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<td>Author(s)</td>
<td>Movva, LR; Ho, KL; Corbet, EF; Leung, WK</td>
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<tr>
<td>Citation</td>
<td>Journal of Dental Sciences, 2014, v. 9 n. 1, p. 1-9</td>
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<td>2014</td>
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<td>Rights</td>
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REVIEW ARTICLE

Type-2 diabetes mellitus, metabolic control, serum inflammatory factors, lifestyle and periodontal status

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Running title: Type 2 DM and periodontitis

Date of submission: September 11, 2013

Conflict of interest and source of funding statement

The authors declare that there are no conflicts of interest in this study. The work described in this paper was in full supported by the University of Hong Kong, Small Project Funding (10204278) and partially supported by the Research Grants Council of the Hong Kong Special Administrative Region, China (772110M).
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Abstract    Type-2 Diabetes mellitus and periodontal disease are complex human
diseases. Pathogenesis of both ailments is multi-factorial, taking chronic disease
courses with varied clinical presentations. It is well established in the scientific
literature that both diseases are interrelated, in particular, individuals suffering from
diabetes are at higher risk of developing periodontitis. The present review analyzed,
using a hypothetical model, the complex factors which may indirectly influence the
two diseases, including lifestyle, obesity, diabetes control, oral health behavior and
serum inflammatory factors, and even quality of life. Special attention was given in
this review to explore plausible theoretical or practical explanations of the
interrelations and the contemporary evidence base underpinning these. As the societal
burden of both diabetes and periodontitis are high, while individual general or oral
health quality of life impacts are substantial, it is very important for healthcare
professionals to appreciate the influence of any relevant factors, appreciating and/or
controlling these, which may assist management of both diseases in those affected, or
prevent development of these two complex diseases and the negative impacts arising
among the at risk individuals in various populations.

KEYWORDS
Diabetes mellitus, type 2; inflammation; life style; periodontitis; quality of life
Introduction

Periodontitis is complex human disease clinically expressed as chronic inflammation at tooth supporting structures resulting from interactions between subgingival plaque biofilm and susceptible host defense system. Diabetes mellitus (DM) is yet another human complex disease characterized by metabolic disorders leading to various levels of chronic hyperglycemia resulting from insufficient insulin production, ineffective insulin action or both. Even though possible contributory interactions between diabetes and periodontitis have been established and the support for a bi-directional link appears to be rather clear, one needs to be aware that available scientific evidence supports controversies over the association between these two complex diseases. Clinical evidence has been presented in the literature supporting direct, indirect or no association between DM and clinical periodontal status. The probable reason over these different findings of associations could be due to the complex and multifactorial nature of these two diseases, such as level of diabetic control, differences arising from different periodontal disease data collection protocols, and differing numbers of clinical subjects used in the studies. Due to the complex nature of these two diseases, there seem to be other factors indirectly associated, apart from the direct basic science mechanisms linking both diabetes and periodontitis. These other factors include general health behavioral, lifestyle and level of serum inflammatory mediators.

The effect of periodontitis on general health quality of life remains ill-defined despite having been studied. Type-2 DM subjects however, were reported to experience dry mouth and in general had inferior physical, role and social functioning. The same study indicated other than type-2 DM, dry mouth,
dissatisfaction with mouth or teeth and poor financial status were significantly
associated with inferior general life quality among the 204 Scandinavians surveyed.

The associated health behavior and lifestyle factors that play major roles in
development of both the type-2 DM and periodontal disease could be general health
behavior, diet and obesity, oral health behavior, psychological factors and their
associations with serum inflammatory factors such as tumor necrosis factor alpha
(TNF-α), respectively. The factors, established, theoretical or conceptual, that may
contribute to type-2 diabetes, and periodontitis and their interactions, and may
potentially modify the corresponding disease(s) outcomes are summarized (Fig. 1).

The aim of this present review is to summarize the clinical evidence available
reporting the associations between the above factors with both type-2 DM and poor
periodontal health. In particular, attention is drawn to the interactions between these
two diseases and the aspects that healthcare professional should play attention to in
attempting to promote good general and oral health for those who are affected.

**The general health behavior**

The optimal general health behavior is defined as not smoking, consuming fewer than
ten alcoholic drinks per week if male, and fewer than five if female, always wearing a
seatbelt in a car whether as a driver or as a passenger, participating at least three times
a week in an exercise activity such as brisk walking, aerobics, sports, or heavy house-
work. Healthy general health behavior measured in terms of smoking, alcohol
consumption, eating breakfast, hours of sleep, hours of work, physical exercise,
nutritional balance, and mental stress are associated with higher natural killer cell
activity, which constitutes the first line of immunological defense. A healthier lifestyle and fewer micro-vascular complications have been shown to be associated in diabetic males with higher education. Among diabetic women, however the more educated perceived themselves as healthier than those with less education, regardless of their concurrent medical status. Diabetic patients with poor metabolic control associated with a lower educational level, report more complications, nervous problems, sick leave days, disability pensions and lower level of physical activity than patients in good or acceptable metabolic control. Females with diabetes and of low social class faced a higher risk of mortality than did both non-diabetic females and diabetic males of low social class.

Poor general health behaviors, regardless of DM status, on the other hand, were shown to be moderately associated with poor periodontal conditions, while those who maintained normal weight, engaged in regular exercise, and had a high-quality diet experienced less periodontitis.

Diet and Obesity

Obesity is defined as excess body weight with an abnormally high proportion of body fat. Body mass index (BMI) is a simple measure of weight for height that correlates with body fat and is used to identify overweight and obesity. Body mass index is defined as weight in kilograms divided by height in meters squared. The World Health Organization (WHO) committee and The National Institute of Health defined overweight as a BMI of 25 to 29.9 kg/m² and obesity as a BMI of 30 kg/m² or higher. BMI cutoffs are based on data showing that health risks increase beginning at a BMI
of 25 kg/m². The current increase in prevalence of obesity has been associated with an increase in the prevalence of type-2 diabetes.

Obesity is a known risk factor for type-2 diabetes, heart disease, stroke, hypertension, osteoarthritis, sleep apnea, and some forms of cancer. Overweight or obesity was the single most important predictor of type-2 diabetes. The risk of diabetes increases approximately 9% with every kilogram increase in self-reported weight and 4.5% with every kilogram increase in measured weight. Duration of obesity was also positively associated with the development of type-2 diabetes.

Obesity is associated with increase in insulin resistance and glucose intolerance, and exacerbates metabolic abnormalities present in type-2 diabetes, such as hyperinsulinemia, hyperglycemia and dyslipidemia. The expression in and secretion from adipose tissue of the pro-inflammatory cytokine serum TNF-α is elevated in obesity, and this may have a role in the insulin resistance of obesity and type-2 diabetes. Adiponectin is another secretory product from adipose tissue that may be involved in the development of type-2 diabetes in susceptible obese individuals.

Obesity thus complicates the management of type-2 diabetes and makes it more difficult to treat the disease pharmacologically. An additional complication is that several of the agents used to treat type-2 diabetes, such as insulin, sulphonylureas, and thiazolidinediones, promote weight gain. Obesity thus increases morbidity and mortality of diabetes.

Patients with type-2 diabetes treated in behavioral weight loss programs who reported the highest exercise levels lost the most weight and had the largest reductions in HbA1c, independent of weight loss at one year from pre-treatment. In persons with type-2 DM, exercise improves cardiopulmonary fitness, reduces blood glucose levels, improves insulin sensitivity, and reduces cardiovascular risk by
lowering blood pressure and improving dyslipidemia.\textsuperscript{25} Behavioral therapy programs generally resulted in modest weight loss.\textsuperscript{24}

Obesity is claimed to be significantly associated with periodontal disease through the pathway of insulin resistance.\textsuperscript{26} The pro-inflammatory cytokine, serum TNF-\(\alpha\) produced from adipose tissues in obese patients is known to play a predominant role in inducing insulin resistance.\textsuperscript{27} Conditions associated with obesity such as the metabolic syndrome may exacerbate periodontitis.\textsuperscript{28} Obesity has a significant association with periodontitis in terms of BMI, body fat, and maximum oxygen consumption.\textsuperscript{29} However, the association is limited to younger obese populations with increased prevalence of periodontal disease,\textsuperscript{30} and periodontal disease is positively associated with total cholesterol and low density lipoprotein cholesterol.\textsuperscript{31} Long term observational studies also showed increased weight and obesity to be positively associated with progression of periodontal disease\textsuperscript{32} and severity of probing pocket depths.\textsuperscript{33} The progression of periodontal disease also seems to be correlated with diagnosed overweight and obesity of at least 5 years, indicating the dose dependent nature of their association.\textsuperscript{34}

\textbf{Psychological factors}

Depression and psychosocial factors are considered as risk factors for both type-2 DM\textsuperscript{35} and periodontal disease.\textsuperscript{36} Older women seem to suffer more from depression than men.\textsuperscript{37} Although the highest rates of depression are found among people under the age of 45, older adults are more likely to be prescribed antidepressants.\textsuperscript{38} Prolonged negative events may disturb the optimal functioning of host defenses, consequently individuals experiencing stress have the potential to develop chronic diseases.\textsuperscript{39}
Stress and depressive symptoms have been shown to be predictive regarding incidence of type-2 diabetes. The possible mechanisms include influence of depressive symptoms on behaviors such as physical activity and diet or their influence on the activity of hypothalamic-pituitary-adrenal axis and sympathetic nervous systems. The odds of type-2 diabetes increased by about 13% with addition of each negative stressful life event. It was also reported that stressful life events related to finance and work are indicators of poor metabolic health.

An underlying bio-behavioral mechanism of stress impact on progression of periodontal disease has been suggested to act through two pathways. Stress may activate several neuroendocrine systems including the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system leading to a reduced potential of the host defense, or may affect the development of the disease through lifestyle factors such as smoking. Increased work and psychological stress is associated with poor oral health status. The psychosocial measures of stress associated with financial strain and distress manifest as depression are associated with severe periodontal disease in the absence of adequate coping behavior, suggesting that the effects of stress on periodontal disease can be moderated by adequate coping behaviors. Dental anxiety is also associated with periodontal attachment loss and numbers of teeth with probing depths more than 6mm, and furthermore satisfaction with life is reported to be associated with flossing frequency. Chronic job and financial strain, depression and inadequate coping are all associated with risk of increased clinical attachment loss. This associated between stress and depression is mediated largely through the behavioral and physiologic mechanisms. Psychological stress is also associated with periodontal disease resistant to periodontal treatment, whereas depression is associated with tooth loss and chronic conditions associated with pain.
**Diabetic control**

With proper control of type-2 DM, therapists and patients can minimize the health risks and burdens for affected individuals and society. It is recently advocated by the International Diabetes Federation (IDF), based on the available evidence, that an HbA1c level of <7.0% is generally compatible with low diabetes related micro-and macro-vascular complications. An IDF treatment algorithm was proposed to the medical team in achieving the target <7.0% HbA1c taking into consideration of the local availability, access and cost of therapeutic agents.

Other than the diabetologist or endocrinologist, general medical practitioner, dietitian, exercise or fitness trainer, podiatrist, ophthalmologist, dentists/hygienist and periodontist are key team members to promote and maintain overall health of those affected by DM or even a pre-diabetic state. Study following up such collaborative comprehensive care have confirmed that favorable DM management outcomes can be achieved. Obviously, to be successful in controlling type-2 DM, a comprehensive approach appears essential because it remains arguable that oral intervention alone could improve glycemic control.

**Oral health behavior**

The optimal oral health behavior is considered as visiting a dentist at least once a year for an examination other than for a dental problem, at least daily tooth brushing, using an inter-dental device such as flossing daily, wooden tooth pick once or more per day, no snacking between meals, and consuming no more than one cariogenic food a day. Physical activity is positively associated with tooth brushing behavior, while alcohol consumption and smoking correlated negatively with proper oral health behavior.
The frequency of tooth brushing is negatively correlated with sugar consumption among adolescents\textsuperscript{58} and is a predictive indicator of general health behavior.\textsuperscript{59} Poor oral health behaviors affected the periodontal status through the accumulation of plaque and calculus deposits.\textsuperscript{4}

Good oral hygiene habits, on the other hand, are positively associated with healthy food consumption, use of vitamins and regular physical exercise among adolescents.\textsuperscript{60} It was also reported that diabetic subjects generally show poor oral health behaviors, however absence of a control group negated the test of association between poor oral health behavior and type-2 diabetes mellitus.\textsuperscript{61} Nevertheless, systemically healthy non-diabetic periodontitis subjects were reported to have a significantly higher mean fasting blood glucose level.\textsuperscript{62}

**Serum inflammatory factors**

A few inflammatory mediators or related serum molecules such as interleukin-1 beta (IL-1\(\beta\)), IL-6, TNF-\(\alpha\), C-reactive protein (CRP), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), are reported to be associated with both type-2 DM and chronic periodontitis.

The pro-inflammatory cytokine TNF-\(\alpha\), is involved in the development of obesity linked insulin resistance\textsuperscript{21} through inhibiting tyrosine kinase activity at insulin receptors. Phosphorylation of the insulin receptor by this tyrosine kinase is known to be a cardinal step in the post-receptor events that follow the binding of insulin to its receptor and interferes with the insulin signaling cascade. The normal level of serum TNF-\(\alpha\) is 0.72 ±0.28 pg/ml. In diabetes mellitus, TNF-\(\alpha\) production was found to be increased\textsuperscript{63} and TNF-\(\alpha\) plasma levels seems to be positively associated to metabolic control.\textsuperscript{11} High levels of serum TNF-\(\alpha\) in patients with insulin resistance may be due
to high levels of fasting insulin. The production and activity of serum TNF-α is modulated by several oral anti-diabetic agents. Beside these relationships between serum TNF-α, metabolic control, anti-diabetic therapy and aging seems to be associated with an increase in serum TNF-α plasma levels. This increase in serum TNF-α levels with aging may be due to age associated increase in percentage of body fat. The levels of serum TNF-α were observed to become lower with weight loss.

More recently, the cause and effect relation between pro-inflammatory cytokines such as IL-1, TNF-α and periodontal attachment loss has been established. The cellular source of serum TNF-α in periodontal diseases include, monocytes, polymorphonuclear leukocytes, fibroblasts, epithelial cells, endothelial cells, and osteoblasts. Once critical levels of pro-inflammatory cytokines production are reached, a local physiologic process becomes a pathologic response. The increased serum TNF-α in turn may exacerbate preexisting periodontal conditions by stimulating fibroblasts to synthesize matrix degrading enzymes, or by stimulating osteoclasts to activate bone resorption. Serum TNF-α can also induce expression of other mediators that amplify or sustain inflammatory responses, such as prostaglandins, and the production of lytic enzymes, and can also enhance bacterial killing and phagocytic activity and over production of serum TNF-α. Further synergistic action with IL-1 can enhance bone resorption. Successful periodontal management decreases circulating serum TNF-α. Additionally, the reduction in circulating serum TNF-α is correlated with an improvement in metabolic control of diabetes, possibly mediated through an improvement in insulin resistance.

Along with pro-inflammatory cytokines, like TNF-α, other inflammatory mediators such as C-Reactive Protein (CRP) and IL-6 also play a major role in development of impaired glucose intolerance prior to the diagnosis of type-2 diabetes.
Probing pocket depths and clinical attachment loss are also linearly associated with impaired fasting glucose levels before development of type-2 diabetes. It has also been reported that increased inflammatory markers such as CRP, matrix metalloproteinases-14 (MMP-14) and tissue inhibitor of matrix metalloproteinases-2 (TIMP-2) are involved in progression of periodontal inflammation associated with type-2 diabetes.

**General and oral health related quality of life**

Obesity and diabetic complications are reported to be the main factors associated with inferior health related quality of life (HRQoL), while dissatisfaction of mouth and teeth and feeling of dry mouth were report to be affecting the HRQoL of type-2 DM subjects. So far reports remain scarce regarding the oral health related quality of life (OH-QoL) for DM subjects. One recent report indicated that dental caries and xerostomia conferred negative impacts on the OH-QoL of adolescents with type-1 DM. The negative impact of advanced periodontal attachment loss in poor OH-QoL, however, was established. Based upon the fact that type-2 DM subjects would experience more periodontitis, it is fair to anticipate type-2 DM subjects may have inferior OH-QoL because of dry mouth and poor periodontal health. Further studies are needed to investigate such relationship.

**Type-2 diabetes and periodontal diseases**

Periodontal disease has been considered as the sixth complication of diabetes and diabetes mellitus is considered as risk factor for periodontal disease. However, the association between diabetes and periodontal disease is complex and to some extend controversial as the evidence has been advanced both for and against the association.
between diabetes and periodontal disease. Emerging evidence portrays the association as bi-directional\textsuperscript{86} as compared to the other belief of unidirectional association,\textsuperscript{87} in which severe periodontitis is considered as a risk of poor glycemic control.\textsuperscript{88} The association between these two complex diseases can be explained by two similar but distinct pathologic pathways, a direct causal association in which the consequences of diabetes act as modifiers of periodontal disease expression\textsuperscript{89} or alternatively a common pathologic defect which results in a host susceptible to either or both diseases.\textsuperscript{90}

The prevalence of diabetes in patients with periodontitis is double (12.5\%) that seen in non-periodontitis patient (6.3\%),\textsuperscript{91} even though no difference is detected in the number of etiologic factors or in the degree of gingival changes between the diabetic and control groups. However patients with poorly controlled diabetes suffer more from gingival bleeding than those with good or moderate control.\textsuperscript{1} Calculus and poor metabolic control were thought to be the best predictors for probing depth; patients with poor metabolic control and calculus has a higher prevalence of and more extensive periodontal pockets than well or moderately controlled diabetics.\textsuperscript{92} Metabolic control seems to be less important in terms of association with attachment loss in the absence of calculus.

Age and number of standing teeth were reported to significantly associated with periodontal attachment loss.\textsuperscript{2} Good or moderate control of any complex human disease is attributed to patient cooperation. Patients with well controlled diabetes might also be more cooperative regarding their oral health care habits and dental care.\textsuperscript{13} Clinical attachment loss is more severe in diabetics compared to non-diabetics. Diabetics with poorly controlled diabetes experience greater attachment loss compared to well controlled diabetics.\textsuperscript{93} Diabetic men have poorer periodontal status
than non-diabetic men.\textsuperscript{94} Diabetic women have poorer periodontal status than non-diabetic women.\textsuperscript{95} Further, diabetic patients aged 55-74 have more severe periodontal disease than patients aged 45-54 and 75-90 and comparable age matched non diabetics.\textsuperscript{3} 

A long duration of diabetes is also considered as a risk factor for periodontitis. An association between longer duration of diabetes and severity of attachment loss has been observed.\textsuperscript{12} This correlation is similar to that of other complications of diabetes, such as retinopathy and vascular disease.

Oral hygiene instructions were able to exert a positive effect on fasting blood glucose levels, gingival crevicular fluid volume, community periodontal index recordings and plaque index.\textsuperscript{96} Mechanical non-surgical periodontal treatment is also reported by a recent meta-analysis to be able to assist reduction of the glycated hemoglobin levels in the blood.\textsuperscript{97} Surgical periodontal treatment responses in diabetics were no different to those in age and sex matched non-diabetics.\textsuperscript{98} Meanwhile, glycemic control has a positive influence on the gingival inflammation condition. It had been demonstrated that there was reduction of inflammation along the gingival margin with the improvement of glycemic control, even no periodontal intervention had been provided.\textsuperscript{99}

**Interrelationship between type-2 DM and periodontitis – a simplified model**

So far it seems that researchers are able to decipher only part of the theoretical relationship between type-2 DM and periodontitis. To a limited extent, certain behavioral and basic science interrelations between these two complex human diseases appears better appreciated (Fig. 2)\textsuperscript{3} and hopefully appropriate intervention aimed at changing key elements of the system may assist management of both type-2
DM and periodontitis. However, there remain substantial knowledge gaps, in particular the common pathogenic mechanisms between diabetic complications and periodontitis causation, as well as how impaired general and oral health life quality could at the end affect the behavior, and hence the compliance of affected individuals for diabetic control and periodontal health maintenance.

**Conclusions**

The scientific evidence presented demonstrates the association between poor type-2 diabetic status and poor periodontal health. This relationship seems to be influenced by complex and multifactorial nature of both the diabetes and periodontitis. Apart from the common pathogenesis pathways of periodontitis and diabetic complications such as impaired immune responses and poor wound healing, other factors including lifestyle, obesity and psychological factors could potential negatively influence local as well as systemic inflammatory mediators, which in turn may indirectly lead to poor diabetic control and periodontal destruction. It is therefore important to understand the indirect associations between lifestyle, obesity and psychological factors for both the type-2 diabetes and periodontal disease, as the modification of these modifiable factors greatly improves the management and prevention of both type-2 diabetes and periodontal disease in our communities.

**Acknowledgements**

The work described in this paper was fully and partially supported by grants from the University of Hong Kong Small Project Funding (10204278) and the Research Grants Council of the Hong Kong Special Administrative Region, China (772110M), respectively.
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Legend

**Figure 1**  Simplified conceptual model regarding interactions between type-2 diabetes mellitus and periodontitis pathogenesis and diseases outcomes.

**Figure 2**  Possible behavioral and basic science interrelatedness between type-2 diabetes mellitus and periodontal disease. A model modified from Kawamura et al.\(^4\) highlighting possible area for disease intervention.