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Review Article

Two Way Relationships between Diabetes Mellitus and Periodontal Disease: A Review

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Abstract: The association between diabetes and inflammatory periodontal diseases has been studied extensively for more than 50 years. The author reviews the two way relationships between diabetes and periodontal diseases. MEDLINE search of the English language literature identified primary research reports published on (a) relationships between diabetes and periodontal diseases since 1990 and (b) effects of periodontal infection on glycemic control and diabetes complications since 1960. Recent research has shown that diabetes may increase the risk of periodontitis, and it has been proposed that chronic periodontal disease may influence the natural course of diabetes. Treatment and longitudinal observational studies provided evidence to support periodontal infection having an adverse effect on glycemic control, although not all investigations reported an improvement in glycemic control after periodontal treatment, evidences is supported periodontal disease increasing the risk for diabetes complications**.** The scientific evidence reviewed supports diabetes having an adverse effect on periodontal health and periodontal disease having an adverse effect on glycemic control and on diabetes-related complications. Further research is needed to clarify these relationships and larger, prospective, controlled trials with ethnically diverse populations are warranted to establish that treating periodontal disease can positively influence glycemic control and possibly reduce the burden of diabetes-related complications.
Keywords: Diabetes Mellitus/Periodontal Diseases/Glycemic Control / Two way relationship.

INTRODUCTION

The human organism is a unity that is composed by an infinite number of biologic processes so strongly linked that abnormalities in any part of the body and/or its processes may have deep effects in many other body areas, exemplified in this review by two highly prevalent diseases: (PD) and Diabetes Mellitus (DM) [1].

Diabetes Mellitus encompasses a group of genetically and clinically heterogeneous metabolic disorders characterized by hyperglycemia that results from a defective insulin secretion and/or activity [2]. DM is classified according to its etiology as type 1 (T1D), type 2 (T2D), gestational diabetes (GDM) and other specific types [3].

People with diabetes and with chronically poor metabolic control can experience micro-vascular and macro-vascular complications leading to a significant burden for the individual and for the society. This burden includes direct costs of medical care and indirect costs, such as loss of productivity, which result from diabetes-related morbidity and premature mortality [4].

Periodontal Disease is a chronic multi-factorial disorder, but mainly due to bacterial infection, that affects both the gingiva and the bone that supports the teeth and is caused by anaerobic Gram-negative microorganisms that are present in the bacterial plaque that adheres to the teeth [5].

The presence of anaerobic Gram-negative bacteria causes a local inflammatory response that becomes chronic and progressive; this inflammation of the gingiva causes alveolar bone destruction and loss of the tissue attachment to the teeth, caused by components of microbial plaque that have the capacity to induce an initial infiltrate of inflammatory cells, such as lymphocytes, macrophages, and polymorphonuclear leukocytes (PMNs).

Some microbial components, especially lipopolysaccharide (LPS), activate macrophages that synthesize and secrete a great variety and amount of pro-inflammatory molecules, such as the cytokines interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α); prostaglandins, especially prostaglandin E2 (PGE2); and some other enzymes .Bacterial toxins can also activate T lymphocytes to produce IL-1 and

lymphotoxin (LT), a molecule with properties that are similar to those of TNF-α. These cytokines show potent pro-inflammatory and catabolic activities, and have important roles in periodontal tissue destruction caused by collagenolytic enzymes such as metalloproteinases (MMPs) [6]. The attachment loss deepens the sulcus, creating a periodontal pocket that contains thousands of millions of bacterial cells. This stage is the transition between gingivitis and periodontitis, the most common PDs [7].

Recently, many advances have occurred in the knowledge of the nature of the infectious agents involved in PD. Approximately 500 different bacterial entities and various human viruses have already been associated with the formation of dental microbial plaque [8]. The most frequently recognized periodontal pathogens belong to three microaerophilic species (*Actinobacillus actinomycetemcomitans, Campylobacter rectus,* and *Eikenella corrodens*) and seven anaerobic species (*Porphyromonas gingivalis, Bacteroides forsythus, Treponema denticola, Prevotella intermedia, Fusobacterium nucleatum, Eubacterium,* and *spirochetes*) [9].

Various herpes viruses, such as the human cytomegalovirus (HCMV) and epstein-Barr virus (EBV-1), have recently also emerged as pathogens in cases of destructive PD [10]. Many conditions can predispose and/or facilitate the occurrence of PD such as smoking [11], genetic influences [12], estrogen deficiency [13], estrogen excess [14], Dyslipidemia and obesity [16].

The prevalence of obesity is increasing worldwide. This epidemic is also associated with an increased occurrence of obesity-related diseases like hypertension, cardiovascular disease, metabolic syndrome and DM that are also linked to PD [17].

INFLUENCE OF DIABETES ON THE PERIODONTIUM

The prevalence and severity of gingivitis has been demonstrated to be higher in individuals with diabetes. In children with type 1 diabetes, the prevalence of gingivitis was greater than in non-diabetic children with similar plaque levels [18]. Poor metabolic control can increase the severity of gingival inflammation in diabetic children [19].

A longitudinal experimental gingivitis study showed more rapid and pronounced development of gingival inflammation in relatively well-controlled adult type 1 diabetic subjects than in non-diabetic controls, despite similar levels of plaque accumulation and similar bacterial composition of plaque, suggesting a hyper inflammatory gingival response in diabetes. These studies suggest that the presence of diabetes is often, but not always, associated with increased gingival inflammation [20].

Greater gingival inflammation was also seen in adults with type 2 diabetes than in non-diabetic controls [21].

The preponderance of evidence suggests that diabetes also increases the risk of periodontitis. A thorough meta-analysis concluded that the majority of studies demonstrate a more severe periodontal condition in diabetic adults than in adults without diabetes [22] In the Pima Indians of Arizona, a population with the highest occurrence of type 2 diabetes in the world, the prevalence and severity of attachment loss and bone loss was greater among diabetic subjects than among non-diabetic control subjects in all age groups [23].

In a multivariate risk analysis, diabetic subjects had 2.8- to 3.4-fold increased odds of having periodontitis compared to non-diabetic subjects after adjusting for the effects of confounding variables such as age, gender, and oral hygiene measures. Smaller cross-sectional and case-control studies generally confirmed a greater risk of attachment loss and bone loss in diabetic adults [21, 24-26].

The relationship between metabolic control of diabetes and periodontal disease is difficult to define conclusively. Research suggests that this association is similar to the association between glycemic control and the classic complications of diabetes such as retinopathy and nephropathy; namely, there is significant heterogeneity in the diabetic population. 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 complications, but there are people with well-controlled diabetes who suffer major diabetic complications nonetheless [27, 28].

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 periodontitis.

ETIO-PATHOGENESIS BY WHICH DIABETES MAY INFLUENCE THE PERIODONTIUM

Influences are Similar to those associated with the classic diabetic complications, including retinopathy, nephropathy, neuropathy, macrovascular diseases, and altered wound healing. Periodontitis should considered as a one of the complications of diabetes [29].

There are few differences in the subgingival micro flora between diabetic and non-diabetic patients with periodontitis, even though showed more

pathogenic microorganisms in un-controlled diabetes patients [30].

Function of immune cells, including neutrophils, monocytes, and macrophages, are altered in diabetes. Neutrophil adherence, chemotaxis, and phagocytosis are often impaired, which may inhibit bacterial killing in the periodontal pocket and significantly increase periodontal destruction [31].

The monocyte/macrophage cell line may exhibit up regulation in response to bacterial antigens results in significantly increased production of pro-inflammatory cytokines and mediators. The net effect of these host defense alterations in diabetes is an increase in periodontal inflammation, attachment loss, and bone loss [32].

High glucose levels in the gingival crevicular fluid may directly hinder the wound-healing capacity of fibroblasts in the periodontium by inhibiting attachment and spreading of these cells that are critical to wound healing and normal tissue turnover [33].

The changes seen in the microvasculature of the retina, glomerulus, and other end organs in people with diabetic complications also occur in the periodontium [34].

In individuals with sustained hyperglycemia, proteins become irreversibly glycated to form advanced glycation end products (AGEs) [35]. The formation of AGEs also occurs in the periodontium, and higher levels of periodontal AGE accumulation are found in those with diabetes than in non-diabetic subjects [36]. AGEs often form on collagen, increasing collagen cross-linking and resulting in the formation of highly stable collagen macromolecules. These molecules accumulate in tissues due to their resistance to normal enzymatic degradation and tissue turnover [37].

AGE formation is also associated with increased production of vascular endothelial growth factor (VEGF), a multifunctional cytokine that induces neo-vascularization and plays a major role in micro-vascular complications of diabetes [38].

Altered levels of glycation in bone collagen appear to affect bone turnover, such that bone formation is reduced with elevated levels of AGE collagen [39].

Changes in collagen synthesis, maturation, and homeostatic turnover are common in diabetes. These changes can contribute to the pathogenesis of periodontal diseases and to alterations in wound healing because collagen is the major structural protein in the periodontium [40].

INFLUENCE OF PERIODONTAL DISEASES ON THE DIABETIC STATE

Periodontal diseases can have a significant influence on the metabolic state in diabetes. The presence of periodontitis increases the risk of worsening of glycemic control over time. For example, in a 2-year longitudinal trial, diabetic subjects with severe periodontitis at baseline had a six-fold increased risk of worsening of glycemic control over time compared to diabetic subjects without periodontitis [41].

Periodontitis may also be associated with an increased risk of other diabetic complications, as seen in a longitudinal case-control study in which 82% of diabetic patients with severe periodontitis experienced the onset of one or more major cardiovascular, cerebro-vascular, or peripheral vascular events compared to only 21% of diabetic subjects without periodontitis [42].

A recent longitudinal trial examined the effect of periodontal disease on overall mortality and cardiovascular disease–related mortality with type 2 diabetes. In subjects with severe periodontitis, the death rate from ischemic heart disease was 2.3 times higher than in subjects with no periodontitis or mild periodontitis, and the mortality rate from diabetic nephropathy was 8.5 times higher in the severe periodontitis group after accounting for other known risk factors. The overall mortality rate from cardio-renal disease was 3.5 times higher in subjects with severe periodontitis [43].

ETIO-PATHOGENESIS BY WHICH PERIODONTAL DISEASES MAY INFLUENCE DIABETES

Acute bacterial and viral infections are known to increase insulin resistance in people without diabetes, a condition which often persists for weeks to months after clinical recovery from the illness. Such illnesses and resultant increases in insulin resistance in people with diabetes greatly aggravate glycemic control [44]. Thus Chronic Gram-negative periodontal infections may also result in increased insulin resistance and poor glycemic control [45].

Studies suggest that periodontitis patients, particularly those colonized by Gram-negative organisms such as P. gingivalis, Tannerella forsythensis, and Prevotella intermedia, have significantly higher serum markers of inflammation such as C-reactive protein (CRP), IL-6, and fibrinogen than subjects without periodontitis. Systemic dissemination of these organisms or their products may induce a bacteremia or endotoxemia, inducing an elevated inflammatory state and stimulating increased levels of serum inflammatory markers [46].

In one study, the simple act of chewing caused systemic endotoxemia in 40% of subjects with

periodontitis compared to only 12% of periodontally healthy subjects; additionally, the concentration of endotoxin in the bloodstream was five-fold higher in those with periodontitis [47].

Periodontal treatment not only reduces clinically evident inflammation, but may also result in decreased serum levels of IL-6 and CRP [48]. This evidence suggests that periodontal diseases have systemic effects that extend beyond the local periodontal environment.

EFFECT OF PERIODONTAL THEPRAY ON DIABETES MELLITUS (GLYCEMIC CONTORL)

The type 1 diabetic patients with periodontitis had a reduction in required insulin doses following scaling and root planing, localized gingivectomy, and selected tooth extraction combined with systemic procaine penicillin G and streptomycin [49].

Several studies of type 1 and type 2 diabetic subjects with severe periodontitis have shown improvements in glycemic control following scaling and root planing combined with systemic doxycycline therapy. In these studies, periodontal treatment was associated with a reduction in HbA1c levels of 10% between pretreatment baseline values and 2-to 3-month post-treatment values [50, 51].

Only limited evidence is available to evaluate the comparative response to periodontal therapy in diabetic and non-diabetic patients with periodontitis. In well-controlled diabetic subjects, the clinical and microbiologic response to scaling and root planing appears similar to that in non-diabetic individuals [52].

Although many diabetic patients show improvement in clinical parameters of disease immediately after therapy, patients with poorer glycemic control may have a more rapid recurrence of deep pockets and a less favorable long-term response [53].

Further longitudinal studies of various periodontal treatment modalities are needed to determine the healing response in individuals with diabetes compared to individuals without diabetes.

CONCLUSION

The scientific evidence reviewed, supports that diabetes having an adverse effect on periodontal health and Periodontal Diseases having an adverse effect on glycemic control and on diabetes-related complications. Further research is needed to clarify these relationships and larger, prospective, controlled trials with ethnically diverse populations are warranted to establish that treating PD can positively influence glycemic control and possibly reduce the burden of diabetes-related complications

REFERENCES

1. Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P et al.; American Journal of Cardiology, Journal of Periodontology J Periodontol. ,2009; 80(7): 101021-32.
2. Skyler J, Oddo C; Diabetes trends in the USA. Diabetes Metab Res Ver., 2002; 18: S21–S26.
3. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care, 1998; 21(Suppl 1): S5–S19.
4. American Diabetes Association Economic costs of diabetes in the US in 2007. Diabetes Care, 2008; 31: 596–615.
5. Negrato CA, Tarzia O; Buccal alterations in diabetes mellitus. Diabetol Metab Syndr. ,2010; 2: 3–3.
6. Sorsa T, Ingman T, Suomalainen K, Haapasalo M, Konttinen YT, Lindy O et al.; Identification of proteases from periodonto-pathogenic bacteria as activators of latent human neutrophils and fibroblast-type interstitial collagenases. Infect Immun, 1992; 60: 4491–4495.
7. Kornman KS, Page RC, Tonetti MS; The host response to the microbial challenge in periodontitis: assembling the players. Periodontal., 2000. 1997; 14: 33–53.
8. Amar S, Han X; The impact of periodontal infection on systemic diseases. Med Sci Monit., 2003; 9: RA291–RA299.
9. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent Jr RL; Microbial complexes in subgingival plaque. J Clin Periodontal., 1998; 25:134–144.
10. Slots J, Kamma JJ, Sugar C; The herpes virus, Porphyromonas gingivalis, periodontitis axis. J Periodontal Res., 2003; 38: 312–323.
11. Grossi SG, Genco RJ, Machtei EE, Ho AW, Koch G, Dunford R et al.; Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. J Periodontal., 1995; 66: 23–29.
12. Kornman KS, Crane A, Wang HY, di Giovine FS, Newman MG, Pirk FW et al.; The interleukin- 1 genotype as a severity factor in adult periodontal disease. J Clin Periodontal., 1997; 24: 72–77.
13. Gomes-Filho IS, Passos JS, Cruz SS, Vianna MI, Cerqueira EM, Oliveira DC et al.; The association between postmenopausal osteoporosis and periodontal disease. J Periodontol., 2007;78: 1731–1740.
14. Haytaç MC, Cetin T, Seydaoglu G; The effects of ovulation induction during infertility treatment on gingival inflammation. J Periodontal., 2004; 75(6): 805–810.

15. Morita M, Horiuchi M, Kinoshita Y, Yamamoto T, Watanabe T; Relationship between blood triglyceride levels and periodontal status. Community Dent Health, 2004; 21: 32–36.
16. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y; A proposed model linking inflammation to obesity, diabetes, and periodontal infections. J Periodontal., 2005; 76(Suppl 11): 2075–2084.
17. Al-Zahrani MS, Bissada NF, Borawskit EA; Obesity and periodontal disease in young, middle-aged, and older adults. J Periodontal., 2003; 74: 610–615.
18. Cianciola L, Park B, Bruck E, Mosovich L, Genco R; Prevalence of periodontal disease in insulin-dependent dependentdiabetes mellitus (juvenile diabetes). J Am Dent Assoc., 1982; 104: 653-660.
19. Gusberti F, Syed S, Bacon G, Grossman N, Loesche W; Puberty gingivitis in insulin-dependent diabetic children. I. Cross-sectional observations. J Periodontol., 1983; 54: 714-720.
20. Salvi GE, Kandylaki M, Troendle A, Persson GR, Lang NP; Experimental gingivitis in type 1 diabetics: A controlled clinical and microbiological study. J Clin Periodontol., 2005; 32: 310-316.
21. Cutler CW, Machen RL, Jotwani R, Iacopino AM; Heightened gingival inflammation and attachment loss in type 2 diabetics with hyperlipidemia. J Periodontol., 1999; 70: 1313-1321.
22. Papapanou PN; Periodontal diseases: Epidemiology. Ann Periodontol., 1996; 1:1-36.
23. Emrich LJ, Shlossman M, Genco RJ; Periodontal disease in non-insulin dependent diabetes mellitus. J Periodontol., 1991; 62:123-131.
24. Bridges RB, Anderson JW, Saxe SR, Gregory K, Bridges SR; Periodontal status of diabetic and nondiabetic men: Effects of smoking, glycemic control, and socioeconomic factors. J Periodontol., 1996; 67: 1185-1192.
25. Collin HL, Uusitupa M, Niskanen L, Kontturi-Närhi V, Markkanen H, Koivisto AM *et al.*; Periodontal findings in elderly patients with non-insulin dependent diabetes mellitus. J Periodontol., 1998; 69: 962-966.
26. Moore PA, Weyant RJ, Mongelluzzo MB, Myers DE, Rossie K, Guggenheimer J *et al.*; Type 1 diabetes mellitus and oral health: Assessment of periodontal disease. J Periodontol., 1999; 70(4): 409-417.
27. Mealey BL, Moritz AJ; Hormonal influences: Effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. Periodontol. 2000; 2003; 32: 59-81.
28. U.K. Prospective Diabetes Study (UKPDS) Group; Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet, 1998; 352: 837-853.
29. Loe H; Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care, 1993; 16(Suppl. 1): 329-334.
30. Zambon JJ, Reynolds H, Fisher JG, Shlossman M, Dunford R, Genco RJ; Microbiological and immunological studies of adult periodontitis in patients with non-insulin dependent diabetes mellitus. J Periodontol., 1988; 59: 23-31.
31. Manouchehr-Pour M, Spagnuolo PJ, Rodman HM, Bissada NF; Comparison of neutrophil chemotactic response in diabetic patients with mild and severe periodontal disease. J Periodontol .,1981; 52: 410-415.
32. Salvi GE, Collins JG, Yalda B, Arnold RR, Lang NP, Offenbacher S; Monocytic TNF-a secretion patterns in IDDM patients with periodontal diseases. J Clin Periodontol., 1997; 24: 8-16.
33. Nishimura F, Takahashi K, Kurihara M, Takashiba S, Murayama Y; Periodontal disease as a complication of diabetes mellitus. Ann Periodontol., 1998; 3: 20-29.
34. Seppala B, Sorsa T, Ainamo J; Morphometric analysisof cellular and vascular changes in gingival connective tissue in long-term insulin-dependent diabetes. J Periodontol., 1997; 68: 1237-1245.
35. Monnier VM, Glomb M, Elgawish A, Sell DR; The mechanism of collagen cross-linking in diabetes. A puzzle nearing resolution. Diabetes, 1996; 45(Suppl. 3): S67-S72.
36. Schmidt AM, Weidman E, Lalla E, Yan SD, Hori O, Cao R *et al.*; Advanced glycation endproducts (AGEs) induce oxidant stress in the gingiva: A potential mechanism underlying accelerated periodontal disease associated with diabetes. J Periodontal Res., 1996; 31: 508-515.
37. Schmidt AM, Yan SD, Wautier J-L, Stern D; Activation of receptor for advanced glycation end products. A mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. Circ Res., 1999; 84: 489-497.
38. Paques M, Massin P, Gaudric A; Growth factors and diabetic retinopathy. Diabetes Metab., 1997; 23: 125-130.
39. Gunczler P, Lanes R, Paoli M, Martinis R, Villaroel O,Weisinger JR; Decreased bone mineral density andbone formation markers shortly after diagnosis of clinical type 1 diabetes mellitus. J Pediatr Endocrinol Metab., 2001; 14: 525-528.

40. Willershausen-Zonnchen B, Lemmen C, Hamm G; Influence of high glucose concentrations on glycosaminoglycan and collagen synthesis in cultured human gingival fibroblasts. J Clin Periodontol., 1991; 18:190-195.
41. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC *et al*.; Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. J Periodontol., 1996; 67:1085-1093.
42. Thorstensson H, Kuylensteirna J, Hugoson A; Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. J Clin Periodontol., 1996; 23: 194-202.
43. Saremi A, Nelson RG, Tulloch-Reid M, Hanson RL, Sievers ML, Taylor GW *et al*.; Periodontal disease and mortality in type 2 diabetes. Diabetes Care, 2005; 28: 27-32.
44. Sammalkorpi K; Glucose intolerance in acute infections. J Intern Med ., 1989; 225: 15-19.
45. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y; A proposed model linking inflammation to obesity, diabetes and periodontal infections. J Periodontol., 2005; 76: 2075-2084.
46. Wu T, Trevisan M, Genco RJ, Falkner KL, Dorn JP, Sempos CT; Examination of the relation between periodontal health status and cardiovascular risk factors: Serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. Am J Epidemiol., 2000; 151: 273-282.
47. Geerts SO, Nys M, De MP, Charpentier J, Albert A, Legrand V *et al*.; Systemic release of endotoxins induced by gentle mastication: Association with periodontitis severity. J Periodontol., 2002; 73: 73-78.
48. D'Aiuto F, Parkar M, Andreou G, Suvan J, Brett PM, Ready D *et al*.; Periodontitis and systemic inflammation: Control of the local infection is associated with a reduction in serum inflammatory markers. J Dent Res., 2004; 83: 156-160.
49. Williams RC Jr., Mahan CJ; Periodontal disease and diabetes in young adults. JAMA, 1960; 172: 776-778.
50. Miller LS, Manwell MA, Newbold D, Reding ME, Rasheed A, Blodgett J *et al*.; The relationship between reduction in periodontal inflammation and diabetes control: A report of 9 cases. J Periodontol., 1992; 63:843-848.
51. Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG *et al*.; Treatment of periodontal disease in diabetics reduces glycated hemoglobin. J Periodontol., 1997; 68: 713-719.
52. Christgau M, Palitzsch KD, Schmalz G, Kreiner U, Frenzel S; Healing response to non-surgical periodontal therapy in patients with diabetes mellitus: Clinical, microbiological, and immunological results. J Clin Periodontol., 1998; 25: 112-124.
53. 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.