to ensure healthy lives and promote well-being for all at all ages.

Keywords: Alveolar Bone Damage; Periodontitis; Dyslipidemia; Public Health; Triglyceride; Inflammation

1. Introduction

Periodontal disease or periodontitis is a disorder that is often found in humans and is a risk factor that has a role in the process of disrupting masticatory function and loss of human teeth. It is generally caused by plaque accumulation on the tooth surface. Plaque is a thin layer of biofilm produced by bacteria or microorganisms' pathogens, such as *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *Tannerella forsythia*, and *Fusobacterium nucleatum* [1]. Several factors that can increase a person's risk of developing periodontitis include social and behavioral factors, systemic factors, genetic factors, the microbial composition of dental plaque, and other risk factors that may arise [2]. Other risk factors that can increase risk of periodontitis is dyslipidemia. Dyslipidemia is an abnormal lipid condition characterized by increased serum triglyceride concentrations, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels, accompanied by decreased high-density lipoprotein (HDL) cholesterol levels [3].

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The relationship between altered lipid states and periodontitis has been investigated in several studies on the grounds that periodontitis may affect individual systemic conditions. A meta-analysis covering 19 scientific studies showed that periodontitis was significantly associated with reduced HDL, increased LDL concentrations, and triglycerides. Serum lipid levels that increase towards the upper limit of the normal physiological range will change the function of immune cells thereby increasing the production of pro-inflammatory cytokines. The release of pro-inflammatory cytokines is believed to interfere with tissue response and affect wound healing thereby increasing susceptibility to periodontitis [4]. We try to explain the mechanism of increased alveolar bone destruction in patients with periodontitis accompanied by dyslipidemia

2. Methods

Inclusion and exclusion criteria were determined. The papers that included are articles on periodontitis, alveolar bone damage, and dyslipidemia; articles that were written in Indonesian and English; nationally and internationally accredited journals; articles that were published from 2011 to 2022; and articles that can be accessed in full text. The exclusion criteria are articles that do not mention 'dyslipidemia as a risk factor for the severity of periodontitis'. The sources of information used in obtaining articles are online journal databases: Google Scholar, Science Direct, NCBI, and PUBMED [5].

Online searches on online journal databases were conducted using keywords of "Dyslipidemia and Periodontitis", "Dyslipidemia or Periodontitis", "Relationship between Periodontitis and Dyslipidemia", "Periodontitis and Alveolar Bone Loss", "Periodontitis or Alveolar Bone Loss", "Dyslipidemia and Alveolar Bone Loss", and "Dyslipidemia or Alveolar Bone Loss".

Authors conducted screening by reading relevant journals, including the title, abstract, and conclusions. Then full selection of articles based on predetermined inclusion and exclusion. After the study selection was carried out, the authors extracted data based on predetermined inclusions. The data extraction included in this review includes:

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

3. Results

3.1. Article Search Results

The flow diagram presents the process of determining the articles to be used in the discussion according to predetermined inclusion and exclusion criteria.

Figure 1 shows the selection of articles on searches through Pubmed and Science Direct with predefined keywords. The results of the articles obtained reached 526 articles. However, there were 517 articles other than the topic of periodontitis and dyslipidemia which were included in the search which were then excluded. Thus, the number of articles included in the review totaling 9 articles.

4. Discussion

Research conducted by Corbi [7] identified differentially expressed genes (DEGs) from circulating lymphocytes and monocytes to reveal potential biomarkers that can be used as molecular targets for future diagnosis of any combination of pathologies of type 2 diabetes mellitus, dyslipidemia, and periodontitis (compared to healthy patients) and provides insight into the molecular mechanisms underlying these diseases.

There were 150 samples in Corbi's study [7] which were divided into several groups: (i) samples that were systemically healthy and did not suffer from periodontal disease (control group); (ii) samples with periodontitis, but systemically healthy; (iii) samples with dyslipidemia and periodontitis; (iv) samples with well-controlled type 2 diabetes mellitus with dyslipidemia and periodontitis; and (v) samples with type 2 diabetes mellitus (2DMT2) that is not well controlled with dyslipidemia and periodontitis. This study used a gene expression dataset generated from peripheral blood mononuclear cells (PBMC) with functional enrichment analysis.

In evaluating the expression profile of circulating lymphocytes and monocytes from group 3 compared to the control group, RT-qPCR results showed that TGFB111 (transforming growth factor beta 1 induced transcript 1) and VNN1 (vanin 1) were found in group 3 compared to the control group. Based on functional network analysis, this gene is related to cellular signaling and movement, cancer, molecular transport, and vitamin/mineral metabolism which can affect poor glycemic control in T2DM patients with dyslipidemia and periodontitis. The TGFB111 gene encodes a ligand secreted from the TGF-beta protein superfamily (transforming growth factor-beta). Ligands from this family bind to various TGF-beta receptors leading to the recruitment and activation of the SMAD family, which are transcription modulator signal transducers that mediate TGF beta signaling, and regulate various cellular processes. The protein encoded by the TGFB111 gene regulates cell proliferation, differentiation, and growth, and modulates the expression and activation of other growth factors including interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α). The conclusion to these results is that circulating TGFB111 overexpression in group 3 subjects may contribute to excessive cellular activation and immune response compared to individuals in the control group [7].

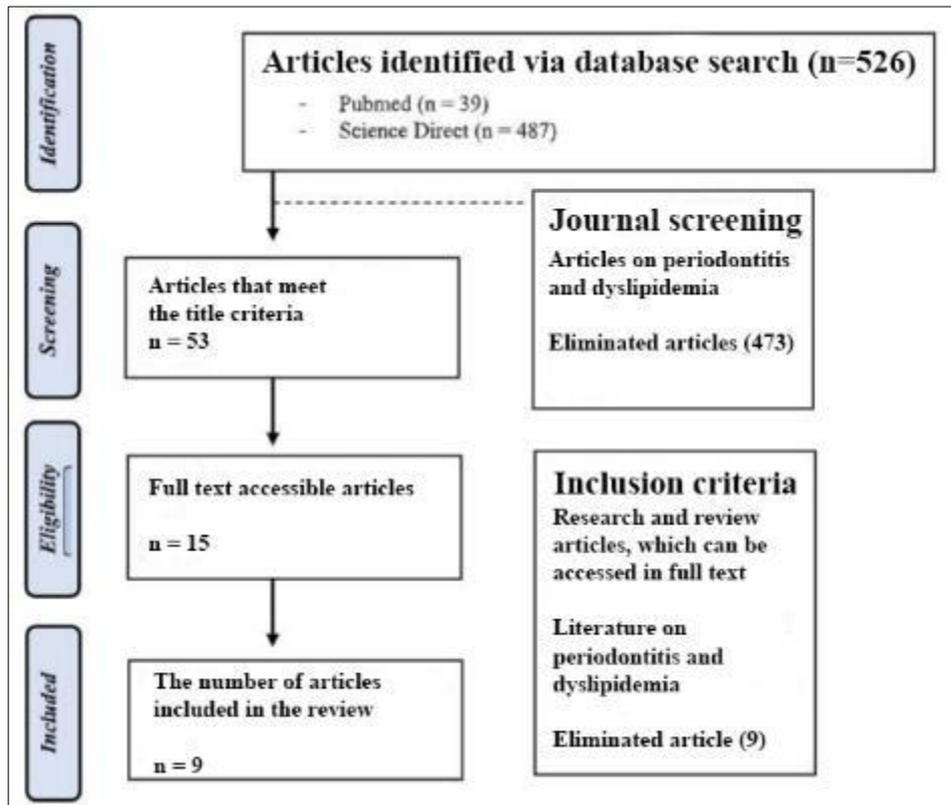


Figure 1 The Flow chart of article selection [5]

CXCL8 gene regulation (CXC Motif Chemokine Ligand 8) was lower in group 3 compared to the control group. The CXCL8 gene, formerly referred to as interleukin 8 (IL-8), encodes a protein that is a key chemokine in the initiation and amplification of acute inflammatory reactions and in chronic inflammatory processes because it attracts and activates neutrophils in areas of inflammation. In periodontitis, there are interactions between microbial species in the subgingival biofilm and adjacent periodontal tissues that elicit innate immunity by releasing chemokines, such as CXCL-8/IL-8 into the gingival sulcus fluid (GCF) required to recruit neutrophils. There must be a balance of CXCL8/IL8 mRNA and protein production to elicit an adequate host immune response against periodontal pathogens leading to a healthy periodontal status. The concentration of IL-8 is higher in the saliva of periodontally healthy individuals compared to those with periodontitis [7].

Corbi et al [7] also found that circulating lymphocytes and monocytes had significantly lower CXCL8/IL8 m-RNA levels in healthy subjects when compared to patients with dyslipidemia and periodontitis simultaneously. In addition, evidence of higher expression of systemic proinflammatory cytokines, such as IL-1 β , IL-6 and TNF- α in PBMCs of dyslipidemia patients, indicates that circulating lymphocytes and monocytes are in a hyper-inflammatory state along with low CXCL8/IL8 expression.

The results of ingenuity pathway analysis (IPA) analysis found that there was downregulation of the CXCL8/IL8 gene in group 3 compared to the control group and an upregulation of the TGFBI1 gene in circulating lymphocytes and monocytes from the same subject. IPA analysis results also show that the integrin subunit beta 2 (ITGB2 gene) and HLA-DRB4 (major histocompatibility complex, class II, DR beta 4) is downregulated in periodontitis patients by interacting via TNF in the same tissue. These results suggest that patients with increased metabolic disturbances may elicit immune responses in a broader and different way from patients who demonstrate adequate metabolic control [7].

The conclusion from the study of Corbi et al [7] is that lymphocytes and monocytes circulating simultaneously in individuals suffering from dyslipidemia and periodontitis show an altered molecular profile mainly related to the inflammatory response and immune cell activity.

Research conducted by Fentoglu et al [8] showed that periodontal disease is associated with an increased severity of hyperlipidemia as well as serum Lp-PLA2 and CRP, which are lipoprotein-related inflammatory markers associated with worsening periodontal conditions and hyperlipidemia. Serum levels of Lp-PLA2 and hsCRP may play an important role in the association between periodontal disease and hyperlipidemia, and the control of these mediators may affect the inflammatory control of patients with hyperlipidemia and periodontal disease.

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet activating factor acetylhydrolase, is a member of the phospholipase A2 family and has an important role in the progression of advanced atheromatous plaque rupture. The main enzyme role of Lp-PLA2 is to hydrolyze oxidized phospholipids which produce proinflammatory products that play an important role in the induction of chemotactic responses, endothelial cell dysfunction, and smooth muscle cell apoptosis. Thus, Lp-PLA2 becomes a key mediator of the inflammatory process in dyslipidemic conditions [8].

C-reactive protein (CRP) is a marker of systemic inflammation and another lipoprotein-associated inflammatory mediator. CRP circulates more in free form than bound to circulating lipoproteins, although CRP can interact with phospholipids and oxidized lipoproteins under in vitro conditions. CRP activates the complement system associated with the immune system and binds to Fc receptors on phagocytic cells activated by IgG antibodies and acts as an opsonin that can facilitate the uptake and clearance of apoptotic and necrotic cells during the acute phase response. High CRP levels can lead to periodontitis, with CRP facilitating extracellular matrix turnover in adipose tissue by increasing MMP production. Increased MMP will stimulate the destruction of the gingival cellular matrix, the attachment of collagen fibers to the epithelium, and the periodontal ligament, and will result in damage to the alveolar bone [8].

Ramos Junior et al in their research [9] showed that chemerin improves osteoclast function and in metabolic dyslipidemia is involved in the pathophysiology of alveolar bone loss observed in rats. Chemerin is an adipokine that regulates adipogenesis and metabolic function of adult adipocytes primarily through activation of chemokine-like receptors 1 (CMKLR1) released by various cell populations, including adipocytes, fibroblasts, keratinocytes, and endothelial cells, which are primarily associated with obesity and the metabolic syndrome. Elevated levels of chemerin have been found in individuals with obesity, type 2 diabetes, and osteoporosis. These adipokines were identified as markers of inflammatory and metabolic syndromes.

Chemerin can bind to three different G protein-coupled receptors: CMKLR1, GPR1, and CCRL2. The CMKLR1 receptor is abundantly expressed in leukocytes, including monocytes, macrophages, and plasmacytoid dendritic cells (pDCs). However, mature osteoclasts express low levels of CCRL2 and GPR1 and CMKLR1 expression is upregulated in late stages of osteoclastogenesis. Chemerin acts as a chemoattractant mediator for immune cells by activating CMKLR1. Chemerin does not affect NFATc1 expression, but is a key regulator of osteoclast differentiation in α -activated preosteoclasts [9].

CMKLR1 activation by chemerin in macrophages induces adhesion to VCAM-1 and fibronectin. In vitro analysis showed downregulation CMKLR1 in the early stages of differentiation and gradual increase in the late stages. Chemerin does not modify markers of osteoclast differentiation or osteoclast formation, but chemerin enhances actin ring formation and bone resorption activity in mature osteoclasts. Chemerin-treated osteoclasts exhibit an F-actin ring that is associated with increased resorptive function. In addition, chemerin activity is inhibited by a chemerin receptor antagonist, CCX832, namely by inhibiting increased matrix dissolving activity in bone resorption [9].

Osteoclasts treated with chemerin had an increased resorption function through CMKLR1 activation. The functional activity of osteoclast resorptive depends on the expression of several genes, including cathepsin K, MMP-9, carbonic anhydrase II, and H⁺-ATPase. Cathepsin K is the most abundant enzyme in the resorption lacunae and together with MMP-9 is essential for organic matrix degradation. Other findings suggest that chemerin does not change some

osteoclast marker genes (NFATc1 and TRAP) but increases the expression of other genes (cathepsin K and MMP-9) which may be related to the timing of CMKLR1 expression. Chemerin increases mature osteoclast activity by involving ERK5 phosphorylation [9].

ERK5 pathway activation is an important cascade of intracellular signaling involved in RANKL-induced osteoclastogenesis. Ramos Junior et al investigated the potential effect of chemerin on ERK5 activation because chemerin can also activate the ERK1/2 pathway in myoblast cells. Ramos Junior et al., (2017) found that chemerin can potentiate RANKL-induced ERK5 phosphorylation in preosteoclasts. ERK5 inhibition was able to suppress the increase in cathepsin K expression induced by chemerin so that chemerin increased osteoclast activity through the ERK5 pathway [9].

Obesity has been associated with changes in bone metabolism, evidenced by several studies emphasizing the bone marrow as a potential regulatory system that controls the interactions between osteoblasts and osteoclasts during bone remodeling. In addition, obesity and dyslipidemia associated with the metabolic syndrome are risk factors for the development of periodontitis in humans and in experimental models, which lead to alveolar bone destruction [9].

The study by Ramos Junior et al used two models of dyslipidemia, mice treated with a high-fat diet [HFD] C57/BL6 and mice with dyslipidemia due to gene mutations, to increase high circulating levels of chemerin. This study demonstrated a significant increase in chemerin levels in serum and gingival tissue. Serum chemerin levels, CMKLR1 expression, and chemerin in gingival tissues were increased in rats with dyslipidemia [9].

Morphometric analysis in the study of Ramos Junior et al showed that mice treated with HFD and mice with dyslipidemia due to gene mutations showed increased alveolar bone loss compared to the respective control mice, which was associated with upregulation of mRNA expression of chemerin, CMKLR1 and cathepsin K in gingival tissue. Treatment of mice with dyslipidemia due to gene mutations with CCX832 effectively inhibits bone loss. Chemerin receptor antagonists also inhibit cathepsin K expression in the gingival tissues [9].

Overall, research by Ramos Junior et al shows that chemerin is involved in the physiological balance of osteoblast and osteoclast activity. Metabolic dyslipidemia induces significant alveolar bone resorption in rats. In addition, chemerin can play an important role in bone homeostasis in dyslipidemia rats with in vitro studies in increasing osteoclast activity [9].

The study by Cavagni et al [10] aimed to evaluate the effect of obesity/hyperlipidemia through a western diet on alveolar bone damage induced in 60 Wistar rats. Wistar rats were chosen because they exhibit a specific immune response that mimics the immunological diversity in humans. Experimental animals were randomly divided into 4 experimental groups: control group, periodontitis, obesity/hyperlipidemia, and obesity/hyperlipidemia with periodontitis. The control group was not given any treatment, the obese/hyperlipidemic and obese/hyperlipidemic groups with periodontitis were given a high-fat hypercaloric diet, and the periodontitis and obesity/hyperlipidemia groups with periodontitis-induced periodontitis at the 12th week with ligature on the upper second molar.

The results in the study of Cavagni et al showed that cholesterol/triglyceride levels in the liver increased in the obese/hyperlipidemic group. The periodontitis and obesity/hyperlipidemia groups with periodontitis showed significantly higher %ABL (Alveolar Bone Loss) compared to the control and obesity/hyperlipidemia groups. Obesity and hyperlipidemia significantly increased %ABL in the obese/hyperlipidemic group with periodontitis compared to the periodontitis group with respective values of 53.60 ± 3.44 and 42.78 ± 7.27 . The obesity/hyperlipidemic group showed a higher %ABL than the periodontitis group. Two parameters of hyperlipidemia measured in the liver are triglycerides and cholesterol. The levels of these two parameters were higher in animals that were given the western diet compared to animals that were not exposed. There is a significant difference between animals with obesity/hyperlipidemia and periodontitis together compared to those without periodontitis [10].

An interesting finding in the study of Cavagni et al was that triglyceride and cholesterol levels were higher in animals with obesity/hyperlipidemia and periodontitis simultaneously compared to animals without periodontitis. It is possible that the microbes in ligature-induced periodontitis in animals exposed to the western diet will be a potential factor for the parameters of hyperlipidemia, so that there is a significant additional impact for someone with periodontitis who also suffers from obesity/hyperlipidemia. Another possibility that can occur is the role of periodontitis in worsening metabolic parameters so that periodontal prevention and treatment can assist in achieving a better metabolic pattern. In general, obesity/hyperlipidemia can lead to a higher risk of alveolar bone loss and diabetes is recognized as a strong modulator of periodontal breakdown [10].

The study of Cavagni et al showed that non-ligature-induced animals exposed to obesity/hyperlipidemia showed a higher level of periodontal damage compared to animals that were not in this condition. With the presence of ligatures, obesity/hyperlipidemia also predisposes to bone destruction, as indicated by significantly higher alveolar bone loss in the obesity/hyperlipidemia and periodontitis group compared to the periodontitis group. It can be concluded that the presence of ligatures and metabolic disorders can cause bone damage which can be associated with an inflammatory burden which includes increased plasma secretion of TNF α , C-Reactive Protein, and IL-6. The findings of this study generally support the hypothesis that obesity and hyperlipidemia are potential factors for periodontal breakdown, especially when the two are combined. The conclusion from the study of Cavagni et al is that obesity/hyperlipidemia can modulate the host response in the periodontium and increase the expression of periodontal damage in spontaneous and ligature-induced periodontitis in rats [10].

The study by Jepsen et al [11] aims to provide an update on the evidence from epidemiological, mechanistic, and interventional studies regarding the association between periodontitis and the metabolic syndrome. Some of the possible mechanisms that can cause periodontitis as a risk factor for metabolic syndrome are:

4.1. Inflammation

Periodontitis is a chronic inflammatory disease caused by a complex of microorganisms in the subgingival biofilm, such as *P. gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. Smoking, genetic predisposition, psychological stress and a number of systemic diseases may also contribute to the initiation and development of periodontitis. Biofilm bacteria interact with infiltrating and resident host cells, resulting in increased release of pro-inflammatory cytokines, such as interleukin-1beta, interleukin-6, and tumor necrosis factor alpha, as well as reactive oxygen species (Jepsen et al., 2020).

The levels of these proinflammatory cytokines and reactive oxygen species are not only increased in the gingival and gingival sulcus fluid but also in the serum of periodontitis patients. Periodontal cells can secrete proinflammatory adipokines, such as visfatin, leptin, and resistin. Gingival tissue and gingival sulcus fluid volume change in periodontitis, suggesting that they may play an important role in the etiopathogenesis of periodontitis. Increased serum levels of visfatin, leptin, and resistin, and decreased serum levels of anti-inflammatory adiponectin adipokines were also found in patients with periodontitis. Periodontitis-related systemic inflammation can inhibit insulin receptors which can increase insulin resistance so that the body tries to compensate by increasing insulin secretion, as evidenced by increased insulin levels (hyperinsulinemia) in periodontitis sufferers, this is because insulin is an anabolic hormone that encourages glucose uptake and fat storage so that in this condition periodontitis sufferers can cause obesity.

4.2. Food supply

Periodontitis contributes to the metabolic syndrome through increased levels of appetite-stimulating ghrelin. Research by Jepsen et al., (2020) found increased serum levels of total ghrelin and acylated ghrelin in periodontitis patients compared to patients with healthy periodontal. This is because periodontitis stimulates hunger through the activation of ghrelin as an anti-inflammatory hormone.

4.3. Gut microbiota

Theoretically, periodontitis might also contribute to an increased risk of metabolic syndrome by altering/disrupting the gut microbiota. Intestinal microorganisms play an important role in nutrient and energy extraction, and energy regulation. Oral administration of the drug will cause dysbiosis of the intestinal microbiota caused by *P. gingivalis* bacteria with an increase in the proportion of Bacteroidetes phylum, a decrease in the proportion of Firmicutes phylum, and an increase in serum endotoxin levels. Disturbance of gut microbiota composition by orally-derived periodontopathic bacteria may be a mechanism linking periodontitis and systemic disease. Dysbiosis that occurs due to *P. gingivalis* bacteria is not the same as that which occurs in obesity [11].

Research by Jepsen et al [11] shows that metabolic syndromes such as dyslipidemia, diabetes/hyperglycemia, and hypertension are related to periodontitis through several pathological mechanisms. Periodontitis is associated with reduced high-density lipoprotein and increased triglycerides and low-density lipoprotein. In addition, a relationship between periodontal bacteria and changes in lipid profile was found. Bacterial infection and inflammation can impact lipid and lipoprotein metabolism. Lipoprotein and lipoprotein changes induced by infection/inflammation can occur as a result of increased secretion of very low-density lipoprotein, lipolysis of adipose tissue, increased de novo hepatic fatty acid synthesis, suppression of fatty acid oxidation, delayed secondary clearance of very low density lipoprotein, and reduced lipoprotein lipase and apolipoprotein-E. In a combined clinical and in vitro investigation, it was found that

lipopolysaccharide increased the lipolytic activity of adipocytes in co-culture with macrophages. It can be concluded that periodontal infection promotes lipolysis and upregulation of circulating triglycerides.

Inflammation also induces changes in core hormone receptors, such as peroxisome proliferator-activated receptors and their target genes involved in fatty acid and triglyceride metabolism. Initially, changes in lipids and lipoproteins in infectious/inflammatory conditions are beneficial to the host and part of the innate immune response. Lipoproteins can neutralize bacterial lipopolysaccharides by accelerating their clearance from plasma, diverting them from monocytes and macrophages, decreasing immune cell activation, and reducing cytokine release, thereby attenuating lipopolysaccharide toxicity. However, chronic dyslipidemia conditions impair this mechanism [11].

Dyslipidemia may contribute to an increased risk of periodontitis because fatty acids and lipids can induce the secretion of pro-inflammatory cytokines. In addition to the activity of high-density lipoprotein in stimulating the removal of excess cholesterol from peripheral tissues and transporting it to the liver for excretion, high-density lipoprotein has antimicrobial, antioxidant and anti-inflammatory properties. Therefore, decreased levels of high-density lipoprotein and increased levels of triglycerides and low-density lipoprotein lead to a severe proinflammatory state. Lipids can interfere with cell membrane-bound receptors and enzyme systems, thereby contributing to the development of periodontal disease. Tartaric acid phosphatase positive cells are not only increased by stimulation with receptor-2 ligands, but when receptor-2 is coupled to oxidized low-density lipoprotein, osteoclastogenesis is significantly accelerated. It can be concluded that periodontitis and dyslipidemia can be linked, but the interaction between infection/inflammation and lipids/lipoproteins requires a complex mechanism [11].

Research by Gomes Filho et al [12] shows a positive relationship between periodontitis, and its severity (moderate and severe), and dyslipidemia. The association between periodontitis and dyslipidemia could be due to several factors, among which are general genetic susceptibility and systemic inflammatory burden. Increased levels of several inflammatory mediators in the form of increased interleukin (IL) -1 β , IL-6, tumor necrosis factor, prostaglandin E2, and matrix metalloproteinase is a host response in response to the periodontal microbiota in inflamed periodontal tissues. In addition, there was a concomitant increase in the burden of systemic inflammation indicating an association between periodontitis and dyslipidemia.

Dyslipidemia is an important atherogenic factor in developing macrovascular complications. Chronic dyslipidemia is dangerous for sufferers and can be associated with many other diseases. These infection/inflammation-induced lipoprotein and lipid changes may result from increased low-density lipoprotein secretion, lipolysis of adipose tissue, increased de novo hepatic fatty acid synthesis, decreased fatty acid oxidation, and low-density secondary clearance. Increased lipolysis in adipose tissue with increased circulating triglyceride production can be caused by periodontal infection. Another conclusion drawn from the study of Gomes Filho et al is the importance of the relationship between periodontitis and systemic health conditions, and highlights the importance of periodontitis in public health [12].

Research by Gao et al [13] aimed to evaluate the association of low-density lipoprotein receptor-related protein 5 (LRP5) and apolipoprotein E (APOE) polymorphisms with serum lipid concentrations and periodontitis in a Chinese population. LRP5 and APOE polymorphisms are involved in immunomodulation processes and inflammatory activity. This study was conducted by comparing the mean serum lipid concentrations of the LRP5 and APOE polymorphisms between the case group (n = 185) and the control group (n = 138).

Gao et al [13] found four important findings arising from their research: (i) compared to the control group, individuals with periodontitis showed significantly lower serum total cholesterol (TC) and lower HDL-c (high-density lipoprotein cholesterol); (ii) individuals with LRP5 SNPs (single-nucleotide polymorphisms) showed higher TC and HDL-c with reduced odds ratios for periodontitis; (iii) individuals with combined polymorphisms have higher serum LDL-c and TC levels with reduced odds ratio values for periodontitis; and (iv) a decrease in the odds ratio for individuals with the LRP5 haplotype in periodontitis.

Inflammation is a process that often causes dyslipidemia. Inflammatory biomarkers include tumor necrosis factor, IL-2, and gamma interferon, increased serum triglyceride levels, and decreased serum cholesterol. In addition, lipopolysaccharide injection and severe sepsis reduced LDL-c and HDL-c levels.

Dyslipidemia is common in individuals with chronic inflammatory conditions, such as rheumatoid arthritis and systemic lupus erythematosus. Patients with periodontitis showed lower TC and HDL-c levels than the control group. Other studies have shown that individuals with periodontitis had higher TC and triglyceride levels compared to the control group and the levels of inflammatory mediators and serum lipid concentrations did not differ significantly between individuals with periodontitis compared to controls. The difference in results in this study compared to other studies

may be due to differences in poor periodontal conditions and severe inflammation in periodontitis. Differences in the distribution of age and race/ethnicity of the samples from Gao et al [13] and other studies also contributed to the difference in the results obtained.

Gao et al [13] also observed a significant combined association between APOE and LRP5 polymorphisms and periodontitis after adjusting for age, sex, smoking status and BMI, these findings suggest that APOE and LRP5 polymorphisms may play an important role in periodontitis. APOE has been shown to play an important role in the immune response and in the passage of lipid antigens to immune cells, while LRP5 is a Wnt/b-catenin signaling co-receptor that mediates leukocyte inflammatory responses.

A study showed that APOE e2 was able to reduce TC and LDL-c levels, while APOE e4 increased TC and LDL-c levels, and a linear relationship was found between APOE polymorphisms (e2/e2, e2/e3, e2/e4, e3/e3, e3/e4, e4 /e4) with LDL-c and TC levels and coronary risk. Research by Gao et al (2015) confirmed the combined association of LRP5 and APOE polymorphisms with TC and LDL-c levels in the Chinese population in periodontitis case and control groups. The results of other studies found that periodontal treatment improves lipid metabolism, especially in individuals who suffer from periodontitis with co-morbidities, such as cardiovascular disease and diabetes mellitus. Therefore, periodontitis may be a cause of dyslipidemia [13].

Research by Su-Jin Han et al [14] aims to confirm the relationship between dyslipidemia, oral health behavior, and periodontal disease according to age group. The data for this study were collected from the Examination Survey Korea National Health and Nutrition (KNHANES) conducted from 2012 to 2015 with 17,004 samples using a cross-sectional study. The results obtained in this study were Hypo High-Density Lipoprotein Cholesterol (HDL-C) was associated with periodontal disease in two groups (under 40 and over 40 years). In the age group above 40 years, the level of low-density lipoprotein cholesterol (LDL-C) is associated with periodontal disease, such as tooth brushing frequency and use of interdental hygiene products associated with periodontal disease [14].

Su-Jin Han et al identified a relationship between dyslipidemia, oral health behavior, and periodontal disease. The OR of hypo-HDL-C for periodontal disease increased, but the risk of developing periodontal disease decreased in hyper-HDL-C for all participants, indicating that HDL-C level is associated with periodontal disease. Specifically, hypo-HDL-C was associated with periodontitis in the age group below and above 40 years. Therefore, health professionals should emphasize management of low HDL levels for young age groups, such as the age group below 40 years, to prevent periodontal disease. However, hyper-LDL-C and pre-hyperLDL-C levels are associated with periodontal disease in the age group above 40 years. Thus, controlling LDL levels is also important for the management of systemic and oral diseases, especially in the age group above 40 years. The conclusion obtained in the study of Su-Jin Han et al (2019) is that good oral health can be maintained through increasing HDL-C in all age groups, including management of LDL-C levels [14].

Research by Vasconcelos et al [15] aims to determine the relationship between periodontitis and liver disorders. The results of this study showed relevant changes in the livers of ligature-induced animals, significant changes in liver histopathology, an increase in the number of binucleate hepatocytes and positive alkaline phosphatase (AlkP) in periodontitis compared to the control group, a significant increase in serum AlkP levels in the periodontitis group. High AlkP levels in rat liver are associated with LPS from bacteria involved in periodontitis because AlkP mediates host-bacterial interactions through its capacity to dephosphorylate lipid A from bacterial cell wall lipopolysaccharide. In addition, AlkP activity is also related to lipid metabolism.

This study used female rats to obtain a higher number of binucleate hepatocytes per gram of liver caused by sexual dimorphism. The study by Vasconcelos et al [15] found microvesicular steatosis in mice with periodontitis and found that steatosis, inflammation scores, and necrosis were higher in mice with periodontitis than mice without periodontitis. Myeloperoxidase (MPO) and cytokine levels, IL-1 β and TNF- α , showed no significant increase between the sample groups. This shows that the process of steatosis caused by periodontitis tends to be milder than steatohepatitis, as evidenced by the presence of an inflammatory process and a significant increase in levels of proinflammatory cytokines [16].

Previous research by Vasconcelos et al [15] showed that microvesicular steatosis is associated with higher levels of glutathione (GSH) and malondialdehyde (MDA) caused by periodontitis. Ultrastructural changes in the liver associated with periodontitis are used to observe the main characteristic of steatosis which is fat accumulation in hepatocytes. Vasconcelos et al (2019) also found total cholesterol and triglycerides in the blood and liver.

To evaluate the ultrastructure of lipid droplets (LD) in hepatocytes, Vasconcelos et al [15] used a Transmission Electron Microscope (TEM) to calculate the number and size of LD. The results obtained in the periodontitis group showed an LD size of 92.3% greater than the control group. Another change observed was that the number of LDs was also higher (53.1%) in the periodontitis group. LD occupies the cytoplasmic space of the hepatocytes thereby reducing the cellular function of the liver. LD is a dynamic organelle that carries out several biological activities and is balanced with blood lipids which functions to increase total cholesterol and triglyceride levels in both blood and liver tissue.

The lipid metabolism and bacteria involved with periodontitis increase the risk of developing NAFLD. The ligature-induced periodontitis model used in the study by Vasconcelos et al [15] is a way of simulating bacterial periodontitis in humans and its systemic effects. To evaluate the ultrastructural, the author also observed that hepatocyte mitochondria from the periodontitis group were larger than mitochondria from the control group. Mitochondria play a key role in ATP production and increased oxidative stress is associated with decreased ATP production causing mitochondrial damage [16].

The overall results in the study by Vasconcelos et al (2019) showed that experimental periodontitis caused changes in LD, mitochondria, and endoplasmic reticulum, both smooth and rough, which were observed with TEM. These findings of ultrastructural changes in mouse hepatocytes are like those found in humans with NAFLD, although these findings should be viewed with caution, because in the ligature model of periodontitis, inflammation is rapid and severe. The conclusion of the research by Vasconcelos et al [15] is that there are major changes in the liver structure and function of animals with periodontitis caused by ligatures.

From the various studies mentioned in this discussion, several things can influence the process of increasing alveolar bone damage in periodontitis accompanied by dyslipidemia through the mechanism of increasing the severity of the metabolic syndrome, serum Lp-PLA2, CRP, chemerin levels, plasma secretion of TNF- α , IL1 β , IL-6, PGE2, IL-2, interferon gamma, matrix metalloproteinase, systemic inflammatory load, serum triglyceride levels, increased HDL and LDL levels, and decreased serum cholesterol.

5. Conclusion

The mechanism of increased alveolar bone damage in patients with periodontitis accompanied by dyslipidemia is through increased severity of metabolic syndrome, serum Lp-PLA2, CRP, chemerin levels, plasma secretion of TNF- α , IL1 β , IL-6, PGE2, IL-2, interferon gamma, matrix metalloproteinase, systemic inflammatory load, serum triglyceride levels, increased HDL and LDL levels, and decreased serum cholesterol.

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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