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## Periodontitis in Patients with Type 2 Diabetes Mellitus.

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### ABSTRACT

Periodontitis is a chronic, inflammatory disease that is characterized by swollen gums, degradation of jaw structure, and potentially tooth loss. Like Periodontitis, Type 2 Diabetes Mellitus is also highly prevalent and largely multifactorial. Type 2 Diabetes is a condition in which higher than normal blood glucose levels cannot be properly maintained as the body's normal mechanism of maintaining proper blood glucose levels, the release of insulin from pancreatic islet  $\beta$ -cells, becomes ineffective. The purpose of this literature review is to explore the relationship between the incidences of Periodontitis and Type 2 Diabetes. The risk that Type 2 Diabetes poses for the incidence of Periodontitis is analyzed. Patients afflicted with Type 2 Diabetes were found to be approximately three times as likely to eventually suffer from Periodontitis, as well. There is also emerging evidence supporting the correlation between the degree of hyperglycemia and severity of Periodontitis. Potential underlying mechanisms linking the two conditions at the cellular level have been discussed. Immune functioning and cytokine biology are among discussed mechanisms. Recent discoveries have also suggested that Periodontitis may also negatively impact glycemic control. As a result, not only should healthcare providers emphasize oral health as part of Type 2 Diabetes management, but healthy eating and physical activity should be among recommendations that make up Periodontal management.

**Keywords:** Periodontitis, diabetes mellitus, type 2 diabetes and gum disease.

### INTRODUCTION

Periodontitis is a chronic inflammatory disease that is marked by the destruction of the supporting structures of the tooth.<sup>[1]</sup> Periodontitis is one of the most common human diseases, with a moderate case of the disease affecting 40-60% of adults and a more advanced case affecting 10-15% of adults.<sup>[2]</sup> While a mere professional cleaning may be sufficient to treat a moderate case of Periodontitis, more severe cases may even require surgery. A known cause of Periodontitis is an infection caused by gram-negative bacteria.<sup>[3]</sup> The bacteria contain a thin peptidoglycan cell wall in between an inner and an outer cell membrane.<sup>[4]</sup> The progression and severity of the conditions is thought to be determined by the host-immune response.<sup>[5]</sup> Symptoms of Periodontitis include swollen gums, gingival bleeding, and persistent halitosis; symptoms of severe Periodontitis include tooth

mobility, drifting of teeth, and tooth loss.<sup>[1]</sup> The risk of suffering from Periodontitis may be exacerbated by both genetic and environmental factors, including ethnicity, smoking, and stress.<sup>[6]</sup> Like Periodontitis, Diabetes mellitus Type 2, more commonly known as Type 2 Diabetes, can also negatively impact one's quality of life. Type 2 Diabetes is marked by higher than normal blood glucose levels. Insulin is a peptide hormone released by pancreatic islet  $\beta$ -cells to increase glucose uptake when blood glucose levels are high to maintain appropriate glucose levels.<sup>[7]</sup> However, in patients afflicted with Type 2 diabetes, somatic cells develop a resistance to insulin leading to long periods of time in which patient suffers from abnormally high blood glucose levels. Like Periodontitis, Type 2 Diabetes is a largely multifactorial disease. In addition to genetics, Type 2 Diabetes may also be caused by obesity and lack of physical activity. Aside from prescribed medication, lifestyle changes including an increase in exercise and consumption of nutritional foods make up a significant portion of Type 2 Diabetes management. Type 2 Diabetes is also similar to Periodontitis in that it is a largely prevalent condition, affecting approximately 380 million people worldwide.<sup>[8]</sup> Severe hyperglycemia can eventually lead to other irreversible health concerns including retinopathy, neuropathy, cardiovascular diseases, and periodontal diseases.<sup>[8]</sup> Many studies

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have been performed supporting the relationship between incidences of Type 2 Diabetes and Periodontitis. Case studies and epidemiological data are studied to explore the significance of Type 2 Diabetes as a risk factor for Periodontitis.

### **Periodontitis**

The severity of the Periodontal infection depends on environmental factors and on genetic susceptibility. The bacteria associated with Periodontitis is identified with a variety of floras with different genetic backbones. Over 500 bacterial species can inhabit one's mouth. Periodontal bacteria diversity and difference of host response does not allow one to understand the etiology of the disease.<sup>[9]</sup> One study evaluated flora differences within patients with Type 2 Diabetes and those without Type 2 Diabetes to indicate the differences in structures, but unsuccessfully tracked variance in mechanisms.<sup>[10]</sup> One recent study targeted certain communities with Periodontitis to explore the underlying mechanism and background of this organism. The results show that the following Periodontitis-associated taxa are prevalent in most cases today. These include: Porphyromonasgingivalis, Tannerella forsythia, and Treponema denticola.<sup>[11]</sup>

### **Type 2 Diabetes Mellitus**

Diabetes Mellitus (DM) ultimately results in increased glucose levels within the bloodstream, termed hyperglycemia. On the cellular level, mechanisms of insulin changing results in the complex changes of carbohydrate, lipid, and protein metabolism. Vital organs including the eyes, kidneys, and liver, as well as neural and connective tissues become direct targets after the diagnosis and the severity of DM. Periodontal tissue become a target for these patients as well. According to a recent study, the National Health and Nutrition Examination Survey (NHANES) III data confirmed that there is a significantly higher prevalence of periodontitis in diabetics than in healthy individuals (17.3% versus 9%).<sup>[12]</sup> The pathogenesis of both diseases, focusing solely on genetic and immune mechanisms can be the tie between both diseases

### **Obesity integrated with Type 2 Diabetes Mellitus**

Type 2 Diabetes is considered an obesity-related disease. Studies exhibit correlations of obese patients having a higher risk of acquiring diabetes. Most obese patients do not acquire the proper nutrition, vitamins, and minerals to gain bone density within the mouth. This leads to tooth decay, and without proper brushing techniques or regular flossing, enamel is scraped away. This leads to a number of dental problems, including gingivitis, tooth erosion, cavities, and Periodontitis.

### **Obesity, Diabetes, and Periodontitis Relationship Study**

Shift work, a major part of today's society, tests an individual's immune system while working odd hours, lack of rest, and scheduling work hours last minute, therefore, putting off stress relieving activities. A recent study using participants from the Forth Korean National Health and Nutrition Examination Survey (KNHANES IV). Shifting patterns were characterized into 5 various shifts and Periodontitis levels were measured. Results indicate that at risk workers working irregular shifts show a higher percentage of periodontitis, with most at risk groups to be less than the age of 45.<sup>[13]</sup> Shift work also results in increased risk of obesity and Type 2 Diabetes due to irregular sleep schedules and irregular metabolism due to eating at wrong times. Activities affecting a person's circadian rhythm can directly impose upon risks such as periodontitis, Type 2 Diabetes, and obesity, which can all be the cause of one another. Persons with periodontitis already show a higher chance of acquiring these diseases within a shift work society.<sup>[13]</sup>

### **Type 2 Diabetes to cause Periodontitis**

It has been determined that susceptibility to Periodontitis is increased almost threefold in patients suffering from Type 2 Diabetes.<sup>[1]</sup> Much of the research gathered to support this relationship comes from studies performed on Pima Indians. Pima Indians make up an indigenous group in the United States who have historically had high rates of diabetic members; 50% of Pima Indians over 30 years of age suffer from Diabetes.<sup>[4]</sup> Results from a cross-sectional study demonstrated that diabetic Pima Indians were 2.8 times more likely to have Periodontitis than non-diabetic Pima Indians.<sup>[14]</sup> In another study demonstrating the relationship of Obstructive Sleep Apnea and Periodontitis, patients in the study who had reported being diabetic, show 2.70 greater chances of being diagnosed with severe periodontitis, with nasal breathing difficulty, and dry mouth in association.<sup>[15]</sup>

### **Mechanistic Relationship Between Periodontitis and Type 2 Diabetes**

There is increasing evidence in support of a two-way relationship between both Periodontitis and Type 2 Diabetes. Not only is Type 2 Diabetes a risk factor for Periodontitis, but Periodontitis has been shown to have a negative impact on glycemic control.<sup>[1]</sup> Oral pathogenic bacteria that is common in patients suffering from Periodontitis increase the level of fructose in the body, causing insulin resistance to worsen.<sup>[16]</sup> Additionally, Periodontal inflammatory cytokines that are released often impair insulin receptor signaling and, thus, contribute to higher than normal blood glucose level.<sup>[17]</sup>

**Triggered Hyperglycemia from Diabetes to initiated Periodontitis**

The degree of hyperglycemia is also associated with the severity of Periodontitis that diabetic patients might suffer from. Higher blood glucose levels correlation with a more advanced, severe case of Periodontitis.<sup>[16]</sup> A study aimed to analyze the effect of periodontitis on bone formation in groups of diabetic and non-diabetic patients. It was found that osteocalcin, a biomarker responsible for bone formation, was lower in diabetic patients.<sup>[4]</sup> The results provide evidence that diabetic patients have a lessened ability to replace the bone loss that is characteristic of Periodontitis. This may also provide additional support for the correlation between the degree of hyperglycemia and severity of the Periodontitis case.

Pathological evidence in the progression of Periodontitis suggests that patients develop this infection through prolonged exposure to hyperglycemia and in those with poor glycemic control.<sup>[18]</sup> Saremi and Associates studying the Pima Indian concluded in their research that death rates related to Periodontal disease is higher in those with diabetes than with those with no diabetes and Periodontal disease. Essentially, within the Pima Indian population in Southern Arizona, patients with type 2 diabetes exhibit more risk factors, including the effects of Periodontitis. These patients, aged between 15-54 show that Periodontitis is exhibited 60% of diabetic patients, while 36% in non-diabetics.<sup>[18]</sup> Similarly, the Gullah African American population, 70.6% of diabetic patients expressed moderate levels of Periodontitis.<sup>[19]</sup>

**Environmental Factors regarding the relationship**

Specific environments allow the risk of acquiring Periodontitis and type 2 diabetes more likely, and both diseases may be related when attained. Studies show that altered immuno-inflammatory responses due to low metabolism levels of connective tissues in diabetic patients lead to the loss of connective tissue within the tooth root attachment site. This site allows for an easy entrance for Periodontitis inducing bacteria due to the open wound site. The presence of hyperglycemia inhibits osteoblastic cell proliferation and therefore, inhibits collagen productivity. There is an increase in apoptosis of both fibroblasts and osteoclasts with the infection of *P. gingivalis* with the hyperglycemic background.<sup>[10]</sup>

**The unknown pairing of both diseases**

The exact underlying mechanisms that connect Type 2 Diabetes and Periodontitis are not yet known. However, it has been determined that these mechanisms do involve immune functioning, cytokine biology, and neutrophil activity.<sup>[1]</sup> A study

performed in Switzerland aimed to analyze the vascular endothelial growth factor (VEGF) mRNA expression levels in the gingival tissues of patients with and without Diabetes Mellitus. The researchers proposed that VEGF was the primary cytokine relating these two conditions. However, the results of the study determined that there was no statistically significant difference in the levels of VEGF mRNA expression levels between the two groups.<sup>[5]</sup>

**Explained Theory of mechanistic relationship**

A recent study outlines connection of the underlying mechanism between Periodontitis and Type 2 Diabetes. Proinflammatory cytokines are produced due to inhibited insulin signaling within Type 2 Diabetes. This ultimately results in the destruction of pancreatic beta cells. The various cytokines include both IL-1 $\beta$  and TNF $\alpha$ . Both are exaggerated due to inflammatory response from Gram-negative bacterial lipopolysaccharide (LPS). Hyperglycemia directly allows for increased levels of pro-inflammatory cytokines by activating pro-transcription factor NF- $\kappa$ B. Increased serum and cytokine levels produce increased levels of gingival crevicular fluid (GCF).<sup>[19]</sup>

**Hyperlipidemia as a cause of Periodontitis**

Hyperlipidemia, an excess of lipids within the bloodstream, is often diagnosed in patients with both Type 1 and Type 2 diabetes, with already acquired hyperglycemia. Blood reports of these patients strikes high levels of low-density lipoprotein (LDL), triglycerides (TRG), and omega-6 fatty acids.<sup>[19]</sup> Hyperlipidemia can directly influence the progression of Periodontitis. Mice with high fat diets show higher levels of developing Periodontitis. After being fed a high-fat diet for 4 weeks, mice show an increase in the following Periodontal pathogens: *Prevotella intermedia* and *Fusobacterium*. This study compares these results to mice fed a normal diet. The mice also show gingival inflammation and alveolar bone loss.<sup>[19]</sup> A study conducted analyzed lipid profile levels in patients with severe Periodontitis as per the American Academy of Periodontology. Lipid profiles results display high LDL levels with patients with DM and periodontitis alongside high total cholesterol (TC) levels.<sup>[20]</sup>

**Gingival Crevicular Fluid (GCF) use in Periodontal studies**

A patient affected with Periodontitis often experiences gingival bleeding as well as the accumulation of gingival crevicular fluid (GCF) around the inflamed gum tissues. GCF consists of "...connective tissue degradation, enzymes from host and bacterial cells, cytokines, and other inflammatory mediators..."<sup>[10]</sup> Saliva is used in a broad range of periodontal studies due to less cost

involved, minimal invasiveness, and a promising number of biomarkers to test.<sup>[21]</sup> A recent study used GCF to test the levels of the glycoprotein YKL-40 in groups of individuals characterized with having periodontitis and some characterized with having diabetes. YKL-40 is a chitin-binding glycoprotein that contains three amino acids (tyrosine (Y), lysine (K), and leucine (L)) at its N-amino terminal, which is increased in certain diseases including Type 2 Diabetes Mellitus, Cardiovascular Diseases, and Tumors. YKL-40 also induces the proliferation of chondrocytes, fibroblasts, and synovial cells. Results show that YKL-40 levels were significantly higher in periodontitis and not in Type 2 Diabetes, therefore, is a biomarker for periodontitis.<sup>[22]</sup>

### **Biomarkers to tag the prevalence of both diseases**

Some of these inflammatory mediators give insight into the progression of both Periodontitis and Type 2 Diabetes.<sup>[10]</sup> A recently discovered biomarker, Orosomuroid, tests the progression of periodontitis in morbidly obese patients. The relationship between obesity and periodontitis was tested in a cross-sectional study focusing on the systemic inflammatory markers. Periodontal risk factors such as age, gender, diabetes, and smoking status were recorded as well as plasma levels of inflammatory markers (CRP, orosomuroid, IL-6) and adipokines (adiponectin, leptin). Results show that the plasma level of orosomuroid ( $p < 0.04$ ) indicate the severity of periodontitis in obese patients.<sup>[23]</sup> Circulating leptin and adiponectin in healthy periodontal patients do not change, but those patients with systemic diseases, including Type 2 Diabetes Mellitus, show elevated leptin serum levels and decreased serum adiponectin levels.<sup>[24]</sup> Procalcitonin (ProCT), another particular biomarker, circulates in very low amounts regularly, but rises in persons with systemic infections. A recent study focused on ProCT levels in patients with both Periodontitis and Type 2 Diabetes to determine if high amounts of this biomarker was exhibited by Periodontitis or Hyperglycemia. Results show that salivary levels of ProCT were significantly higher in patients with both chronic infections than in regular serum levels in these patients. ProCT salivary levels were measured at 152 pg/mL compared to regular serum levels at 78 pg/mL (25). ProCT levels reflect the progression of both periodontitis and hyperglycemia. Therefore, various inflammatory cytokines prove to be used as potential biomarkers to associate the incidence both Periodontitis and Type 2 Diabetes along with the progression of both diseases.

### **Use of Chemical Elements to show disease**

Various micronutrient levels, including Zinc, Iron, and Copper, can be used as biomarkers comparing

patients with both Type 2 Diabetes and Periodontitis and those with healthy individuals and those just with Periodontitis. Biju Thomas and his team conducted a group case study that showed variance in serum levels with micronutrients across various groups. Serum levels of zinc decreased, while serum levels of both iron and copper increased in patients with both Periodontitis and Type 2 Diabetes.<sup>[26]</sup> This imbalance in serum levels can diagnose an incoming prognosis for a patient developing these conditions. Zinc levels within diabetic patients are significantly decreased due to the uptake by liver cells, which stores the metal by binding to cytosolic proteins. An excess of Zinc ions can lead to oxidative damage in the mitochondria and therefore, the intracellular depletion of Zinc is visualized by measuring serum levels.<sup>[27]</sup> This imbalance in serum levels can diagnose an incoming prognosis for a patient developing these conditions.

### **The effect of Oxidative Stress, Shortened Leukocyte Telomere Length (LTL), and Ascorbic Acid Level Deficiency on Periodontitis and Type 2 Diabetes**

Oxidative Stress can be measured to determine the interrelationship between both Periodontitis and Type 2 Diabetes. According to the Scottish Medical Journal, that diabetic patients with periodontitis receive treatments that essentially improve metabolic control. The oxidative stress-inflammatory pathways common in both diseases show that the relationship between both diseases prove to be synergistic.<sup>[28]</sup>

Shortened Leukocyte Telomere Length (LTL) and the diagnosis of Periodontitis both can induce a higher risk of Type 2 Diabetes. According to a recent study, Dental examinations characterized the levels of periodontitis and LTL was measured by PCR after DNA Extraction. Patients with periodontitis demonstrated shorter LTL ( $P = 0.04$ ) in those with a higher prevalence of Type 2 Diabetes (29). Shortened LTL may also be used as a forthcoming measure in those with periodontitis who may or will develop Type 2 Diabetes.

Ascorbic Acid Level deficiency also proves to show the progression of both Periodontitis and Type 2 Diabetes together. The Journal of Dietary Supplements published a recent study that concluded that deficient ascorbic acid levels (AALs) and Type 2 diabetes mellitus (T2DM) are both associated with periodontal disease. The methodology of the study proves that AAL plasma levels were higher in a group without periodontal disease than compared to a group with chronic periodontitis and freshly diagnosed T2DM ( $p = 0.0003$ ).<sup>[30]</sup> After being given a dietary supplementation of Vitamin C, there was a great reduction in the Sulcus Bleeding Index (SBI), a measure for chronic periodontitis, in the group with



both periodontal disease and T2DM ( $p=0.036$ ).<sup>[30]</sup> Water soluble Vitamin C levels can directly determine the extent of periodontal disease in patients with Type 2 Diabetes.

### **Overall Effect of both diseases**

The presence of Periodontitis may even lead to additional chronic health complications in Type 2 Diabetic patients. In a longitudinal study of 529 individuals, it was determined that the incidences of macroalbuminuria were 2.0 and 2.1 times as high in subjects who suffered from moderate and severe forms of Periodontitis, respectively, compared to subjects who did not have or only suffered from a mild form of Periodontitis.<sup>[31]</sup> The study also suggested that Periodontitis predicts the incidence of overt nephropathy and end-stage renal disease in patients afflicted with Type 2 Diabetes.

### **Treatment for Both Diseases**

Low-level laser therapy (LLLT) is a common treatment option that is effective in reducing the inflammations and swelling common in patients with Periodontitis. In a study that was performed to test the effectiveness of (LLLT) in Type 2 diabetic patients with Periodontitis, results suggested that LLLT was an effective means of treating Periodontitis in diabetics. Several treatments used to decrease the symptoms of Type 2 Diabetes have been found to help decrease the risk of Periodontitis, as well. In a study aimed to verify the effect of physical activity on several chronic diseases, it was found that the receiving the recommended level of physical activity was associated with a lower prevalence of Periodontitis.<sup>[32]</sup> The efficacy of Type 2 Diabetes treatment options on reducing the prevalence of Periodontitis, and vice versa, provides additional support for the interrelated nature of the two conditions.

## **CONCLUSION**

Periodontitis and Type 2 Diabetes Mellitus are both highly prevalent, chronic disorders that can not only negatively impact the quality of life of patients suffering from the conditions individually, but can also aggravate each other's prognoses. While the exact underlying mechanisms linking the two conditions are not yet known, there is emerging evidence in support of the Type 2 Diabetes as a risk factor for Periodontitis, and vice versa. Further research can be done to test different biomarkers and micronutrients to further understand this relation on a cellular level. Because of the two-way relationship between the two conditions, oral health should be promoted as part of Type 2 Diabetes management just as the healthy diet, physical activity, and other lifestyle changes recommended to diabetic patients should be promoted as part of

Periodontitis management. Individuals suffering from either Type 2 Diabetes or Periodontitis must be made aware of this interrelated tie and the risk they may be at for potentially becoming afflicted with the other condition.

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