The Relationship Between Periodontitis and Glycaemic Control in Type 2 Diabetes

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Abstract

Periodontitis is a chronic, inflammatory condition in the tissues surrounding teeth that is stimulated by dental plaque bacteria and results in the destruction of tooth supporting tissues. Type 2 diabetes is associated with an increased prevalence and severity of periodontitis that is related to underlying glycaemic control. It has been suggested that the presence of chronic periodontal inflammation has a converse and negative effect on glycaemic control in diabetes with most evidence emerging from studies of type 2 diabetes. This article reviews the evidence from cohort, prospective and meta-analysis studies that have been conducted to examine the relationship between periodontitis and glycaemic control in type 2 diabetes and suggests underlying pathogenic mechanisms that may explain the relationship between these conditions.

Keywords

Periodontitis, diabetes, glycaemic control

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Periodontitis is a bacteria-related, chronic inflammation that results in destruction of the bone and connective tissue support of teeth forming periodontal pockets between the tooth and gingival soft tissue.[1] It is initiated by inadequate oral hygiene and the development of a biofilm colonised with pathogenic bacteria on the tooth surface that results in direct damage to local tissues by bacterial virulence factors (see *Figures 1* and *2*).[2] The stimulation, an inflammatory/immune response to the offending bacteria, is further associated with indirect tissue damage[3,4] mediated by cytokines including interleukin-1 beta (IL-1β),[5] IL-6, tumour necrosis factor-alpha (TNF-α) prostaglandins and collagenolytic enzymes.[6,7] Oxidative damage to the tissues is also a feature of the periodontitis lesion,[8,9] thought to result from hyper-reactive neutrophils generating excessive reactive oxygen species (ROS) during bacterial phagocytosis[10] causing both direct damage and stimulating redox-sensitive pro-inflammatory transcription factors.

Individuals vary in their susceptibility to periodontitis and the key determinant appears to be a phenotype coding for a particularly exaggerated inflammatory and immune response to pathogenic bacteria.[11]

Within worldwide populations, periodontitis is a common condition with a prevalence of between 5 to 20 %.[12] The rate of progression varies among individuals but the most common form of the disease has a chronic, slowly progressing nature and patients may be burdened by the chronic inflammatory condition for years or decades before diagnosis and treatment.

Progression of untreated periodontitis can result in pain, aesthetic problems, functional difficulties and complete tooth loss in severe cases.[13]

Systemic Effects of Periodontitis

There is evidence of an 'over-spill' from chronic periodontal lesions to more peripheral tissues; plasma levels of periodontitis-associated markers including IL-6, TNF-α, and high-sensitivity C-reactive protein (hsCRP) are elevated[14,15] and systemic oxidative status is compromised in patients with periodontitis compared with healthy controls.[16–18] Indeed, pro-inflammatory cytokines released at the diseased periodontal site[19,20] translocating to distant sites via the circulation, are thought to induce changes in vascular endothelium and increase the risk for cardiovascular disease.[21,22] A recent cross-sectional study of more than 6,000 adults reported that participants with diabetes and periodontitis had an increased likelihood of intimal media thickening and coronary heart disease (CHD).[23] Periodontal treatment lowers systemic levels of inflammatory markers[24] and improves haemostatic parameters in cardiac patients.[25]

Diabetes and Periodontitis

There is substantial evidence from cross-sectional and prospective studies that people with types 1 and 2 diabetes have more than double the risk of developing periodontitis;[26–36] reviewed by Taylor and Borgnakke.[37] Diabetes can also result in more severe periodontal destruction than in matched non-diabetes groups.[38,39] The increased risk for periodontitis is dependent on glycaemic control[40] and not the duration of diabetes.[41]

Figure 1: Plaque Accumulation and Resulting Bone Loss and Connective Tissue Attachment Loss Around a Tooth in Periodontitis

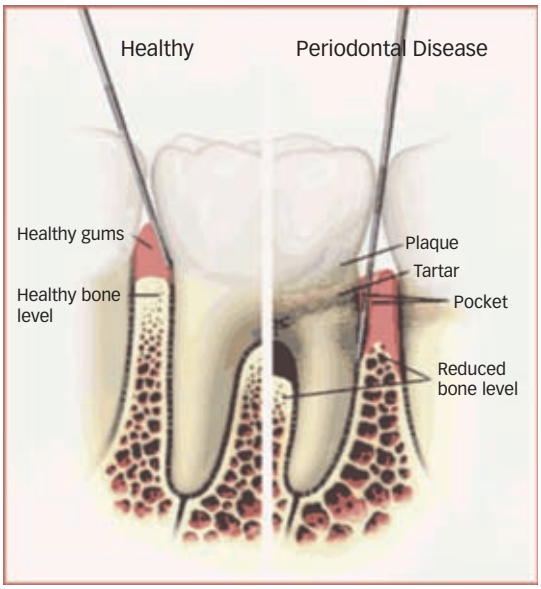
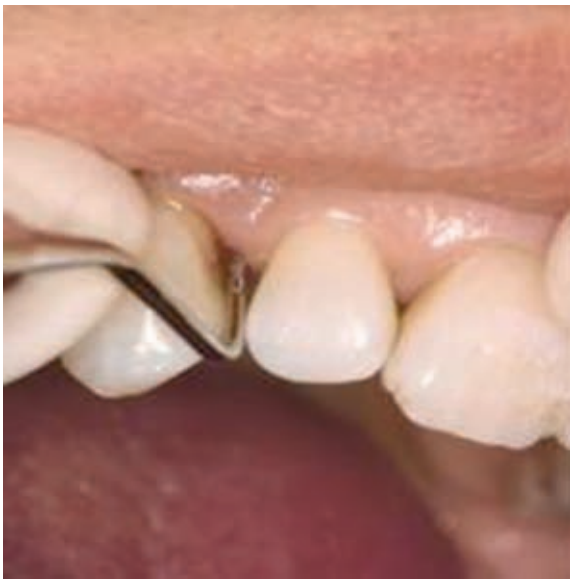


Figure 2: A Periodontal Pocket Between a Tooth and Gingival Soft Tissue Due to Periodontal Destruction



The Impact of Periodontitis on Glycaemic Control

A bi-directional relationship between periodontitis and type 2 diabetes has been suggested with the presence of chronic periodontitis thought to have a reciprocating negative effect on diabetes control. Early evidence came from studies in a distinct population group of Pima Indians who have a very high prevalence of type 2 diabetes. These studies indicated that severe periodontal inflammation was predictive of a greater deterioration in glycaemic control over time compared with a non-periodontitis group,[42] and was a strong predictor of mortality from the common diabetes-associated complications of ischaemic heart disease and diabetic nephropathy.[43,44] These results could not be directly extrapolated to other population groups due to genetic homogeneity within the Pima Indian group who may be particularly susceptible to hyper-inflammation and derangement in glycaemic control.

Epidemiological surveys within more diverse population groups have therefore been conducted. A US-based cross-sectional study examined the electronic medical records and dental insurance data of more than 5,000 dually insured people with diabetes and insurance claims for periodontal care were taken as a proxy measure for periodontitis. Mean glycated haemoglobin (HbA_{1c}) was 7.66 % and was 0.08 % higher in the 38.00 % of patients who had received periodontal care, but insufficient information about the periodontal status of participants were available within this study to draw firm conclusions from the results.[45]

Many cross-sectional studies have undertaken comprehensive periodontal examination in diabetes patients although the logistical difficulties of doing so has led to relatively small sample sizes within many studies. A survey of 35 people with type 2 diabetes (17 with periodontitis matched with 18 without periodontitis)[46] and a larger survey of 181 type 2 diabetes adults[47] both reported correlations between periodontal status and HbA_{1c}. The severity of periodontitis was an independent predictor of both elevated HbA_{1c} and hsCRP in a group of 140 type 2 diabetes participants.[48]

A large-scale, prospective study has been conducted in Japan that addresses some of the limitations of the smaller studies and had two strands; study 1 examined the risk of developing periodontal pockets in 5,856 participants over five years with baseline HbA_{1c} levels ≥6.5 %, while study 2 examined 6,125 participants with HbA_{1c} <6.5 % at baseline and determined their relative risk for elevated HbA_{1c} over five years with baseline periodontal status. Relative risk of developing a periodontal pocket was 1.17 times greater in those with HbA_{1c} of ≥6.5 % at baseline, confirming the accepted evidence of an increased risk of periodontitis with poor glycaemic control. The risk of having elevated HbA_{1c} (≥6.5 %) over the five years was increased 2–3 fold, depending on the severity of the periodontal lesion at baseline.[49] Periodontitis was also associated with increased risk for diabetes incidence in a seven-year prospective study of 5,848 non-diabetic individuals but significance was lost when adjusting for confounding factors.[50]

HbA_{1c} levels correlated with the surface area of the inflamed periodontal lesions and therefore the extent of periodontal inflammation in one study conducted within a type 2 diabetes group.[51]

Some studies have examined the relationship between periodontal condition and plasma glucose levels; non-diabetics with periodontitis are reported to have higher resting plasma glucose and HbA_{1c} levels than matched controls.[52–54]

Analysis of data from 12,254 participants in the Third National Health and Nutrition Examination Survey (NHANES III), showed that participants with the most severe periodontal destruction had an increased odds ratio for both impaired fasting glucose (≥100 but <126 mg/dl) and diabetes (≥126 mg/dl) after adjustment for potential confounders.[55]

Animal studies (while limited in their ability to provide direct evidence applicable to humans) have confirmed the destabilisation of glycaemic control by periodontal inflammation. Periodontitis is readily initiated in Wistar rats by the tying of ligatures around teeth for a period of weeks. These periodontitis rats (PD rats) had increased blood glucose compared with non-PD rats.[56]

The precise mechanism underlying the effect on glycaemic control by periodontal inflammation has been investigated using this

same animal model (n=48) with half the animals having a ligature applied (PD rats) and the other half remaining as controls. Plasma concentration of TNF-α was higher in PD rats compared with controls. The PD group showed decreased insulin sensitivity and insulin signal transduction in adipose and skeletal muscle tissues compared with the control group, which may have been mediated by the increased plasma TNF-α.[57]

When taken together, the cross-sectional surveys and prospective studies described above, supported by the limited animal model studies, do offer some compelling evidence of a disruptive influence on glycaemic control by chronic periodontal inflammation. Intervention studies have been conducted to provide further clarity on the relationship between periodontitis and glycaemic control and to explore interventive therapies that may improve the outcome for diabetes patients. Periodontal therapy involves professional removal of the biofilm and home care instruction to prevent re-accumulation of the plaque bacteria and re-development of the biofilm.

The Impact of Periodontal Therapy on Diabetes Status

The results from the earliest treatment studies are limited as they were conducted within the Pima Indian group[58] or because of inadequate controls between groups for possible confounding variables such as age, body mass index (BMI), alcohol consumption, health motivation and behaviour, psychosocial stressors and smoking.

A small sample size and/or a short follow-up time further limits the conclusions that can be drawn from some individual studies. An example of this is a study in which 13 well-controlled (HbA_{1c} <7 %) and 12 poorly controlled (HbA_{1c} >7 %) participants with type 2 diabetes and periodontitis and 15 healthy patients with periodontitis received periodontal treatment, and HbA_{1c} decreased significantly in the poorly controlled group only, three months post-therapy.[59] These results are similar to an earlier treatment study of 44 type 2 diabetes people re-examined after three months.[60]

Conflicting reports found a more beneficial effect of periodontal therapy on HbA_{1c} in well-controlled diabetes patients.[61,62]

In a larger group of 165 US veterans with poorly controlled type 2 diabetes, the group that received periodontal therapy was less likely to need an increase in insulin over four months compared with those who did not receive periodontal care.[63]

Longer follow-up periods have been employed; a small treatment study in a type 2 diabetes group (n=10) and non-diabetes group (n=10) reported a reduction in HbA_{1c} within the diabetes group at six-month follow-up.[64] The removal of all teeth and inevitable resolution of periodontitis in a type 2 diabetes group with advanced periodontitis, led to a reduction in HbA_{1c} from 8.6 to 7.3 % after six months compared with a matched group (no treatment) in which HbA_{1c} reduced from 7.7 to 7.5 %.[65] However, baseline differences in HbA_{1c} between the groups may have influenced the results. Indeed, the problem of unbalanced randomisation in which control groups had better glycaemic control at baseline was highlighted in a meta-analysis of studies conducted to January 2005.[66] Many subsequent studies have addressed this issue.

In a recently published Australian randomised controlled trial (RCT), 40 people with type 2 diabetes and chronic periodontitis were matched for gender, age, periodontal and biochemical parameters (including HbA_{1c}) and after three months HbA_{1c} decreased in only the treatment group.[67]

Another RCT assigned the 60 type 2 diabetes participants into either a periodontal treatment arm or a delayed treatment arm that received periodontal care after six months. Baseline matching for HbA_{1c} and other confounding variables was again achieved and HbA_{1c} levels decreased significantly more in the intervention group versus the control group.[68]

There has not been a universal improvement in fasting glucose or HbA_{1c} within treatment studies with a few studies showing little or no improvement in glycaemic control after periodontal therapy.[69,70]

These conflicting results and the problem of low power within individual studies has been addressed with meta-analysis studies and a 2005 meta-analysis of 10 intervention studies reporting a weighted mean reduction in HbA_{1c} of 0.66 % in diabetes patients following periodontal therapy, although this reduction did not reach statistical significance.[66] A second meta-analysis conducted in 2009 included 371 type 2 diabetes participants and demonstrated a weighted mean difference of HbA_{1c} before and after therapy of -0.40 %.[71] The Cochrane Collaboration has recently reported on three studies deemed suitable for meta-analysis and also reported a mean HbA_{1c} reduction of 0.40 %, 3–4 months after periodontal therapy.[72]

Type 1 Diabetes

Most studies have concentrated on the relationship between type 2 diabetes and periodontitis as early studies highlighted a reciprocating relationship between these conditions. A study published in 2011 examined the effects of intensive periodontal therapy on HbA_{1c} in 93 participants with either type 1 or type 2 diabetes and moderate periodontitis. One group received intensive periodontal therapy (IPT, n=44) and the other received conventional periodontal therapy (CPT, n=49) with an eight-month follow-up. After eight months, the IPT group presented with a significantly greater reduction in HbA_{1c} than the CPT group and the difference in HbA_{1c} was greater in individuals with type 2 diabetes compared with those with type 1 diabetes. Therefore, periodontal therapy appears to be more successful in improving glycaemic control in type 2 diabetes.[73]

Potential Mechanisms Underlying the Bi-directional Relationship Between Periodontitis and Diabetes

The precise relationship between diabetes and periodontitis remains unclear but the increased risk for periodontitis in diabetes patients may be due to a change in the local periodontal environment, either because of glycation of proteins (including collagen) making them more susceptible to breakdown[74,75] or increased oxidative stress and an associated pro-inflammatory stimulus.[76]

Recent treatment studies have explored a wider range of clinical parameters in an effort to uncover more knowledge and have focused on inflammatory markers as both periodontitis and type 2 diabetes are known to have an underlying state of hyper-inflammation. Higher levels of CRP were detected in a group with type 2 diabetes and periodontitis at levels that could not be explained by either of the conditions alone, suggesting a synergystic pro-inflammatory stimulus when these conditions co-exist.[77] The role of TNF-α has been

particularly explored because it is elevated in periodontitis[78] and is associated with insulin resistance, mediated by serine phosphorylation of the insulin receptor.[79] An investigation of 190 people with type 2 diabetes (HbA_{1c} 7.5–9.5 %) randomly assigned into treatment and control groups examined a wide range of biochemical measures at pre- and three months post-treatment. The serum levels of hsCRP, TNF-α, IL-6, fasting plasma glucose, HbA_{1c}, fasting insulin and homeostasis model of insulin resistance (HOMA-IR) decreased in the treatment group compared with the control group, suggesting that periodontal intervention does improves glycaemic control in association with a reduction in serum inflammatory markers, cytokine levels and an improvement in insulin resistance in type 2 diabetes.[80] A significant reduction in both HbA_{1c}, hsCRP and inflammatory cytokines following periodontal therapy has been reported in other studies.[59,81]

A state of underlying oxidative stress is known to exist in both periodontitis and diabetes[76] due to hyperactive neutrophils in periodontitis,[16] and generated within cellular mitochondria in hyperglycaemic conditions.[82] Oxidative stress directly stimulates pathways associated with pro-inflammatory cytokine production,[77] insulin resistance[83] and diabetes complications,[84–86] and may be a central pathological feature leading to an amplification of inflammatory processes when both chronic periodontitis and type 2 diabetes co-exist.[87] Further investigations into the role of the oxidative stress/inflammation axis may suggest novel therapeutic strategies in the management of periodontitis and diabetes.

Conclusion

Periodontal inflammation appears to have a de-stabilising effect on glycaemic control in type 2 diabetes and a clinically significant reduction in HbA_{1c} of approximately 0.40 % is detectable 3–4 months after periodontal therapy received by people with concurrent type 2 diabetes and periodontitis. There may also be increased incidence of diabetes in association with periodontitis which is very undesirable when considering the predicted increase in type 2 diabetes worldwide. Larger-scale clinical trials are required to establish the exact relationship between the conditions, independent of the many confounding factors. The maintenance of periodontal health should be an important part in the overall management of type 2 diabetes to optimise glycaemic control. ■

1. Goodson JM, Haffajee AD, Socransky SS, The relationship between attachment level loss and alveolar bone loss, *J Clin Periodontol*, 1984;11:348–59.
2. Haffajee AD, Socransky SS, Microbial etiological agents of destructive periodontal diseases, *Periodontol 2000*, 1994;5:78–111.
3. Kornman KS, Page RC, Tonetti MS, The host response to the microbial challenge in periodontitis: assembling the players, *Periodontol 2000*, 1997;14:33–53.
4. Teng YT, The role of acquired immunity and periodontal disease progression, *Crit Rev Oral Biol Med*, 2003;14:237–52.
5. Richards D, Rutherford RB, The effects of interleukin 1 on collagenolytic activity and prostaglandin-E secretion by human periodontal-ligament and gingival fibroblast, *Arch Oral Biol*, 1988;33:237–243.
6. Dixon DR, Bainbridge BW, Darveau RP, Modulation of the innate immune response within the periodontium, *Periodontol 2000*, 2004;35:53–74.
7. Sorsa T, Tjäderhane L, Konttinen YT, et al., Matrix metalloproteinases: contribution to pathogenesis, diagnosis and treatment of periodontal inflammation, *Ann Med*, 2006;38:306–21.
8. Katsuragi H, Ohtake M, Kurasawa I, Saito K, Intracellular production and extracellular release of oxygen radicals by PMNs and oxidative stress on PMNs during phagocytosis of periodontopathic bacteria, *Odontology*, 2003;91:13–8.
9. Canakçi CF, Tatar A, Canakçi V, et al., New evidence of premature oxidative DNA damage: mitochondrial DNA deletion in gingival tissue of patients with periodontitis, *J Periodontol*, 2006;77:1894–900.
10. Fredriksson MI, Gustaffson AK, Bergström KG, Asman BE, Constitutionally hyperreactive neutrophils in periodontitis, *J Periodontol*, 2003;74:219–24.
11. Van Dyke TE, Cellular and molecular susceptibility determinants for periodontitis, *Periodontol 2000*, 2007;45:10–3.
12. Petersen PE, Bourgeois D, Ogava H, et al., The global burden of oral diseases and risks to oral health, *Bull World Health Organ*, 2005;83(9):661–9.
13. Al-Shammari KF, Al-Khabbaz AK, Al-Ansari JM, et al., Risk indicators for tooth loss due to periodontal disease, *J Periodontol*, 2005;76(11):1910–8.
14. Noack B, Genco RJ, Trevison M, et al., Periodontal infections contribute to elevated systemic C-rective protein, *J Periodontol*, 2001;72:1221–7.
15. Bretz WA, Weyant RJ, Corby PM, et al., Systemic inflammatory markers, periodontal diseases, and periodontal infections in an elderly population, *J Am Ger Soc*, 2005;53:1532–7.
16. Chapple IL, Matthews JB, The role of reactive oxygen species and antioxidant species in periodontal tissue destruction, *Periodontol 2000*, 2007;43:160–232.
17. Takane M, Sugano N, Ezawa T, et al., A marker of oxidative stress in saliva: association with periodontally-involved teeth of a hopeless prognosis, *J Oral Sci*, 2005;47:53–7.
18. Tsai CC, Chen HS, Chen SL, et al., Lipid peroxidation: a possible role in the induction and progression of chronic periodontitis, *J Periodontal Res*, 2005;40:378–84.
19. D'Aiuto F, Parkar M, Nibali L, et al., Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial, *Am Heart J*, 2006;151(5):977–84.
20. Baker PJ, Dixon M, Evans RT, et al., CD4(+) T cells and the proinflammatory cytokines gamma interferon and interleukin-6 contribute to alveolar bone loss in mice, *Infect Immun*, 1999;67:2804–9.
21. Scannapieco FA, Bush RB, Paju S, Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review, *Ann Periodontol*, 2003;8:38–53.
22. Bahekar AA, Singh S, Saha S, et al., The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis, *Am Heart J*, 2007;154:830–7.
23. Southerland JH, Moss K, Taylor GW, et al., Periodontitis and diabetes associations with measures of atherosclerosis and CHD, *Atherosclerosis*, 2012;222:196–201.
24. D'Aiuto F, Parkar M, Andreou G, et al., Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers, *J Dent Res*, 2004;83:156–60.
25. Montebugnoli L, Servidio D, Miaton et al., Periodontal health improves systemic inflammatory and haemostatic status in subjects with coronary heart disease, *J Clin Periodontol*, 2005;32:188–92.
26. Cohen DW, Friedlabetesan LA, Shapiro J, et al., Diabetes mellitus and periodontal disease: two-year longitudinal observations. I., *J Periodontol*, 1970;41:709–12.
27. Bacić M, Plancak D, Granić M, CPITN assessment of periodontal status in diabetic patients, *J Periodontol*, 1988;59:816–22.
28. Shlossman M, Knowler WC, Pettitt DJ, Genco RJ, Type 2 diabetes mellitus and periodontal disease, *J Am Dent Assoc.*, 1990;121:532–6.
29. Nelson RG, Shlossman M, Budding LM, et al., Periodontal disease and NIDDM in Pima Indians, *Diabetes Care*, 1990;13:836–40.
30. Emrich LJ, Shlossman M, Genco RJ, Periodontal disease in non-insulin dependent diabetes mellitus, *J Periodontol*, 1991;62:123–31.
31. Seppälä B, Seppälä M, Ainamo J, A longitudinal study on insulin-dependent diabetes mellitus and periodontal disease, *J Clin Periodontal*, 1993;20:161–5.
32. Grossi SG, Zambon JJ, Ho AW, et al., Assessment of risk for periodontal disease. I. Risk indicators for attachment loss, *J Periodontol*, 1994;65:260–7.
33. Firati E, The relationship between clinical periodontal status and insulin-dependent diabetes mellitus. Results after 5 years, *J Periodontol*, 1997;68:136–40.
34. Taylor GW, Burt BA, Becker MP, et al., Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years, *J Periodontol*, 1998;69:76–83.
35. Tsai C, Hayes C, Taylor GW, Glycaemic control of type 2 diabetes and severe periodontal disease in the US adult population, *Community Dent Oral Epidemiol*, 2002;30:182–92.
36. Hodge PJ, Robertson D, Paterson K, et al., Periodontitis in non-smoking type 1 diabetic adults: a cross-sectional study, *J Clin Periodontol*, 2012;39:20–9.
37. Taylor GW, Borgnakke WS, Periodontal disease: associations with diabetes, glycemic control and complications, *Oral Dis*, 2008;14:191–203.
38. Collin HL, Uusitua M, Niskanen L, et al., Periodontal findings in elderly patients with non-insulin dependent diabetes mellitus, *J Periodontol*, 1998;69:962–6.
39. Rodrigues DC, Taba MJ, Novaes AB, et al., Effect of non-surgical periodontal therapy on glycaemic control in patients with type 2 diabetes mellitus, *J Periodontol*, 2003;74:1361–7.
40. Sandberg GE, Sundberg HE, Fjellstrom CA, Wikblad KF, Type 2 diabetes and oral health: A comparison between diabetic and non-diabetic subjects, *Diabetes Res Clin Pract*, 2000;50:27–34.
41. Tervonen T, Oliver RC, Long-term control of diabetes and periodontitis, *J Clin Periodontol*, 1993;20:431–5.
42. Taylor GW, Burt BA, Becker MP, et al., Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus, *J Periodontol*, 1996;67(10 Suppl.):1085–93.
43. Saremi A, Nelson RG, Tulloch-Reid M, et al., Periodontal disease and mortality in type 2 diabetes, *Diabetes Care*, 2005;28:27–32.
44. Shultis WA, Weil EJ, Looker HC, et al., Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes, *Diabetes Care*, 2007;30:306–11.
45. Spangler L, Reid RJ, Inge R, et al., Cross-sectional study of periodontal care and glycosylated hemoglobin in an insured population, *Diabetes Care*, 2010; 33:1753-8.
46. Akalin FA, Işiksal E, Baltacioğlu E, et al., Superoxide dismutase activity in gingiva in type-2 diabetes mellitus patients with chronic periodontitis, *Arch Oral Biol*, 2008;53:44–52.
47. Lim LP, Tay FB, Sum CF, Thai AC, Relationship between markers of metabolic control and inflammation on severity of periodontal disease in patients with diabetes mellitus, *J Clin Periodontol*, 2007;34:118–23.
48. Chen L, Wei B, Li J, et al., Association of periodontal parameters with metabolic level and systemic inflammatory markers in patients with type 2 diabetes, *J Periodontol*, 2010;81:364–71
49. Morita I, Inagaki K, Nakamura F, et al., Relationship between periodontal status and levels of glycated hemoglobin, *J Dent Res*, 2012;91:161–6.
50. Ide R, Hoshuyama T, Wilson D, et al., Periodontal disease and incident diabetes: a seven-year study, *J Dent Res*, 2011;90:41–6.
51. Nesse W, Linde A, Abbas F, et al., Dose-response relationship between periodontal inflamed surface area and HbA1c in type 2 diabetics, *J Clin Periodontol*, 2009;36:295–300.
52. Lösche W, Karapetow F, Pohl A, et al., Plasma lipid and blood glucose levels in patients with destructive periodontal disease, *J Clin Periodontol*, 2000;27:537–41.
53. Hayashida H, Kawasaki K, Yoshimura A, et al., Relationship between periodontal status and HbA1c in nondiabetics, *J Public Health Dent*, 2009;69:204–6.
54. Wolff RE, Wolff LF, Michalowicz BS, A pilot study of glycosylated hemoglobin levels in periodontitis cases and healthy controls, *J Periodontol*, 2009;80:1057–61.
55. Choi YH, McKeown RE, Mayer-Davis EJ, et al., Association between periodontitis and impaired fasting glucose and diabetes, *Diabetes Care*, 2011;34:381–6.
56. Holzhausen M, Garcia DF, Pepato MT, et al., The influence of short-term diabetes mellitus and insulin therapy on alveolar bone loss in rats, *J Periodontol Res*, 2004;39:188–93.
57. Colombo NH, Shirakashi DJ, Chiba FY, et al., Periodontal disease decreases insulin sensitivity and insulin signaling, *J Periodontol*, 2012;83:864–70.
58. Grossi SG, Skrepcinski FB, DeCaro T, et al., Treatment of periodontal disease in diabetics reduces glycated hemoglobin, *J Periodontol*, 1997;68:713–9.
59. Kardeşler L, Buduneli N, Cetinkalp S, Kinane DF, Adipokines and inflammatory mediators after initial periodontal treatment in patients with type 2 diabetes and chronic periodontitis, *J Periodontol*, 2010;81:24–33.
60. Kiran M, Arpak N, Unsal E, Erdoğan MF, The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus, *J Clin Periodontol*, 2005;32:266–72.
61. Promsudthi A, Pimapansri S, Deerochanawong C, Kanchanavasita W, The effect of periodontal therapy on

uncontrolled type 2 diabetes mellitus in older subjects, *Oral Dis*, 2005;11:293–8.
62. Dağ A, Fırat ET, Arıkan S, et al., The effect of periodontal therapy on serum TNF-alpha and HbA1c levels in type 2 diabetic patients, *Aust Dent J*, 2009;54:17–22.
63. Jones JA, Miller DR, Wehler CJ, et al., Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study, *J Clin Periodontol*, 2007;34:46–52.
64. Navarro-Sanchez AB, Faria-Almeida R, Bascones-Martinez A, Effect of non-surgical periodontal therapy on clinical and immunological response and glycaemic control in type 2 diabetic patients with moderate periodontitis, *J Clin Periodontol*, 2007;34:835–43.
65. Khader YS, Al Habashneh R, Al Malalheh M, Bataineh A, The effect of full-mouth tooth extraction on glycemic control among patients with type 2 diabetes requiring extraction of all remaining teeth: a randomized clinical trial, *J Periodontal Res*, 2010;45:741–7.
66. Janket SJ, Wightman A, Baird AE, et al., Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies, *J Dent Res*, 2005;84:1154–9.
67. Moeintaghavi A, Arab HR, Bozorgnia Y, et al., Non-surgical periodontal therapy affects metabolic control in diabetics: a randomized controlled clinical trial, *Aust Dent J*, 2012;57:31–7.
68. Koromantzos PA, Makrilakis K, Dereka X, et al., A randomized, controlled trial on the effect of non-surgical periodontal therapy in patients with type 2 diabetes. Part I: effect on periodontal status and glycaemic control, *J Clin Periodontol*, 2011;38:142–7.
69. Correa FO, Gonçalves D, Figueredo CM, et al., The short-term effectiveness of non-surgical treatment in reducing levels of interleukin-1beta and proteases in gingival crevicular fluid from patients with type 2 diabetes mellitus and chronic periodontitis, *J Periodontol*, 2008;79:2143–50.
70. da Cruz GA, de Toledo S, Sallum EA, et al., Clinical and laboratory evaluations of non-surgical periodontal treatment in subjects with diabetes mellitus, *J Periodontol*, 2008;79:1150–7.
71. Teeuw WJ, Gerdes VE, Loos BG, Effect of periodontal treatment on glycemic control of diabetic patients: a systematic review and meta-analysis, *Diabetes Care*, 2010;33:421–7.
72. Simpson TC, Needleman I, Wild SH, et al., Treatment of periodontal disease for glycaemic control in people with diabetes, *Cochrane Database Syst Rev*, 2010;(5):CD004714.
73. Calabrese N, D'Aiuto F, Calabrese A, et al., Effects of periodontal therapy on glucose management in people with diabetes mellitus, *Diabetes Metab*, 2011;37:456–9.
74. Katz J, Caudle RM, Bhattacharyya I, et al., Receptor for advanced glycation end-product (RAGE) upregulation in human gingival fibroblasts incubated with nornicotine, *J Periodontol*, 2005;76:1171–4.
75. Lalla E, Lamster IB, Stern DM, Schmidt AM, Receptor for advanced glycation end-products, inflammation and accelerated periodontal disease in diabetes: mechanisms and insights in therapeutic modalities, *Ann Periodontol*, 2001;6:113–8.
76. Allen EM, Matthews JB, O'Connor R, et al., Periodontitis and type 2 diabetes: is oxidative stress the mechanistic link?, *Scott Med J*, 2009;54:41–7.
77. Wu CL, Chen FL, [Evaluation of C-reactive protein levels in serum and gingival crevicular fluid in type 2 diabetes patients with periodontitis], *Shanghai Kou Qiang Yi Xue*, 2009;18:132–5.
78. Engebretson S, Chertog R, Nichols A, et al., Plasma levels of tumour necrosis factor-alpha in patients with chronic periodontitis and type 2 diabetes, *J Clin Periodontol*, 2007;34:18–24.
79. Löfgren P, van Harmelan V, Reynisdottir S, et al., Secretion of tumor necrosis factor-alpha shows a strong relationship to insulin-stimulated glucose transport in human adipose tissue, *Diabetes*, 2000;49:688–92.
80. Sun WL, Chen LL, Zhang SZ, et al., Inflammatory cytokines, adiponectin, insulin resistance and metabolic control after periodontal intervention in patients with type 2 diabetes and chronic periodontitis, *Intern Med*, 2011;50:1569–74.
81. Chen L, Luo G, Xuan D, et al., Effects of non-surgical periodontal treatment on clinical response, serum inflammatory parameters, and metabolic control in patients with type 2 diabetes: a randomized study, *J Periodontol*, 2012;83:435–43.
82. Brownlee M, Biochemistry and molecular cell biology of diabetic complications, *Nature*, 2001;414(6865):813–20.
83. Ceriello A, Motz E, Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited, *Arterioscler Thromb Vasc Biol*, 2004;24:816–23.
84. Sakai K, Matsumoto K, Nishikawa T, et al., Mitochondrial reactive oxygen species reduce insulin secretion by pancreatic beta-cells, *Biochem Biophys Res Commun*, 2003;300:216–22.
85. Chen S, Mukherjee S, Chakraborty C, Chakrabarti S, High glucose-induced, endothelin-dependent fibronectin synthesis is mediated via NF-kappa B and AP-1, *Am J Physiol Cell Physiol*, 2003;284:C263–72.
86. Romeo G, Liu WH, Asnaghi V, et al., Activation of nuclear factor-kappaB induced by diabetes and high glucose regulates a proapoptotic program in retinal pericytes, *Diabetes*, 2002;51:2241–8.
87. Allen EM, Matthews JB, O' Halloran DJ, et al., Oxidative and inflammatory status in type 2 diabetes patients with periodontitis, *J Clin Periodontol*, 2011;38:894–901.