Review Article

Open Access

Relation between Periodontitis and Diabetes

Vinutna Buddiga¹, Srinivas Pentyala^{*3} and Naveen Ramagoni^{*3}

¹Department of Periodontics, GSL Dental College, Rajahmundry, AP, India

²Department of Anesthesiology, Stony Brook Medical Center, New York, USA

³Department of Periodontics and Preventive Dentistry, Navodaya Dental College, Raichur, Karnataka, India

Corresponding Author(1): Naveen Ramagoni, Department of Periodontics and Preventive Dentistry, Navodaya Dental College, Raichur, Karnataka, India. Tel 9912935146, Email: ramagoni14@gmail.com

Corresponding Author(2): Srinivas Pentyala, Department of Anesthesiology, Stony Brook Medical Center, Stony Brook, New York. 11794-8480, Tel: (631)444-2974; Fax: (631)444-2907, Email: srinivas.pentyala@stonybrook.edu

Citation: Naveen Ramagoni, Srinivas Pentyala et al. (2017), Relation between Periodontitis and Diabetes. Int J Dent & Oral Heal. 3:3, 31-37. DOI: [10.25141/2471-657X-2017-3.0020](https://doi.org/10.25141/2471-657X-2017-3.0020)

Copyright: ©2017 Naveen Ramagoni et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Received: Feb 23, 2017; **Accepted:** March 06 2017; **Published:** April 6, 2017

Abstract

Over the last 50 years, numerous studies have been conducted to demonstrate the relationship between Periodontal Disease (PD) and Diabetes Mellitus (DM). Both these diseases share a similar pathophysiology in that they are immune related and the severity of one affects the outcomes of the other. DM and PD are both chronic diseases, which mostly affects the elderly and if left untreated can have deleterious effects on the standard of living. The exact mechanism by which DM affects the periodontium is not clear but it is thought that DM alters the harmonious oral environment making it more suitable for the growth of gram-negative bacteria. In this information on oral microbiota associated with DM, periodontal infection and systemic inflammation associated with DM, effects of DM on PD and the treatment of PD associated with DM are presented.

Keywords: Periodontitis, Diabetes Mellitus, Lipopolysaccharides, Glycated Hemoglobin

Introduction

Diabetes Mellitus (DM) and Periodontitis (PD), both are pyogenic disorders with immune-regulatory dysfunction. The relatively high incidence of these diseases in the world population with similar pathogenesis had ultimately lead to the conclusion that there is definitely an inter-relation between these two diseases. But some authors agree otherwise¹.

DM a metabolic disorder characterised by hyperglycemia due to defective secretion or activity of insulin that results in the inability of glucose to be transported from blood stream in to the tissues. This in turn results in high blood glucose levels and excretion of sugar in the urine².

PD is defined as an infectious disease resulting in inflammation within the supporting tissues of the teeth, resulting in progressive attachment loss of teeth and bone loss³. Most of the connective tissue destruction which takes place in a periodontal disease is usually from the interaction of bacteria and their products with mononuclear cells⁴.

Clinicians have long considered diabetes as an important risk factor for PD in adults and the American Diabetes Association has listed periodontitis as a risk for diabetics. Periodontal disease has also been recognized as a sixth complication of DM⁵. In the most recent classification of PD, researchers have listed DM associated Gingivitis as a specific entity⁴⁸.

Diverse studies carried out by the WHO confirm that the prevalence and severity of PD tends to be on the rise in the adult population compared to younger groups. In India, DM affects more than 62 million Indians, which is more than 7.1% of India's Adult Population. Where as in US, 9.6% of the population is effected⁶.

DM is known to have profound oral effects mainly on the periodontium, and the dentist is often the first health care provider to encounter an individual with undiagnosed or untreated disease. Even more commonly, the dentist may be called on to provide oral health care for diabetic patients⁷.

Diabetic patients who maintained reasonably good metabolic control had less periodontal attachment loss and good response to periodontal treatment when compared to poorly controlled diabetics⁵. In patients aged 35 and older who are suffering from DM for over 10 years showed more attachment loss than those with less than 10 years⁴⁹.

Diabetes and Periodontal disease has been a very interesting and complex subject for discussion. This review focusses primarily on various effects of diabetes on periodontal tissues and the effects of periodontal infections on the glycemic control and the response to periodontal treatment.

Oral microbiota in diabetics

Diabetes-associated changes occur in the subgingival environment which may favour the growth of some microbial species. Increased urea and glucose levels in crevicular fluid of diabetic subjects have been reported⁸. Weinberg et al reported that the glucose level at a healthy gingival site reflects the glucose content of plasma, but in the presence of inflammation, glucose concentration in crevicular fluid decreases dramatically, indicating that serum glucose may be utilized by inflamed periodontium⁹.

Induction of experimental diabetes in rats is known to cause a shift in subgingival flora from a nearly equal mixture of Gram-positive and Gram-negative cocci and short rods to predominantly Gram-negative rods and filaments and subsequent deepening of periodontal pockets¹⁰.

According to Mashimo et al, Capnocytophaga species predominated in most periodontal lesions of young insulin-dependent diabetes mellitus (IDDM) patients averaging 24% of the cultivable flora¹¹. Aggregatibacter actinomycetemcomitans was found in cultures of the subgingival flora in 3 of the 9 diabetics with periodontitis, but in none of those with gingivitis or normal periodontal tissues¹². A number of subsequent studies have failed to show any significant association of Capnocytophaga species with periodontal disease in Type I diabetic patients¹³. Zambon et al found *P. intermedia*, *W. recta*, and *P. gingivalis* as the 3 most predominant pathogens in subgingival dental plaque of non-insulin dependent diabetes mellitus (NIDDM) patients¹⁴.

Patients with poor control of diabetes are known to be at high risk for periodontitis. The lack of any significant association between the presence of periodontal disease-associated pathogens and metabolic control of diabetes most likely means that, more periodontitis in poorly-controlled diabetics is due to factors other than greater pathogenesis of the subgingival flora¹⁵.

Periodontal infection and systemic inflammation

Recognition of subgingival dental plaque as and a microbial biofilm has contributed substantially to the understanding of periodontal disease pathophysiology and treatment modalities¹⁶. As previously mentioned, Diabetes can increase the severity of gingivitis and periodontitis. On the contrary, periodontitis may also deteriorate and increase the risk of diabetic complications⁵⁰.

Periodontal bacteria shedding off lipopolysaccharide (LPS) provides either a direct or indirect stimulus to endothelial cells,

monocytes, and macrophages, increasing endothelial reactivity and activating a pro-inflammatory cascade with sustained elevations of pro-inflammatory cytokines. Interleukin-1 β (IL-1), interleukin-6 (IL-6), Tumor necrosis factor- α (TNF) and prostaglandin-E2 (PGE2) in turn signals different target cells and tissues, such as the liver to produce an acute-phase response, and pancreatic beta cells and adipose tissue affecting functions such as insulin sensitivity and glucose transport^{8,51}.

Formation of the subgingival biofilm appears to be a convenient adaptation that permits long-term microbial survival even in the presence of full range of host defences. Porphyromonas gingivalis acts as an etiological agent of periodontal disease as opposed to merely being associated with disease. The disease-causing capacity of *P. gingivalis* resides in its ability to secrete a number of virulence factors and extracellular proteases which, in addition, provide a source of nutrients able to sustain and support growth of the of the subgingival plaque community¹⁶.

LPS from subgingival *P. gingivalis* has both endotoxic and immunologic activities. Specifically *P. gingivalis* LPS is a potent inducer of IL-1, TNF, PGE2 and matrix metalloproteinases (MMP). *P. gingivalis* LPS is able to activate a proinflammatory response by direct activation of nonmyeloid cells; i.e., endothelial cells. Recently, it has been demonstrated that *P. gingivalis* is able to directly invade endothelial cells¹⁶.

Persistent elevations of IL-1, IL-6, and TNF in the diabetic state have an effect on the liver, stimulate the release of acute-phase proteins, produce the dysregulation of lipid metabolism associated with type 2 diabetes and have effects on pancreatic beta cells as well. Thus, the accentuated inflammatory and cytokine response seen in diabetes is responsible for the dysregulation of lipid metabolism, insulin resistance, and micro vascular long-term complications¹⁷. Persistent elevation of these mediators in diabetics is also somewhat due to diminished physical activity, poor diet, obesity and infection⁵².

Mandell et al examined a group of poorly-controlled IDDM patients in a cross-sectional design for total microbial levels, microbial incidence, and the percentage levels of selected periodontal microorganisms. Increased prevalence of the organisms *Prevotella intermedia*, *Prevotella melaninogenica* spp., and *Campylobacter rectus* were found at the diseased sites. A significantly higher percentage of *Prevotella intermedia* was found at the sites exhibiting deep pockets and attachment loss¹⁸.

Ebersole et al conducted a study to relate periodontal status, periodontal microorganisms, and host-response characteristics in Hispanic Americans with type 2 diabetes. Plaque and serum samples were obtained from 63 Hispanic American subjects with and without type 2 diabetes. The increased severity of periodontal disease with type 2 diabetes reflected an alteration of the pathogenic potential of periodontal bacteria and/or a modification of the characteristics of the host's inflammatory response that may contribute to a breakdown in the homeostasis of the periodontium¹⁹.

Effects of Diabetes on the periodontium

Examination of the available data reveals strong evidence that diabetes is a risk factor for gingivitis and periodontitis, and the level of glycemic control appears to be an important determinant in this relationship. Although some authors have not found a significant association between diabetes and gingival inflammation, in many studies, the prevalence and severity of gingivitis has been demonstrated to be higher in individuals with diabetes²⁰. A study carried out by the NHANES III, reports patients with good glycemic control ($HbA1c \leq 9\%$) had better periodontal prognosis than patients with poor glycemic control ($HbA1c > 9\%$), suggesting a dose response relationship between glycemic control and periodontitis⁵³.

A number of oral diseases have been associated with DM, and PD has been identified as a possible risk factor for poor metabolic control in subjects with diabetes. Evidence suggests that periodontal changes are the first clinical manifestation of diabetes²¹. Longitudinal research has also shown an increased risk of progressive periodontal destruction in people with diabetes. In a study of the Pima Indians, the incidence and prevalence of periodontal disease were determined in 2,273 subjects 15 years of age or older. The prevalence of periodontitis was 60% in subjects with diabetes and 36% in those without diabetes²². In another 2-year longitudinal study, subjects with type 2 diabetes had a fourfold increased risk of progressive alveolar bone loss compared to non-diabetic subjects. The relationship between metabolic control of diabetes and periodontal disease is difficult to define conclusively²³.

Research suggests that this association is similar to the association between glycemic control and the classic complications of diabetes such as retinopathy and nephropathy, suggesting a significant heterogeneity in the diabetic population²⁴. Thus, although poor control of diabetes clearly increases the risk of diabetic complications, there are many poorly controlled diabetic individuals without major complications. Conversely, good control of diabetes greatly decreases the risk of diabetic complications²⁴.

In a similar fashion, the body of evidence suggests that some diabetic patients with poor glycemic control develop extensive periodontal destruction, whereas others do not. On the other hand, many well-controlled diabetic patients have excellent periodontal health, but others develop periodontitis²³. Ervasti et al studied the periodontal health status of 50 adult diabetics and 53 healthy controls. The diabetic group was further divided into three subgroups according to the control of diabetes. No correlation was found between duration, complications and medication of diabetes and gingival bleeding. The reason for increased bleeding in poorly controlled diabetics could be either inflammation or vascular changes in the gingiva²⁵.

Diabetes has been associated with an increased risk of periodontitis even at a young age. Lalla et al studied the association between diabetes mellitus and periodontal attachment and bone loss in children (6-18 years of age). Findings demonstrated an association between diabetes and an increased risk for periodontal destruction very early in life, and suggest that programmes to address

periodontal needs should be the standard of care for diabetic youth²⁶.

Insulin-dependent or Type 1 diabetes mellitus (IDDM) has been associated with an increased severity of periodontal disease. Diabetic cell isolates exhibited significantly lower alkaline phosphatase activity than the non-diabetic isolates when exposed to either TGF, Platelet derived growth factor- BB (PDGF-BB), Insulin like growth factor-1 (IGF-1) or a combination of PDGF-BB and IGF-1. These results suggest that the populations of periodontal ligamental cells in insulin-dependent diabetics may be altered in their ability to form mineralized tissue and to respond to growth factors, functions affecting the maintenance and regeneration of the periodontium²⁷.

Mechanisms by which diabetes may influence the periodontium

Mechanisms by which diabetes may contribute to periodontitis include vascular changes, neutrophil dysfunction, altered collagen synthesis, and genetic predisposition.

Vascular changes

The primary causal factor in the development of vascular changes in diabetes is prolonged exposure to hyperglycaemia. The vascular pathophysiologic alterations include accumulation of Periodic acid-Schiff (PAS)-positive deposits of carbohydrate-containing extravasated plasma proteins, thickening of vessel walls through matrix expansion, and selective cellular proliferation. The fundamental structural lesion in small blood vessels is thickening of basement membranes²⁸. The gingival capillaries of diabetic patients not only have significantly greater basement membrane thickness, but also other aberrations such as disruption of the membrane, presence of collagen fibres within the true membrane, and swelling of endothelium. It has been hypothesized that the above changes may impede oxygen diffusion, metabolite waste elimination, leukocyte migration, delivery of nutrients and diffusion of immune factors thereby contributing to increased severity of periodontitis in diabetic patients and delayed healing^{29, 54}.

Neutrophil dysfunction - Defects in Host Response

Immunologic research concluded that several defects in polymorphonuclear leukocyte (PMN) function including impaired migration, phagocytosis, intracellular killing, and chemotaxis have been considered a potential cause of bacterial infection in the diabetic individual³⁰. Molenaar et al. extended neutrophil dysfunction studies to include non-diabetic, first-degree relatives of diabetics and found that they also had a decreased chemotactic index. A number of studies indicate that the abnormalities in PMN functions can be corrected by insulin therapy³¹. Diabetics with severe periodontitis have been shown to have depressed chemotaxis of peripheral blood leukocytes when compared to diabetics with mild periodontitis or non-diabetics with severe or mild periodontitis. McMullen and co-workers found decreased PMN chemotaxis in patients with a family history of diabetes and severe periodontitis and suggested that the PMN defect was of genetic origin³². The association between diabetes, abnormal PMN function, and periodontal disease may be explained by: 1) Impairment of PMN function as a result of bacterial infection

associated with periodontal disease; or 2) Primary impairment of the PMN response predisposing these patients to periodontitis. Cutler et al. were the first to report a case of an IDDM patient who's PMNs showed decreased chemotaxis and phagocytosis of a putative periodontal pathogen, *P. gingivalis* isolated from a site of periodontal destruction³³.

Collagen Metabolism

Collagen is the predominant component of the gingival connective tissue accounting for approximately 60% of the connective tissue volume and 90% of the organic matrix of alveolar bone. Altered collagen metabolism would be expected to contribute to periodontal disease progression and wound healing in diabetes²³. Golub and his group found that diabetes impaired the production of bone matrix components by osteoblasts, decreased collagen synthesis by gingival and periodontal ligament fibroblasts, and increased gingival Collagenase activity³⁴. The increased collagenase activity can also be attributed to a neutrophil type of collagenase (MMP-8) secreted by fibroblast, under certain circumstances⁵⁵. Collagen undergoes non-enzymatic glycosylation when subjected to a hyperglycaemic environment and the glucose-derived cross-links between the molecules contribute to reduced collagen solubility and turn-over rate. Diabetic gingival collagen also shows decreased solubility properties; a return to near-normal condition can be achieved by insulin treatment³⁴.

Genetic Predisposition

Type I diabetes has been associated with specific human lymphocyte antigen (HLA) types. A clear association of IDDM with HLA-B8 and B15 has been found. The HLA associations are even stronger for antigens DR3 and DR4. Approximately 95% of IDDMs have DR3 or DR4 or both³⁵. In a non-diabetic population with Aggressive periodontitis, HLA-DR4 was found in 80% of the patients compared with 38% of the control population, which was interpreted to mean that HLA-DR4 antigen may predispose to the development of aggressive periodontitis¹⁵. The prevalence of DR4 in a control population was 30%. The authors concluded that HLA-DR4 molecules on peripheral blood antigen cells may signal greater susceptibility to periodontitis. More studies are, however, needed to clarify the role of this antigen in the periodontal disease of diabetics¹⁵.

The mechanisms of action whereby diabetes increases the risk for periodontitis remain unclear. Again, metabolic control, duration, and extent and severity of periodontitis are important variables. Diabetics differ in the degree of vascular changes, neutrophil dysfunction and genetic predisposition¹⁵.

Effects of Periodontal diseases on the diabetic state

Long-term diabetic complications and the presence of periodontal disease constitute a serious health hazard for the diabetic individual. Once periodontal disease is established, the chronic nature of this infection may contribute to worsening of diabetic status leading to more severe diabetes-related complications. Studies examining the association between periodontal disease and diabetes metabolic control give the evidence of periodontal diseases worsening diabetic conditions. Mean glycated hemoglobin (HbA1c), a

measure of long-term glucose control, increased 0.5% in type 2 diabetics with severe periodontitis over an observation period of 2 to 3 years, whereas this measure of glucose control was reduced 0.9% in those with little or no periodontal disease, independent of the effect of diabetes medication³⁶. Diabetics experience increased destruction of periodontal tissues as a result of an abnormal immune response, altered fibroblast function and levels of collagen, as well as the micro vascular effects of advanced glycation end products (AGE).

The accumulation of AGE in the periodontium is correlated with an increase in the level of inflammatory mediators, which are associated with tissue destruction. These inflammatory mediators may contribute to the severity of tissue destruction in diabetics with periodontal disease. The increased prevalence of periodontal disease in diabetics is an example of an oral/systemic relationship. There is evidence that this relationship may be two-dimensional as well, as diabetics with active periodontitis tend to have poor glycemic control when compared to patients without periodontitis³⁷. Karjalainen et al studied the association of the severity of periodontal disease with organ complications in type 1 diabetic patients³⁸. Thorstensson et al studied the medical complications in relation to periodontal disease in type 1 diabetics. Results from these studies consistently indicate that diabetics with severe periodontal disease exhibit more diabetes complications compared to diabetics with no or mild periodontal disease, suggesting that presence of severe periodontal disease confers a significant risk for exhibiting other diabetes-related complications³⁸. Periodontal diseases can have a significant impact on the metabolic state in diabetes. The presence of periodontitis increases the risk of worsening of glycemic control over time.

Kiran et al conducted a study to investigate the effect of improved periodontal health on metabolic control in type 2 DM patients. The results of the study showed that non-surgical periodontal treatment is associated with improved glycaemic control in type 2 patients and could be undertaken along with the standard measures for the diabetic patient care³⁹. Taylor et al conducted a study to test the hypothesis that severe periodontitis in persons with NIDDM increases the risk of poor glycemic control. These results support considering severe periodontitis as a risk factor for poor glycemic control and suggest that physicians treating patients with NIDDM should be alert to the signs of severe periodontitis in managing NIDDM⁴⁰.

Effects of diabetes on the response to periodontal therapy

The initial dental therapy for patients with DM, as with all patients, must be directed towards control of acute oral infections. It is important to advise the 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 a pilot study conducted by Miller, the relationship between periodontal inflammation and diabetes control showed the reduction of inflammation in poorly-controlled diabetic subjects (measured by bleeding on probing) correlated with reduced blood glucose levels⁴¹. Seventy-five patients with DM were studied (59% IDDM and 41% NIDDM). Blood glucose was monitored

using glycosylated hemoglobin. It was found that the patients with poor diabetic control had significantly more calculus, while both groups had similar levels of plaque control. The prevalence of severe attachment loss increased with decreasing control of diabetes⁴². Patients with well-controlled NIDDM or IDDM can be treated similarly to non-diabetic patient for most routine dental needs. Procedures should be short, atraumatic, and as stress-free as possible⁴². Diabetes mellitus and periodontal diseases are common chronic diseases in the world. Periodontal infection may adversely affect glycemic control in people with diabetes. Taylor reviewed the evidence regarding how treatment of periodontal diseases affects glycemic control. Sufficient evidence exists to incorporate oral examinations and periodontal care in management regimens for people with diabetes. It is prudent to assess patients' glycemic control status and communicate the importance of referring patients with diabetes for thorough oral health evaluations and necessary care⁴².

Treatment of periodontal infection in diabetics

The resistance of subgingival biofilms to normal host defences, which are notoriously resistant to removal, has important consequences for the patient and for periodontal therapy. Subgingival biofilms cannot be removed by daily oral hygiene methods physical removal is essential. It is for this reason that mechanical scaling and root planing are essential components of treatment for periodontitis⁴³. This fundamental requirement of periodontal therapy is even more relevant in patients in whom periodontal infection constitutes a health risk, such as those suffering from DM. One additional feature of periodontal infection and biofilm formation is the recurrent nature of this infection⁴³. Thus a near ideal oral hygiene is the only way to prevent the re-formation of dental plaque and further progression of the attachment and bone loss⁵⁶.

A large number of studies have addressed periodontal treatment in diabetics. Earlier studies focused strictly on parameters of tissue inflammation and destruction. The short-term response to nonsurgical periodontal therapy in diabetics is similar to that observed in non-diabetics, regardless of the degree of diabetes control⁴⁴. A study by Seppala and Ainamo of 38 subjects with poorly-controlled type 1 diabetes reported no effect on levels of blood glucose or glycated hemoglobin after subgingival scaling, periodontal surgery and dental extraction⁴⁵. Christgau et al showed the healing response (clinical, microbiological, and immunologic results) to non-surgical periodontal therapy in patients with DM. In his study *P. gingivalis* was still present post-treatment in 12 of the 20 diabetic patients⁴⁶.

Mechanical periodontal therapy combined with subgingival application of minocycline gel resulted in a 0.8% reduction in glycated hemoglobin in 13 Japanese patients with type 2 diabetes. Total counts of subgingival bacteria and circulating levels of TNF were significantly reduced as well⁴⁷. Various studies along with the above studies suggest that periodontal therapy will have effect on the control of DM to some extent and vice versa.

Conclusion

Diabetes is a complex disease with significant variations which influence the development of complications including PD. Periodontal diseases and DM are closely associated and are highly prevalent chronic diseases with many similarities in pathophysiology. Although exact mechanisms of action remain unclear, poor metabolic controls as well as extended duration of the diabetes are risk factors for PD. Both DM and PD increase with age. Diabetes clearly increases the risk of periodontal diseases; less clear is the impact of periodontal diseases on glycemic control of diabetes and the mechanisms through which this occurs. It is possible that periodontal diseases may serve as initiators or propagators of insulin resistance in a way similar to obesity, thereby aggravating glycemic control. Further research is needed to clarify this aspect of the relationship between periodontal diseases and diabetes.

References

1. Malik G, Lehl G, Talwar M. [Association of periodontitis with diabetes mellitus: A review. journal a/medical college Chandigarh 2011;1:10-14.](#)
2. Tan M, Daneman D, Lau D, others a. Diabetes in Canada: strategies towards 2000. Toronto; 1997.
3. Flemming TF. [Periodontitis. Ann Periodontol 1999;4:32.](#)
4. Denis FK, Bartold PM. [Clinical relevance of the host responses of periodontitis. Periodontology 2000; 43: 278-93.](#)
5. Oliver RC, Tervonen T. [Diabetes-A Risk Factor for Periodontitis in Adults? Journal of Periodontology 1994;530 – 8s](#)
6. World Health Organization. [The WHO Global Oral Health Data Bank. Geneva: World Health Organization 2003.](#)
7. Ress TD. [The Diabetic Dental Patient. Dental Clinics of North America 1994;38:](#)
8. Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis A, Taylor R. [Periodontitis and diabetes: a two-way relationship. Diabetologia 2012; 55:21–31.](#)
9. Weinberg A, Krisanaprakornkit S, Dale B A. [Epithelial antimicrobial peptides: review and significance for oral applications. Crit Rev Oral Biol Med 1998;9:399–414.](#)
10. Kumar HVV, Kumar KPM, Gafoor A, Santhosh VC. [Evaluation of subgingival microflora in Diabetic and Nondiabetic patients. The Journal of Contemporary Dental Practice 2012;13:157-62.](#)
11. Zambon JJ, Reynolds H, Fisher JG, Shlossman M, Dunford R, Genco RJ. [Microbiological and immunological studies of adult periodontitis in patients with NIDDM. J Periodontol. 1988;59:23–31.](#)
12. Abdullah Seckin Ertugrul,¹ Ugur Arslan,² Recep Dursun,³ and Sema Sezgin Hakki⁴ [Periodontopathogen profile of healthy and oral lichen planus patients with gingivitis or periodontitis. Int J Oral Sci. Jun 2013; 5\(2\): 92–7.](#)

13. Xiaojing li,1* kristin m. Kolltveit,1 leif tronstad,2 and ingar olsen1 systemic diseases caused by oral infection. *Clinical microbiology reviews*, oct. 2000, p. 547–558.
14. Zambon JJ. Microbiology of Periodontal Disease. The nature of periodontal tissues in health and disease. 147p.
15. Richard C. Oliver and TellervoTervonen. *Diabetes-A Risk Factor for Periodontitis in Adults?* *Journal of Periodontology*, 1994 May Supp. (530 - 538).
16. Dimitris N. Tatakis, Purnima S. Kumar,. *Etiology and Pathogenesis of Periodontal Diseases*. *Dent Clin N Am* 49 (2005) 491–516.
17. Ira B. Lamster and Evanthia Lalla. *Periodontal Disease and Diabetes Mellitus: Discussion, Conclusions, and Recommendations*. *Ann Periodontol* Volume 6 Number 1 December 2001.
18. Robert L. Mandell, John Dirienzo, Ralph Kent, Kaumudi Joshipura, and Jerome Haber. *Microbiology of Healthy and Diseased Periodontal Sites in Poorly Controlled Insulin Dependent Diabetics*. *J Periodontol* 1992; 63:274-279.
19. Ebersole JL, Holt SC, Hansard R, Novak MJ. Microbiologic and immunologic characteristics of periodontal disease in Hispanic americans with type 2 diabetes. *J Periodontol*. 2008 Apr; 79(4):637-46.
20. Kalyani Deshpande, Ashish Jain, Ravi Kant Sharma, Savita Prashar, and Rajni Jain. *Diabetes and periodontitis*. *J Indian Soc Periodontol*. 2010 Oct-Dec; 14(4): 207–212.
21. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. *J Am Dent Assoc*. 2008 Oct; 139 Suppl:19S-24S.
22. Nelson RG, Shlossman M, Budding LM, et al. Periodontal disease and NIDDM in Pima Indians. *Diabetes Care* 1990; 13:836-840.
23. Brian L. Mealey. *Periodontal disease and diabetes A two-way street*. *JADA* 2006; 137(10 supplement):26S-31S.
24. Ferdinando Giacco, Michael Brownlee. *Oxidative Stress and Diabetic Complications*. *Circulation Research*. 2010; 107: 1058-1070.
25. Tellervo Ervasti, Matti Knuuttila, Leena Pohjamo and Kyösti Haukipuro. *Relation Between Control of Diabetes and Gingival Bleeding*. *J Periodontol* 1985 Mar (154 - 157).
26. Lalla E, Cheng B, Lal S, Kaplan S, Softness B, Greenberg E, Goland RS, Lamster IB. *Diabetes mellitus promotes periodontal destruction in children*. *J Clin Periodontol* 2007; 34: 294-8.
27. Hana C. Hobbs, Dorothy J. Rowe, and Paul W. Johnson. *Periodontal Ligament Cells from Insulin-Dependent Diabetics Exhibit Altered Alkaline Phosphatase Activity in Response to Growth Factors*. *J Periodontol* 1999; 70:736-742
28. Giuseppina Bastaa, Ann Marie Schmidtb, Raffaele De Caterinaa,c. *Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes*. *Cardiovascular Research* 63 (2004) 582 – 92.
29. Wedad Hanna, M.B., B.Ch.aDianne Friesen, M.Sc.Clair Bombardier, M.Dafna Gladman, M.D.Amir Hanna, Pathologic features of diabetic thick skin. *Journal of the American Academy of Dermatology*. Volume 16, Issue 3, Part 1, Pages 546–553, March 1987.
30. Edward J. Boyko, MD, MPH, and Benjamin A. Lipsky, MD. *Infection and Diabetes*.
31. Position Paper: *Diabetes and Periodontal Diseases*. *Journal of Periodontology*, April 2000, Vol. 71, No. 4, Pages 664-78.
32. McMullen JA, Van Dyke TE, Horowitz HU, Genco RJ. Neutrophil chemotaxis in individuals with advanced periodontal disease and genetic predisposition to diabetes mellitus. *J Periodontol* 1981; 52:217-24.
33. Cutler SW, Eke P, Arnold RR. *Defective neutrophil function in an insulin dependent diabetes mellitus patient: a case report*. *J Periodontol* 1991; 62:394-401.
34. Rajkumar Daniel, Subramaniam Gokulanathan, Natarajan Shanmugasundaram, Mahalingam Lakshmi Gandhan, and Thangavelu Kavin. *Diabetes and periodontal disease*. *J Pharm Bioallied Sci*. Aug 2012; 4(Suppl 2): S280–S282.
35. Janelle A. Noble1 and Henry A. Erlich1,2 *Genetics of Type 1 Diabetes Cold Spring Harb Perspect Med*. Jan 2012; 2(1): a007732.
36. Shital Hungund and Bhruvesh J. Panseriya. *Reduction in HbA1c levels following non-surgical periodontal therapy in type-2 diabetic patients with chronic generalized periodontitis: A periodontist's role*. *J Indian Soc Periodontol*. 2012 Jan-Mar; 16(1): 16–21.
37. Perrino ma. *Diabetes and periodontal disease: an example of an oral/systemic relationship*. *N Y State Dent J*. 2007 Aug-Sep; 73(5):38-41.
38. Karjalainen K et al. *Association of the severity of periodontal disease with organ complications in type 1 diabetic patients*. *Journal of Periodontology*. 1994. 65;11: 1067-1072.
39. Kiran M, Arpak N, Unsal E, Erdogan MF. The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. *J Clin Periodontol* 2005; 32: 266-272.
40. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ. *Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus*. *J Periodontol*. 1996 Oct; 67(10 Suppl):1085-93.
41. Miller LS, Manwell, MA, Newbold D, et al. The relationship between reduction in periodontal inflammation and diabetes control: A report of 9 cases. *J Periodontol* 1992; 63: 843-848.
42. Taylor GW. *The effects of periodontal treatment on diabetes*. *J Am Dent Assoc*. 2003 Oct; 134 Spec No: 41S-48S.
43. Tervonen T, Karjalainen K. *Periodontal disease related to diabetic status. A pilot study of the response to periodontal therapy in type 1 diabetes*. *J Clin Periodontol* 1997; 24:505-510.
44. Tervonen T, Knuuttila M, Pohjamo L, Nurkkala H. *Immediate response to non-surgical periodontal treatment in subjects with*

diabetes mellitus. J ClinPeriodontol 1991; 18:65-68.

45. Seppala B, Ainamo J. A site by site follow –up study on the effect of controlled versus poorly controlled insulin dependent diabetes mellitus. J ClinPeriodontol 1994; 21:161-165.

46. Christgau M, Palitzsch K.D, Schmalz G, Kreiner U, Frezel S. Healing response to non-surgical periodontal therapy in patients with diabetes mellitus; clinical microbiological and immunologic results. J ClinPeriodontol 1998; 25:112-124.

47. Iwamoto Y, Nishmura F, Nakagawa M, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor – alpha and glycated haemoglobin level in patients with type 2 diabetes. J Periodontol 2001; 72:774-778.

48. Armitage GC. Development of a Classification on system for periodontal diseases and conditions. Ann Periodontal 1999; 4(1): 1-6.

49. Loe H. Periodontal Disease: Sixth Complication of Diabetes Mellitus. Diabetes Care, American Diabetes Association 1993.

50. Salvi GE,Carollo-BittelB,Lang NP. Effect of diabetes mellitus

on periodontal and peri-implant conditions: update on associations and risks. J. Clin. Periodontal. 2008; 35 (8 suppl):398-409.

51. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontal.2005;76:(8 Suppl):2106-15

52. King GL. The role of inflammatory cytokines in diabetes and its complications. J Periodontol 2008;79 (8 suppl):1527-34.

53. Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Community Dent Oral Epidemiol. 2002; 30(3):182-92.

54. Frantzis T, Reeve C, Brown A Jr. The ultra structure of the capillary basement membranes in the attached gingival of diabetic and non diabetic patients with periodontal disease. J Periodontol. 1971; 42:406-11

55. Salo T, Kylmaniemi M, Helaakoski T, et al. MMP-8/neutrophil collagenase mRNA may also be expressed in other cells than PMN's(abstract 1036). J Dent Res 1995; 74(Special Issue):530

56. Darre L, Vergnes JN, GourdyP,Sixou M. Efficacy ofPeriodontal treatment on glycemic control in diabetic patients: A meta analysis of interventional studies. Diabetes Metab. 2008; 34:497-506