Diabetes and Periodontal Disease: The Reciprocal Relationship

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Abstract

Diabetes is a metabolic disorder whereas Periodontal disease is an infectious disease, the bi-directional relationship between them occurs through the ability of both conditions to induce an inflammatory response leading to over-production of pro-inflammatory mediators. On the other hand, inflammation is known to cause increased insulin resistance. These pro-inflammatory cytokines such as IL-6, TNF-α, are known to impair the glucose-stimulated release of insulin from the pancreas, resulting in to increase in sugar levels. As a result, Periodontal disease has also been considered as the 6th complication of diabetes mellitus. In prolonged hyperglycemic states, advanced glycation end products form which crosslinks with collagen, making it less soluble, less likely to be replaced, and more susceptible to breakdown. A combination of genes could also result, in a host who, under the influence of a variety of environmental stressors, could develop periodontal disease and diabetes. Regular periodontal therapy, on the other hand, can stabilize glycemic control and help reduce complications arising from unstable blood sugar levels. This review comprises the effect of diabetes on the periodontium and its co-relation in the progression of periodontal disease.

Keywords: Diabetes mellitus periodontal disease • Advanced glycation end products

Introduction

Diabetes Mellitus (DM) encompasses a heterogeneous group of disorders with the common characteristic of altered glucose tolerance or impaired lipid and carbohydrate metabolism. DM develops from either a deficiency in insulin production or an impaired utilization of insulin. Based upon these 2 conditions, diabetes mellitus can be divided into 2 main types: Type 1 (formerly insulin-dependent diabetes mellitus) and Type 2 (formerly non-insulin-dependent diabetes). Diabetes insipidus results from a deficiency in the pituitary hormone vasopressin (anti-diuretic hormone), or resistance to this hormone by the kidney. The decrease in production or action of vasopressin results in excessive urine production and polyuria but does not have any effect on blood glucose levels [1,2]. Insulin is secreted by the β cells of the pancreas directly into the portal circulation. Insulin suppresses hepatic glucose output by stimulating glycogen synthesis and inhibiting glycogenolysis and gluconeogenesis, thus decreasing the flow of gluconeogenic precursors and free fatty acids to the liver. In type 2 diabetes, increased rates of hepatic glucose production result in the development of overt hyperglycemia especially fasting hyperglycemia [3].

Periodontal disease could be more commonly referred to as a chronic inflammatory response to the bacterial challenge. According to the models of the periodontal disease progression, bacterial biofilm alone is not responsible for the progression of periodontal disease, but it is the host's inflammatory response to the bacterial challenge. The correlation of diabetic patients and various conditions associated with them like xerostomia, candidal infection, and periodontitis has been known to the dentist for a long [4]. Periodontal disease has been commonly referred to as a "sixth complication of diabetes mellitus [5].

Hence, the main aim of this review is to make clinicians aware of the bi-directional relationship between diabetes mellitus and periodontal disease.

History

- 5 BC- a condition called Madhirmedha- Urine resembling honey
- 1500 BC- Egyptian papyrus Ebers- described diabetes
- 2nd century- Arateus of Cappadocia- gave name diabetes
- China and Japan -symptoms of Diabetes described
- 3rd and 4th century- AVICENNA the Arab physician-described how diabetes mellitus complexes diseases and its hereditary tendency
- 1674- Willis added his observation where the urine is Honey or sugar like in diabetes mellitus
- 1784- Matthew dobson of America demonstrated the sweetness of urine in diabetes mellitus is due to Excess sugar which is excreted from the bloodstream
- 1889- Josef Von Mehring and Oscar Minkowisky- surgical removal of pancreas produced diabetes in dogs
- 1921- Banting and Best- isolated substance from the pancreas which induced a state of hypoglycemia
- Sir Edward Sharpe -proposed the term 'Insulin'-derived from the latin word "insular" meaning Island
- 1955- hypoglycemic agents introduce for treatment of diabetes [6-9]

Literature Review

Oral manifestations of gingivitis and periodontitis in diabetic individuals

- Enlarged, red, velvety hemorrhagic tissues with a purplish hue
- Increased calcium and glucose levels cause more plaque formation
- Deeper periodontal pockets
- Increased clinical attachment loss
- Multiple loose teeth
- Delayed wound healing due to glycosylation of wound margins
- Multiple or recurrent periodontal abscesses
- Unexplained edematous gingival enlargement
- Rapid and advanced alveolar bone destruction
- Tongue anomalies- Median rhomboid glossitis
- Xerostomia
- Increased incidence of bacterial and fungal infections
- Halitosis (Ketone breathe)

- Increased incidence of dry socket
- Impairment in taste sensation
- Salivary dysfunction
- Burning mouth sensation due to desiccation of oral mucosa
- Concomitant enlargement of parotid salivary gland
- Increased incidence of dental caries [10-12]

Pathophysiology

- Lack of insulin or insulin resistance results in instability of insulin-dependent cells to utilize glucose
- Triglycerides are broken down to fatty acids which increase blood Ketone levels thereby leading to diabetic ketoacidosis and further emanating ketone breathe from a diabetic individual
- As blood sugar level becomes elevated glucose, is excreted in the urine, and excess urination occurs leading to polyuria
- Increase fluid loss leads to dehydration and polydipsia
- The patient experiences polyphagia since cells are starved of glucose [13,14]

Influence of Diabetes on Oral Health

- Periodontal diseases are multifactorial diseases characterized by the presence of gram-negative anaerobic bacterial infections Although, chronic periodontitis affects an estimated 7%-13% (moderate to severe) to 22%-40% (mild) of the adult population, respectively, studies have suggested that the bacterial challenge accounts for a relatively small proportion (around 20%) of the variance in disease expression. On the other hand, studies involving adult twins have demonstrated that host factors account for about 50% variance in disease expression. Although bacterial biofilms are an essential prerequisite for periodontal disease development, a susceptible host is required. Hence, a new concept of periodontal disease pathogenesis has been proposed. In this recent concept, the model of a biofilm-dominated process was extended to one in which the host response emerged as the dominant effect modifier in periodontal disease expression [15,16]
- Diabetes does not cause gingivitis or periodontal pockets, but there are indications that it alters the response of the periodontal tissues to local factors hastening bone loss and retarding post-surgical healing of the periodontal tissues. Diabetes is often associated with increased gingival inflammation in response to bacterial plaque. Frequent periodontal abscesses appear to be an important feature of periodontal disease in diabetics [17]
- A large body of evidence demonstrates that diabetes is a risk factor for gingivitis and periodontitis. The degree of glycemic control is an important variable in the relationship between diabetes and periodontal diseases, with a higher prevalence and severity of gingival inflammation and periodontal destruction being seen in those with poor control
- Large epidemiological studies have shown that diabetes increases the risk of alveolar bone loss and attachment loss approximately three-fold when compared to non-diabetic individuals These findings have been confirmed in meta-analyses of studies in various diabetic populations In longitudinal analyses, diabetes increases the risk of progressive bone loss and attachment loss over time The degree of glycemic control is likely to be a major factor in determining risk. For example, in a large epidemiological study in the U.S. (NHANES III), adults with poorly controlled diabetes had a 2.9-fold increased risk of having periodontitis compared to non-diabetic subjects; conversely, subjects with well-controlled diabetes had no significant increase in the risk for periodontitis. Similarly, poorly controlled type 2 diabetic subjects had an 11-fold increase in the risk for alveolar bone loss over 2 years compared to non-diabetic control subjects. On the other hand, well-controlled type 2 patients had no significant increase in risk for longitudinal bone loss compared to non-diabetic controls [18]

Infections in Patients with Diabetes

It is generally accepted that patients with diabetes are more susceptible to the development of infections than those without diabetes. It also is believed that infections in diabetic patients are more severe than the same infection in a non-diabetic individual. However, conclusive studies supporting these clinical impressions do not currently exist. Insulin resistance is a condition that exists during acute infections. The molecular basis for infection-induced insulin resistance is not clearly understood. Vascular changes are common in patients with diabetes. Basement Membrane (BM) proteins become glycosylated in a hyper-glycaemic environment, with thickening and changes in the physical properties. Gingival capillaries of diabetic subjects have thickened BM, as well as disruption of the BM, collagen fibers within the BM, and swelling of the endothelium. These changes can be hypothesized to impede oxygen diffusion, metabolic waste elimination, PMN migration, and diffusion of serum factors including antibodies. Other studies have failed to show any difference in the thickness of the basement membrane of gingival vascular tissue in diabetic patients. Collectively, defects in PMN function, induction of insulin resistance (or increased insulin resistance in the diabetic subject), and vascular changes can all contribute to increased susceptibility to infection. Importantly, control of serum glucose levels appears to partly reverse these factors and should therefore be closely monitored with infections [19,20].

Integrin-mediated tissue damage

Cell-matrix interactions are mediated by specific cell surface receptors, termed integrins for corresponding matrix molecules. Excess matrix proteins in the tissues of diabetic patients can directly alter cellular functions via integrin molecules. An increase in glucose concentration exhibited a higher expression of fibronectin receptor (VLA-5) and a decrease in glucose concentration showed a time-dependent decrease in VLA-5 expression. Thus, varied glucose concentrations regulate VLA-5 levels in these cells [21-23].

It is known that the increased levels of fibronectin receptors directly alter cellular functions such as proliferation and migration by increased adhesiveness to its ligand or by nonspecific binding. This increased adhesiveness resulted in a decreased chemotactic response from the PDL cells when they were challenged by platelet-derived growth factor, a potent chemoattractant for PDL cells.

Hypoglycemia also has been shown to affect PDL cells. It was observed that PDL cells cultured in a glucose-free medium lost VLA-5 expression in a time-dependent manner and eventually died by apoptosis. PDL fibroblast seems to be more susceptible to glucose starvation than other fibroblastic cells such as dermal and gingival fibroblastic cells such as dermal and gingival fibroblasts.

Advanced glycation end products (Ages)

Hyperglycemic environment leads to the non-enzymatic glycosylation process of various proteins including collagen leading to the formation of Advanced Glycation End products (AGEs). It is well established that exposure of the body's proteins and lipids to reducing sugars leads to the initial formation of reversible products of non-enzymatic glycation and oxidation, the Schiff bases and Amadori products. The best known of these products is glycosylated HbA1c. After a series of further complex molecular rearrangements, the irreversible Advanced Glycation End-products (AGEs) are formed. AGEs form and accumulate in several circumstances, such as aging, renal failure, and diabetes. Indeed, the presence of AGEs in diabetic plasma and tissues has been linked to the development of diabetic complications [24-30].

Interestingly, recent studies suggested that certain AGEs, carboxymethyl (lysine) modifications of proteins, may form as a consequence of activation of the myeloperoxidase-hydrogen peroxide-chloride system, thereby providing a mechanism for direct generation of AGEs in inflammatory milieu, even in euglycemia. Accumulation of AGEs in the tissues may result in significant alteration of normal cellular composition and structure. Cross-linking of long-lived proteins such as collagen, for example, may lead to abnormal barrier function and integrity, as well as the trapping of macromolecules, such as low-density lipoproteins. In addition, non-enzymatic glycoxidation of basement

membrane-associated structures may prevent their facilitation of cell attachment, and modification of growth factors may suppress mitogenic activity.

In addition to apparently receptor-independent mechanisms, AGEs may also interact directly with cell surfaces. While several putative cell surface binding sites for AGEs have been identified, the best characterized of these is the receptor for AGE (RAGE), a member of the immunoglobulin superfamily of cell surface molecules. RAGE consists of a 332-amino-acid extracellular region containing one ''V''-type immunoglobulin domain, followed by two ''C''-type domains. A hydrophobic transmembrane spanning domain follows this portion of the molecule, and, lastly, by a highly charged cytosolic tail of 42 amino acids, which is essential for RAGE-mediated signal transduction.

The Interaction of AGEs with RAGE Perturbs Specific Cellular Function: In homeostasis, RAGE is present at low levels in several cell types, including endothelial cells, smooth muscle cells, neurons, and monocytes. However, in perturbed states, such as diabetes, renal failure, Alzheimer's disease, and inflammation, for example, increases the expression of RAGE on critical target cells is strikingly enhanced [31].

Endothelial cells

RAGE is present at low levels on endothelial cells under normal conditions; upon perturbation, however, the expression of RAGE is increased. The interaction of AGEs with endothelial RAGE results in the development of a range of perturbations likely linked to the development of vascular lesions in diabetes. For eg, the interaction between AGEs and endothelial RAGE leads to increased monolayer permeability and increased production of Vascular Cell Adhesion Molecule-1 (VCAM-1).

Mononuclear phagocytes

After PMN, the major cell line necessary for effective periodontal defense mechanisms is the monocyte/macrophage cell line. The interaction between AGEs in the periodontium in a diabetic state and RAGEs on the surface of monocytes and macrophages makes these cells hyper-responsive to bacterial antigens. This up-regulation results in significantly increased production of pro-inflammatory cytokines and mediators. Thus, the patient with diabetes may have a decreased ability for PMNs to kill periodontal pathogens, resulting in their proliferation, combined with an exuberant pro-inflammatory and destructive monocyte/macrophage response that produces severe local damage to periodontal tissues. The net clinical effect of these host defense alterations is an increase in periodontal inflammation, attachment loss, and bone loss [32-37].

Changes in collagen metabolism

Collagen is the primary structural protein in the periodontium. Changes in the collagen metabolism in patients with diabetes contribute to wound healing alterations and periodontal destruction. Increased collagenase production readily degrades the newly formed collagen that is critical to the healing of the periodontium. At the same time, AGE modification of existing collagen extensively cross-links it and thereby decreases its solubility. The net results of these changes in collagen metabolism are a rapid combination of rapid dissolution of recently synthesized collagen by host collagenases and accumulation of older, AGE-modified collagen. Thus, diabetes induces a shift in the normal homeostatic mechanism by which collagen is formed, stabilized, and eventually turned over; a shift that alters wound healing responses to physical or microbial wounding of the periodontium [38-41].

Fibroblasts

In vivo studies have shown that interaction of AGEs on RAGEs on fibroblast results in decreased production of Type 1 collagen and increased production of collagenases [42,43].

Smooth muscle cells

The interaction of AGEs with RAGE's on smooth muscle cells resulted in their increased migration and activation. This increases the thickness of vessel walls. These changes decrease periodontal tissue perfusion and oxygenation. Other contributing factors to vascular perturbation and injury are: 1) formation of AGEs resulting in collagen accumulation in the periodontal capillary basement membranes, causing membrane thickening, and 2) binding of AGE-modified collagen in gingival blood vessels to circulating low-density lipoprotein (which is frequently increased in diabetes), resulting in atheroma formation and further narrowing of the vessel lumen [44].

Two Way Inter-Relationship Between Diabetes Mellitus and Periodontal Disease

Periodontal diseases are inflammatory in nature; as such, they may similarly alter glycaemic control to obesity, another inflammatory condition. Studies have shown that diabetic patients with periodontal infection have a greater risk of worsening glycaemic control over time compared to diabetic subjects without periodontitis Because cardiovascular diseases are so widely prevalent in people with diabetes, and because studies suggest that periodontal disease may be a significant risk factor for myocardial infarction and stroke, a recent longitudinal trial examined the effect of periodontal disease on mortality from multiple causes in over 600 subjects with type 2 diabetes. In subjects with severe periodontitis, the death rate from ischemic heart disease was 2.3 times higher than the rate in subjects with no periodontitis or only slight disease, after accounting for other known risk factors. The death rate from diabetic nephropathy was 8.5 times higher in those with severe periodontitis. The overall mortality rate from cardio-renal disease was 3.5-fold higher in subjects with severe periodontitis, suggesting that the presence of periodontal disease poses a risk for cardiovascular and renal mortality in people with diabetes [45-52].

Periodontal intervention trials suggest a significant potential metabolic benefit of periodontal therapy in people with diabetes. Several studies of diabetic subjects with periodontitis have shown improvements in glycaemic control following scaling and root planning combined with adjunctive systemic doxycycline therapy. The magnitude of change is often about 0.9%-1.0% in the HbA_1C test. There are some studies in which periodontal treatment was associated with improved periodontal health, but the minimal impact was seen on glycaemic control. Most of these studies used scaling and root planning alone, without adjunctive antibiotic therapy. Conversely, a recent study of well-controlled type 2 diabetic patients who had only gingivitis or mild, localized periodontitis examined the effects of scaling and localized root planning without systemic antibiotics. A diabetic control group with a similar level of periodontal disease received no treatment. Following therapy, the treated subjects had a 50% reduction in the prevalence of gingival bleeding and a reduction in mean HbA_1C from 7.3% to 6.5%. The control group, which received no periodontal treatment, had no change in gingival bleeding, as expected, and no improvement in HbA_1C. These results suggest that changes in the level of gingival inflammation after periodontal treatment may be reflected by changes in glycaemic control [53].

Several mechanisms may explain the impact of periodontal infection on glycaemic control. As discussed above, systemic inflammation plays a major role in insulin sensitivity and glucose dynamics. Evidence suggests that periodontal diseases can induce or perpetuate an elevated systemic chronic inflammatory state, as reflected in increased serum C-reactive protein, interleukin-6, and fibrinogen levels seen in many people with periodontitis Inflammation induces insulin resistance, and such resistance often accompanies systemic infections [54].

Acute non-periodontal bacterial and viral infections have been shown to increase insulin resistance and aggravate glycaemic control. Periodontal infection may similarly elevate the systemic inflammatory state and exacerbate insulin resistance. TNF-α, produced in abundance by adipocytes, increases insulin resistance by preventing autophosphorylation of the insulin receptor and inhibiting second messenger signaling *via* inhibition of the enzyme tyrosine kinase IL-6 is important in stimulating TNF-α production; thus, elevated IL-6 production in obesity results in higher circulating levels of both IL-6 and TNF-α Periodontal infection can induce elevated serum IL-6 and TNF-α levels and may play a similar role as obesity in inducing or exacerbating insulin resistance [55-59].

Diabetic patients with periodontal disease benefit from systemic administration of tetracycline derivatives in the following ways. As potent antimicrobial agents effective in eliminating most periodontal pathogens and as a potent modulator of the diabetic patient's host response to periodontal infection by:

- Suppressing or inhibiting collagenolytic processes and increasing protein synthesis and secretion
- Retention of membrane-associated TNF-α, thereby preventing the release of TNF-α from the monocyte membrane
- Found to block protein kinase-C activity, an important step in the secretion of IL-1β and TNF-α in LPS-stimulated human monocytes

- Inhibition of non-enzymatic glycation of proteins *via* a non-anti-collagenase mechanism

Thus, there is a two-way relationship between periodontal diseases and diabetes mellitus. Most of the connective tissue destruction taking place in periodontal disease results from the interaction of bacteria and their products with mononuclear cells. This triggers an infection-mediated pathway of cytokine regulation, especially with the secretion of TNF-α and IL-1 and a state of insulin resistance, affecting glucose utilizing pathways. The insulin receptor tyrosine kinase, the expression of secondary messengers, and the action of protein kinase C may, either individually or in combination, mediate some of the insulin effects such as translocation and activation of glucose transporting proteins. TNF-α has been suggested as the mediator of insulin resistance in infection by suppressing insulin-induced tyrosine phosphorylation of insulin receptor substrate-1(ISR-1), thus impairing insulin action [60].

Monocytes in diabetic individuals may be "primed" by AGE protein binding. Periodontal infection challenge to these "primed" phagocytic cells, may in turn amplify the magnitude of the macrophage response to AGE-protein, enhancing cytokine production and oxidative stress. Simultaneously periodontal infection may induce a chronic state of insulin resistance, contributing to the cycle of hyperglycemia, non-enzymatic irreversible glycation, AGE protein binding, and accumulation, thus amplifying the classical pathway of diabetic connective tissue degradation, destruction, and proliferation, which is AGE-mediated. Hence, Genco and Grossi proposed that periodontal infection-mediated cytokine synthesis and secretion may amplify the magnitude of the AGE-mediated cytokine response and *vice versa*. In doing so and like other bacterial infections, the relationship between diabetes mellitus and periodontal disease/infection becomes two-way. This dual mechanism of tissue destruction suggests that control of periodontal infection is essential to achieve long-term control of diabetes mellitus [61].

Although diabetes is a metabolic disorder while periodontitis is a bacterial disease, the inter-relationship occurs through the ability of both the conditions to induce an inflammatory response leading to the production of inflammatory mediators like TNF-α, IL- β, IL-1, IL-6. All of these are known to impair the glucose-stimulated release of insulin from the pancreas (Figure 1). He stated that under certain conditions of hyperglycemia lipids and numerous proteins including collagen undergo a non-enzymatic glycosylation process to produce AGE products (Figure 2) [62].

As a result, both conditions aid in connective tissue destruction thereby leading to periodontitis.

The Rationale for Improved Glycemic Control after Periodontal Therapy

The systemic levels of mediators involved in the pathogenesis of vascular diseases such as high-sensitivity C-reactive protein (Hs-CRP) and soluble E-selectin were significantly reduced following non-surgical periodontal debridement (Figure 3) [63-68].

Dental Implant Considerations in the Diabetic Patients

The placement of dental implants in diabetic patients remains controversial. Defined guidelines with objective criteria are to be established. Presently, anecdotal clinical judgments are the only parameter available to the clinician.

A clinical judgment is assessing the risk level of an individual patient. The following are the possible risk factors for the diabetic implant patient [69,70].

- Type of diabetes
- Age of onset
- Elevated blood glucose levels
- A regimen of glycaemic control
- Increased HbA_{1c} levels
- History of tooth loss due to periodontitis
- Poor or insufficient wound healing history
- The extent of edentulism
- Smoking as a cofactor for implant failure

Diabetes is often considered a relative contraindication to implant placement, but in well-controlled diabetes, there is no reason to avoid implant therapy. Patients with poorly controlled diabetes may not respond well to any surgical treatment, including implant placement, due to impaired wound healing. In animal models, diabetes has been associated with decreased bone-to-implant contact and decreased bone density in the peri-implant region. It is not known if this occurs in humans.

The following are the effects of diabetes on bone formation and homeostasis:

- Inhibition of collagen matrix formation: Qualitative and quantitative changes in extracellular matrix components such as collagens, laminin, and vitronectin are caused by advanced glycation end products These changes induced by advanced glycation end-products affect cell adhesion and growth and matrix accumulation; thereby inhibiting the lateral association of collagens and preventing the normal network-like assembly
- Alterations in proteins synthesis hyperglycaemic states may alter DNA and nuclear proteins since these are also targets of advanced glycation end products

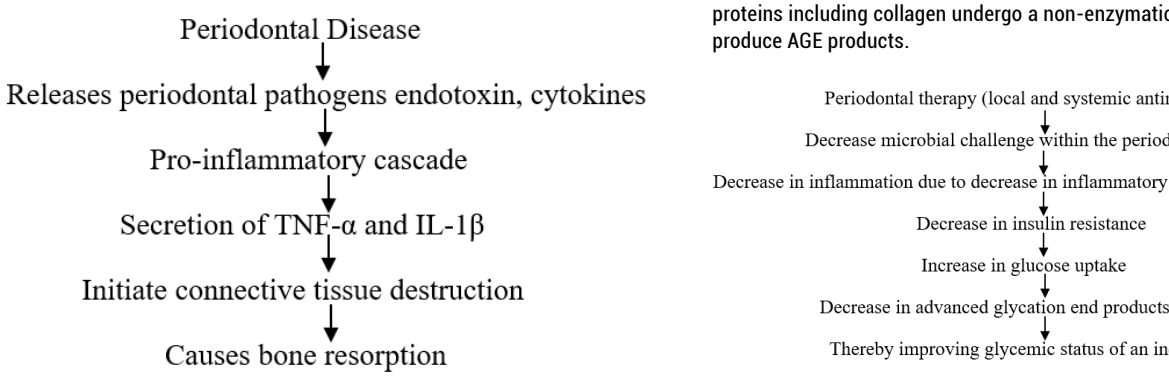

Figure 1. Diabetes is a metabolic disorder while periodontitis is a bacterial disease, the inter-relationship occurs through the ability of both the conditions to induce an inflammatory response leading to the production of inflammatory mediators like TNF-α, IL- β, IL-1, IL.

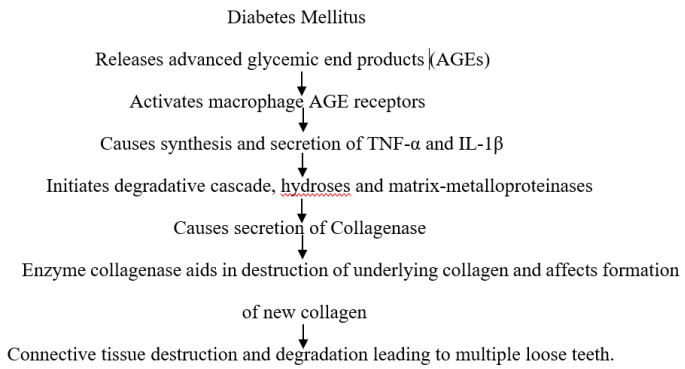

Figure 2. Under certain conditions of hyperglycemia lipids and numerous proteins including collagen undergo a non-enzymatic glycosylation process to produce AGE products.

Figure 3. The systemic levels of mediators involved in the pathogenesis of vascular diseases such as high-sensitivity C-reactive protein (Hs-CRP) and soluble E-selectin were significantly reduced following non-surgical periodontal debridement.

- Increased time for mineralization of osteoid
- Reduced bone turnover
- Decreased number of osteoblasts and osteoclasts
- Altered bone metabolism: Insulin effects are both direct and indirect on bone metabolism. Directly it stimulates osteoblastic matrix synthesis and indirectly it stimulates insulin-like growth factor-I production by the liver. Insulin-like growth factor-I then increases matrix synthesis by two mechanisms by increasing the number of osteoblasts present and by upregulating the function of differentiated osteoblasts
- Reduction in osteocalcin productions

All these factors together contribute to altered bone formation and influence osteointegration

A patient with late-onset disease, diet control, tooth loss not associated with periodontitis and a single-tooth indication may have the lowest risk of implant failure. Conversely, a patient with insulin-dependent juvenile diabetes, tooth loss as a result of periodontal disease, and a total edentulous indication may be at the highest risk of implant loss. Bone-implant contact is known to reduce, further affecting osseointegration. The bone formation disturbances reported are known to affect the prognosis of endo-osseous implants. There have been no controlled studies correlating diabetes to the success or failure of dental implants. Well-controlled preclinical and clinical studies are required to examine the biological pathways that may affect osseointegration. On the other hand, high blood glucose levels are also known to alter immune defense and encourage the growth of certain bacteria and fungi like candida, increasing the chances of peri-mucositis and peri-implantitis.

Periodontal Management of Patients with Diabetes

General considerations: Patients who present to the dental office with intraoral findings suggestive of a previously undiagnosed diabetic condition should be questioned closely. Questions should be targeted towards eliciting a clear history of polydipsia, polyuria, polyphagia, or recent unexplained weight loss. Patients should also be asked about their family history of diabetes. If the clinician suspects undiagnosed diabetes, laboratory evaluation and physician referral are indicated. Communication may be established with the patient's physician of the periodontal status, since the presence of infections including advanced periodontal disease may increase insulin resistance and contribute to a worsening of the diabetic state.

In known diabetic patients, it is important to establish the level of glycaemic control early in the examination process. This can be done through physician referral or review of medical records. Assessing the patient's most recent glycosylated hemoglobin values, gives a measure of glycaemic control over the preceding 2 to 3 months, and comparing with past values provides information on the stability of glycaemic control over time. The patient with well-controlled diabetes with no significant complication can generally be managed in a fashion similar to the non-diabetic dental patient, with the notable exception of the need to monitor for signs and symptoms of hypoglycemia during treatment. The procedure should be short, atraumatic, and as stress-free as possible [70,71].

Periodontal Considerations

Periodontal treatment of the patient with diabetes depends on both the periodontal diagnosis and on the patient's degree of glycaemic control. Patients with gingivitis should receive thorough home care instructions and complete debridement of the teeth. The response to therapy may not be as favorable in patients with poor glycaemic control (HbA1c >10%) as it is in those with better control (HbA1c <8%). Patients with poorly controlled diabetes may continue to exhibit gingival redness and bleeding, despite improved plaque control. For patients with periodontitis, the type of periodontal therapy is highly dependent on glycaemic control [71-76].

Once a diagnosis of periodontitis has been established, the clinician should determine the level of glycaemic control through evaluation of recent glycated hemoglobin values and physician consultation, as indicated. If the patient has well-controlled diabetes (HbA1c <8%), periodontal therapy can generally be provided in a fashion similar to a non-diabetic person with periodontitis. This includes non-surgical, surgical, and maintenance care. During maintenance, it is important for the clinician to not only assess the state of the periodontium but also to continuously evaluate the patient's glycaemic control. Once a relationship has been established with a patient and his or her physician, this is a simple matter of obtaining HbA_1c values whenever they are accomplished. Comparison with past values can provide knowledge of the stability of the patient's diabetic condition. A patient with diabetes and periodontitis has two chronic diseases, each of which impacts the other. Therefore, ongoing assessment of both diseases is critical to successful patient management. Because periodontal therapy usually involves multiple office visits over extended periods, the dentist and hygienist are in the perfect position to encourage patient compliance and control.

If diabetes is poorly controlled (HbA_1c >10%). therapeutic pathways may need modification. The clinician should provide treatment for any emergent periodontal condition, such as a periodontal abscess. If an infection is associated with systemic signs or symptoms such as increased temperature or lymphadenopathy, a systemic antibiotic also may be indicated. Thorough scaling and root planning to remove plaque and calculus should follow the management of acute lesions. A systemic antibiotic such as doxycycline (100 mg/day for 14 days), used in combination with scaling and root planning, may help improve glycaemic control. Meticulous plaque control should be emphasized, as should the importance of improving glycaemic control. Physician consultation is often indicated to describe for the physician the extent of the patient's periodontal condition and any therapy planned. After scaling and root planning, a period of 2 to 3 months should be allowed before re-evaluation. At this time, the periodontal condition should be assessed for response to initial debridement. Home care should be evaluated. In patients who require further periodontal therapy, another HbA1c should be requested to determine any changes between initial therapy and re-evaluation. If glycaemic control remains poor, the patient should be placed on frequent maintenance intervals, with continued periodontal supportive care given. Glycaemic control can be evaluated periodically in consultation with the physician to determine the patient's glycaemic status. Only when glycaemic control has improved should further periodontal therapy, such as surgical care, be considered. Otherwise, the response to treatment may be less than favorable.

Key Considerations Related to Dental Treatment of the Diabetic Patient Include

Stress reduction

Stress reduction and adequate pain control are important in treating diabetic patients. Epinephrine and cortisol secretion often increases in stressful situations. Both these hormones elevate blood glucose levels and interfere with glycaemic control. Efforts to ally patient apprehension and minimize discomfort are important and may include preoperative sedation and analgesia. Appropriate vasoconstrictor agents may be included in local anesthetics to ensure profound anesthesia [77-81].

Diet modifications

Periodontal therapy often requires surgical procedures that may result in mild to moderate post-operative discomfort. Modification of the diabetic patient's diet may be needed as a result of compromised chewing and swallowing that can accompany extensive dental procedures. It may be necessary to consult the patient's diabetes management team before the appointment for suggested liquid or semi-solid dietary alternatives.

In-patient *versus* outpatient care

Most diabetic patients can be easily managed in the dental office on an outpatient basis. However, for those with very poor glycemic control, severe medical complications, and extensive treatment needs that will alter dietary and medication regimens for extended periods, hospitalization may be considered. Diabetic patients with severe head and neck infections should be treated in a controlled medical environment to avert possible life-threatening complications.

Antibiotic Use

Antibiotics are not necessary for routine dental procedures in diabetic individuals, but may be considered in the presence of overt oral infections due to the potential for lower host resistance and delayed wound healing in diabetic patients. The need for antibiotics may vary depending on the patient's metabolic control, but the choice of antibiotic, dosage, and route of administration is usually the same as for non-diabetic individuals. Since elective procedures are generally deferred until adequate glycemic control is achieved, this most often applies to emergencies such as periodontal

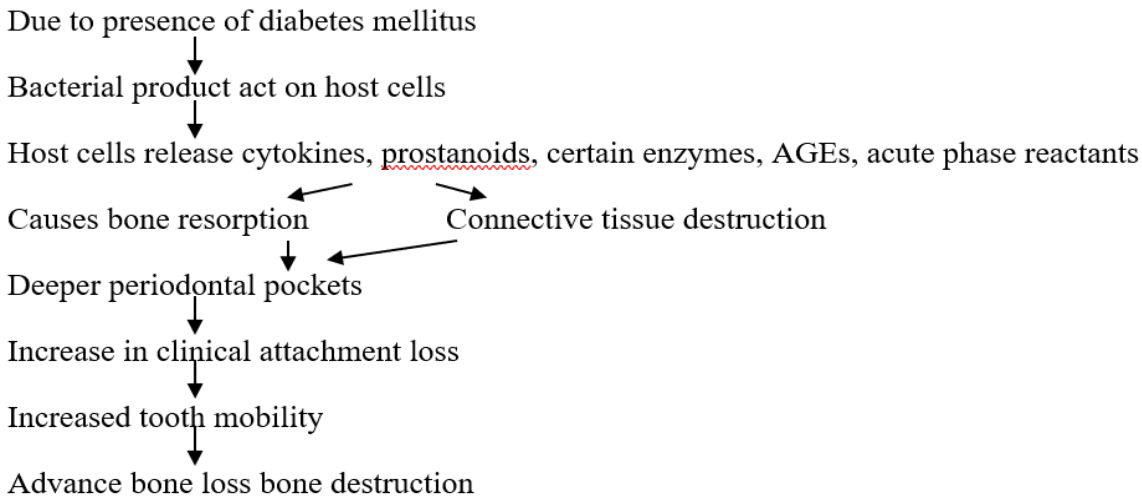

Figure 4. Aftermath of progression of periodontal disease [62, 81-84].

and periapical abscesses or other acute odontogenic infections. Adjunctive antibiotic therapy may also be considered in the management of a periodontal disease. Systemic tetracycline antibiotics in conjugation with mechanical root debridement may have beneficial effects not only on the periodontium but on glycaemic control as well.

Changes in medications and appointment timings

Early morning appointments are often preferred because levels of endogenous corticosteroids are generally higher at that time and stressful procedures may be better tolerated. While morning appointments may be preferable for some diabetic patients, others may be better treated in the afternoon. The periodontitis needs to know the medication and diet regimen being used by the patient. Appointment timing often depends on the particular medication regiment used by each patient. When possible it is best to plan dental treatment either before or after periods of insulin activity because hypoglycaemic reactions are more likely to occur when insulin levels are high.

For many dental procedures, no change in insulin regimen or oral agents is necessary for long or stressful procedures; patients may alter their usual regimen in consultation with their physician. Type 2 DM patients may reduce or omit oral hypoglycaemic medications on the day of the procedure followed by a return to normal dosage the following day. For patients taking insulin, changes in the timing, amount, or type of insulin injected may be warranted. On the day of the procedure, the patient may reduce or eliminate the dose of insulin taken before the procedure. Assuming a normal diet would be resumed following treatment the patient may take the usual insulin dose at the next regularly scheduled time.

Interval after the dental procedure

If the patient is unable to resume a normal diet after dental treatment, longer-term alterations in insulin or oral agents may be needed. Diet supplementation with liquid or semi-soft nutritional substances may also be useful. In diabetic cases, especially in patients taking multiple injections of insulin daily, periodontal treatment may occur at a time coinciding with peak insulin activity. The periodontist must be aware of the risk for hypoglycemia during the dental appointment and be ready to manage such occurrences [76-78].

The two best means of preventing hypoglycemia are patient questioning and assessment of capillary blood glucose. Before each dental appointment, patients should be asked what medications they have taken in the last 12 hours, what they have had to eat that day, and when they last checked their blood glucose. They also should be questioned about any history of hypoglycaemic episodes. One of the most common causes of hypoglycemia in the dental office is a patient taking their normal medication regimen, but then reducing or eliminating a meal before the appointment. Because several medications increase insulin levels, including sulfonylureas and injected insulin, the patient must not skip meals or snacks that they would normally consume. To have an accurate, up-to-the-minute assessment of blood glucose, patients with diabetes should be instructed to bring their glucometers to the dental office. Before treatment, patients can assess their blood glucose in a matter of seconds. If they are at or near the lower limits of normal glucose (about 70 mg/dL to 90 mg/dL), patients can be given carbohydrates orally to increase the glucose level before commencing treatment. Likewise, if symptoms of hypoglycemia develop in the patient during the appointment they can immediately assess their blood glucose level using their glucometer.

Management of Medical Emergencies in Diabetics

If hypoglycemia or insulin shock develops during dental treatment, it should be treated immediately. If the patient can take food by mouth, about 15 gm oral carbohydrates should be given. If the oral route cannot be used, emergency drugs may include 50% dextrose given intravenously, or 1 mg glucagon given intravenously, intramuscularly, or subcutaneously. Glucagon causes the immediate release of stored glucose from the liver into the bloodstream. The patient should respond to either agent within 10 to 15 minutes and should check the blood glucose again to confirm recovery. The patient should then remain in the office for approximately 1 hour to ensure stability before release. The emergency medical system should be activated if the patient fails to respond, and the patient should be transported to the hospital emergency room [82,83].

A diabetic crisis may develop when blood glucose levels over 200 mg/dl are present for an extended period. Hyperglycaemic crisis, which develops slowly and generally requires prolonged periods of hyperglycemia, is much less common in the dental office than in a hypoglycaemic emergency. In the Type 1 DM patient, diabetic ketoacidosis may occur. It presents with characteristics similar to those found in the uncontrolled diabetic. In the later stages, as acidosis develops, the affected individual may become disoriented, with rapid and deep breathing and hot, dry skin. Acetone breath may be evident. While the Type 2 DM patient is resistant to ketoacidosis, prolonged hyperglycemia may cause hyperosmolar non-ketotic diabetic acidosis. In this condition, acidosis occurs in the absence of blood ketones. In both ketoacidosis and hyperosmolar non-ketotic acidosis, severe hypotension and loss of consciousness develop without proper treatment, so the conscious patient should be transferred to the hospital. The unconscious patient should be managed using basic life support procedures including airway maintenance and administration of 100% oxygen, followed by administration of intravenous fluids to prevent vascular collapse. Affected patients should not be given insulin before obtaining serum electrolyte and glucose values at the hospital. Recovery is usually slower than seen in patients with insulin shock.

It may not be possible to differentiate between hypo- and hyperglycemia in the disoriented or unconscious diabetic patient. In this case, treatment should be initiated for hypoglycemia, since hypoglycaemic patients may deteriorate more rapidly to a life-threatening condition. Further, treatment for hypoglycemia or insulin shock with glucose will not significantly worsen the hyperglycaemic state in the case of an incorrect diagnosis. Monitoring the patient's condition using a glucometer may differentiate between hypoglycemia and hyperglycemia, and may be useful in evaluating recovery from a hypoglycaemic crisis. (Figure 4)

Conclusion

Diabetic patients are commonly encountered in the dental office. Proper patient management requires close interaction between the dentist

and physician. Dentists and other oral health care providers should understand the diagnostic and therapeutic methodologies used in diabetes care. They must be comfortable with the parameters of glycemia that are used to establish a diagnosis and an assessment of patients' ongoing glycaemic control. A thorough understanding of the pharmacological agents commonly encountered in this patient population is a must. The dentist should know how these agents can affect the risk for hypoglycemia and should be able to manage such events should they occur in the office. Dentists must educate patients and their physicians about the interrelationships between periodontal health and glycaemic control, with an emphasis on the inflammatory nature of periodontal diseases and the potential systemic effects of periodontal infection. Working with diabetic patients can be challenging and rewarding when open lines of communication are established and thorough patient education is attained.

References

1. American Diabetes Association. "Diagnosis and classification of diabetes mellitus." *Diabetes Care* (2004): 005-010.
2. Blair, M. "Diabetes mellitus review." *Urolog Nurs* (2016):36(1).
3. Skyler, J.S. "Diabetes mellitus: pathogenesis and treatment strategies". *J Medic Chem* (2004): 4113-4117.
4. Wheat, L.J. "Infection and diabetes mellitus." *Diabet Care* (1980):187-197.
5. Taylor, G.W & Borgnakke, W.S. "Periodontal disease: Associations with diabetes, glycemic control and complications". *Oral diseases*. (2008):191-203.
6. Ahmed, AM. "History of diabetes mellitus." *Saudi Medical Journal* (2002):373-378.
7. Lakhtakia, R. "The history of diabetes mellitus." *Sultan Qaboos Uni Medi J* (2013) 368.
8. Skyler, J.S., et al. "Differentiation of diabetes by pathophysiology, natural history, and prognosis" *Diabet* (2017): 241-255.
9. Karamanou, M., et al. "Milestones in the history of diabetes mellitus: The main contributors." *Wor Journ Diabet* (2016): 1.
10. Albrecht, M., et al. "Dental and oral symptoms of diabetes mellitus." *Comm Dent Oral Epiderm* (1988): 378-380.
11. Murrah, V.A. "Diabetes mellitus and associated oral manifestations: A review." *J Oral Pathol* (1985): 272-228.
12. Sharon, A., et al. "Salivary composition in diabetic patients." *J Oral Med* (1985): 23-26.
13. Finestone, A.J. & Boorujy, S.R. "Diabetes mellitus and periodontal disease." *Diabetes* (1967): 336-340.
14. Baltzis, D., et al, "Pathogenesis and treatment of impaired wound healing in diabetes mellitus: New insights." *Advanc Therap* (2014): 817-836.
15. Nibali, L. "What is the heritability of periodontitis? A systematic review." *J Dent Res* (2019): 632-641.
16. Loos, B.G., et al. "Identification of genetic risk factors for periodontitis and possible mechanisms of action." *J Clinic Periodont* (2005): 159-179.
17. Taylor, G.W., et al. "Glycemic control and alveolar bone loss progression in type 2 diabetics." *Ann Periodontol* (1998): 30-39.
18. Borrell, L.N., et al. "Prevalence and trends in periodontitis in the USA: From the NHANES III to the NHANES, 1988 to 2000." *Journ Dent Res* (2005): 924-930.
19. Bartolucci, E.G. & Parks, R.B. "Accelerated periodontal breakdown in uncontrolled diabetes. Pathogenesis and treatment." *Oral Radiol Endod* (1981): 387-390.
20. Rajhans, N.S., et al. "A clinical study of the relationship between diabetes mellitus and periodontal disease." *Journal India Society Period* (2011): 388.
21. Ryan, M.E., et al. "The influence of diabetes on the periodontal tissues." *The Journ Americ Dent Assoc* (2003): 34S-40S.
22. Maruyama, K. & Sato, S. "Effect of high-glucose conditions on human periodontal ligament endothelial cells: *In vitro* analysis ." *Odontol* (2017): 76-83.
23. Smith, PC., et al. "Role of fibroblast populations in periodontal wound healing and tissue remodeling" *Front physio* (2019): 270.
24. Lalla, E., et al. "Receptor for advanced glycation end products, inflammation, and accelerated periodontal disease in diabetes: Mechanisms and insights into therapeutic modalities." *Ann Periodontol* (2001): 113-118.
25. Vlassara, H. "The AGE-receptor in the pathogenesis of diabetic complications." *Diabetes Metab Res* (2001): 436-443.
26. Wong, R.K. "Advanced glycation end products stimulate an enhanced neutrophil respiratory burst mediated through the activation of cytosolic phospholipase A2 and generation of arachidonic acid." *Circulation* (2003): 1858-1864.
27. Santana, R.B. et al. "A role for advanced glycation end products in diminished bone healing in type 1 diabetes." *Diabet* (2003): 1502-1510.
28. Cortizo, A.M., et al, "Advanced Glycation End-Products (AGEs) induce concerted changes in the osteoblastic expression of their receptor RAGE and in the activation of Extracellular Signal Regulated Kinases (ERK)." *Mol Cell Biochem* (2003): 01-10.
29. Demmer, R.T., et al. "Periodontal status and A1C change: longitudinal results from the study of health in Pomerania (SHIP)." *Diabet Car* (2010): 1037-1043.
30. Vlassara, H. & Bucala, R. "Recent progress in advanced glycation and diabetic vascular disease: Role of advanced glycation end product receptors." *Diabet* (1996): S65-S66.
31. Lalla, E., et al. "Enhanced interaction of advanced glycation end products with their cellular receptor RAGE: Implications for the pathogenesis of accelerated periodontal disease in diabetics." *Ann Periodontol* (1998): 13-19.
32. Brownlee, M. "GlycatVion and diabetic complications." *Diabetes* (1994): 836-841.
33. Alba-Loureiro, T.C., et al. "Neutrophil function and metabolism in individuals with diabetes mellitus." *Braz J Med Biol Res* 40: (2007): 1037-1044.
34. Alba-Loureiro, T.C., et al. "Diabetes causes marked changes in function and metabolism of rat neutrophils." *J Endocrinol* (2006): 295-303.
35. Manouchehr-Pour, M., et al "Impaired neutrophil chemotaxis in diabetic patients with severe periodontitis." *J Dent Res* (1981): 729-730.
36. Graves, D.T., et al. "Diabetes-enhanced inflammation and apoptosis-impact on periodontal pathology" *J Dent Res* (2006): 15-21.
37. Ueta, E., et al. "The prevalence of diabetes mellitus in odontogenic infections andoral candidiasis: An analysis of neutrophil suppression." *J Oral Pathol Med* (1993): 168-175.
38. Grant-Theule, D.A., et al. "Periodontal disease, diabetes, and immune response: A review of current concepts." *J Western Society Periodont* (1996): 69-77.
39. Rangaraj, A., et al. "Role of collagen in wound management." *Wounds UK* (2011): 54-63.
40. Daniel, R. "Diabetes and periodontal disease." *J Pharm Bioallied Sci* (2012):S280.
41. Pucher, J. & Stewart, J. "Periodontal disease and diabetes mellitus." *Current Diab Reports* (2004): 46-50.
42. Ravari, H., et al. "Treatment of non-healing wounds with autologous bone marrow cells, platelets, fibrin glue and collagen matrix." *Cytotherapy* (2011): 705-711.
43. Ayuk, S.M., et al. "Collagen production in diabetic wounded fibroblasts in response to low-intensity laser irradiation at 660 nm." *Diabet Tech Therap* (2012): 1110-1117.
44. Ma, H., et al. "Effect of low-level laser therapy on proliferation and collagen synthesis of human fibroblasts *in vitro*." *J Wound Management Research* (2018): 1-6.
45. Gorecka, J., et al. "Induced pluripotent stem cell-derived smooth muscle cells increase angiogenesis and accelerate diabetic wound healing." *Regen Med* (2020): 1277-1293.
46. Taylor, G.W., et al. "Bidirectional interrelationships between diabetes and periodontal diseases: An epidemiologic perspective." *Ann Periodontol* (2001): 099-112.

47. Soskolne, W.A., & Klinger, A., "The relationship between periodontal diseases and diabetes: An overview" *Ann Periodontol* (2001): 91-98

48. Chavarry, N.G.M., et al. "The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis." *Oral Health Prev Dent* (2001): 107-127.

49. Casanova, L., et al. "Diabetes and periodontal disease: A two-way relationship." *British Dent Journ* (2014): 433-437.

50. Khader, Y.S., et al. "Periodontal status of diabetics compared with nondiabetics: A meta-analysis." *J Diabetes Complicat* (2006): 59-68

51. Mealey, B.L. & Ocampo, G.L. "Diabetes mellitus and periodontal disease." *Periodontol* (2007): 127-153.

52. Grover, H.S. & Luthra, S. "Molecular mechanisms involved in the bidirectional relationship between diabetes mellitus and periodontal disease." *J Indian Soc Periodontol* (2013) 292-301.

53. Taylor, G.W., et al. "Glycemic control and alveolar bone loss progression in type 2 diabetics." *Ann Periodontol* (1998): 30-39.

54. Kiran, M., et al. "The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus." *J Clin Periodontol* (2005): 266-272.

55. Krishna, R., et al, "Understanding inflammation: The key to targeted preventive measures for diabetes and periodontitis. In new Strategies to Advance Pre/Diabetes Care." *Integrative Approach by PPPM* (323-353)

56. Preshaw, P.M., & Taylor, J.J. "How has research into cytokine interactions and their role in driving immune responses impacted our understanding of periodontitis?" *J Clin Periodontol* (2011): 60-84.

57. Vassiliadis, S., et al. "The destructive action of IL-1alpha and IL-b in IDDM is a multistage process: Evidence and confirmation by apoptotic studies, induction of intermediates and electron microscopy". *Mediators Inflamm* (1999): 85-91.

58. Sjoholm, A., et al. "Aspects of the involvement of interleukin- 1 and nitric oxide in the pathogenesis of insulin-dependent diabetes mellitus." *Cell Death Diff* (1998): 461-468.

59. Moller, D.E., et al. "Potential role of TNF-alpha in the pathogenesis of insulin resistance and type 2 diabetes." *Trends Endocrinol Metab* (2000): 212-217.

60. Jitprasertwong, P., et al. "The role of IL-18 in cross-susceptibility between periodontal disease and diabetes." Doctoral Dissertation, Newcastle University.

61. Pihlstrom, B.L. & Buse, J.B. "Diabetes and periodontal therapy." *J Americ Dent Assoc* (2014): 1208-1210.

62. Grossi, S.G., et al. "Treatment of periodontal disease reduces glycated haemoglobin." *J Periodontol* (1997): 713-719.

63. Offenbacher, S., "Periodontal diseases: pathogenesis." *Annal Periodont* (1996): 821-878.

64. O'Connell, P.A.A., et al. "Effects of periodontal therapy on glycemic control and inflammatory marker." *J Periodontol* (2008): 774-783.

65. Kneckt, M.C., et al. "Attributions to dental and diabetes health outcomes." *J Clin Periodontol* (2007):205-211.

66. Janket, S.J. "Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies." *J Dent Res* (2005): 1154-1159.

67. Simpson, T.C. "Treatment of periodontal disease for glycaemic control in people with diabetes." *Cochrane Database Syst Rev* (2010).

68. Spangler, L., et al. "Cross-sectional study of periodontal care and glycosylated hemoglobin in an insured population." *Diabetes Care* (2010): 1753-1758.

69. Jones, J.A., et al. "Does periodontal care improve glycemic control?" The Department of Veterans Affairs Dental Diabetes Study." *J Clin Periodontol* (2007): 52-81.

70. Katyayan, P.A., et al. "Rehabilitative considerations for dental implants in the diabetic patient." *J Indian Prosthodontic Soc* (2013): 175-183.

71. Pavya, G., et al. "Effect of diabetes in osseointegration of dental implant-A review." *Biomed Pharmacol J* (2015): 353-358.

72. Rees, T.D. et al. "Periodontal management of the patient with diabetes mellitus." *Periodontology* (2000): 63-72.

73. Westfelt, E., et al. "The effect of periodontal therapy in diabetics: results after 5 years" *J Clinical Periodontology* (1996): 92-100.

74. Madianos, P.N. & Koromantzos, P.A. "An update of the evidence on the potential impact of periodontal therapy on diabetes outcomes." *Journ Clinperiodont* (2018): 188-195.

75. Grossi, S.G., et al. "Response to periodontal therapy in diabetics and smokers." *Journ of Periodont* (1996): 1094-1102.

76. Wang, T.F., et al. "Effects of periodontal therapy on metabolic control in patients with type 2 diabetes mellitus and periodontal disease: A meta-analysis." *Medicine* (2014): 93-98.

77. Naiff, P., et al. "Importance of mechanical periodontal therapy in patients with diabetes type 2 and periodontitis." *Internat Journ Dentist* (2018).

78. Tripathi, B.K. & Srivastava, A.K. "Diabetes mellitus: complications and therapeutics." *Medic Scien Mon* (2006): 130-147.

79. Engebretson, S.P., et al. "The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial." *Jama* (2013) 2523-2532.

80. Navarro-Sanchez, A.B., et al. "Effect of non-surgical periodontal therapy on clinical and immunological response and glycaemic control in type 2 diabetic patients with moderate periodontitis." *Journ Clinic Periodont* (2007): 835-843.

81. Gurav, A.N., "Periodontal therapy-an adjuvant for glycemic control: Diabetes & Metabolic Syndrome." *Clin Res & Rev* (2012): 218-223.

82. Pucher, J. & Stewart, J. "Periodontal disease and diabetes mellitus." *Current Diabetes Reports* (2004): 46-50.

83. Brownlee, M., "The pathobiology of diabetic complications: A unifying mechanism." *Diabet* (2005): 1615-1625.

84. Stratton, I.M. "Microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study." *BMJ* (2021):405-412.

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