REVIEW ARTICLE

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

Leela R. Movva*, Dominic K. L. Ho Esmonde F. Corbet, W. Keung Leung†

Faculty of Dentistry, The University of Hong Kong, Hong Kong SAR, China

†Corresponding author. Faculty of Dentistry, The University of Hong Kong, Room 1B25, 34 Hospital Road, Prince Philip Dental Hospital, Hong Kong SAR, China.

E-mail address: ewkleung@hkucc.hku.hk (W. K. Leung)

*Current address: Geelong Periodontics and Dental Implants, 68 Bellarine Street, Geelong, Victoria, Australia-3220

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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 multi-factorial nature of these two diseases, such as level of diabetic control,[1] differences arising from different periodontal disease data collection protocols,[2] and differing numbers of clinical subjects used in the studies.[3] 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.[4]

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.[5] 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.[6] 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.[7] A healthier life style and fewer micro-vascular complications have been shown to be associated in diabetic males with higher education.[8] Among diabetic women, however the more educated perceived themselves as healthier than those with less education, regardless of their concurrent medical status.[9] 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.[10] 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.[11]

Poor general health behaviors, regardless of DM status, on the other hand, were shown to be moderately associated with poor periodontal conditions,[12] while those who maintained normal weight, engaged in regular exercise, and had a high-quality diet experienced less periodontitis.[13]

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/m^2 and obesity as a BMI of 30 kg/m^2 or higher. BMI cutoffs are based on data showing that health risks increase beginning at a BMI

of 25 kg/m^2.[14] The current increase in prevalence of obesity has been associated with an increase in the prevalence of type-2 diabetes.[15]

Obesity is a known risk factor for type-2 diabetes, heart disease, stroke, hypertension, osteoarthritis, sleep apnea, and some forms of cancer.[16] Overweight or obesity was the single most important predictor of type-2 diabetes.[17] The risk of diabetes increases approximately 9% with every kilogram increase in self-reported weight[18] and 4.5% with every kilogram increase in measured weight.[19] Duration of obesity was also positively associated with the development of type-2 diabetes.[20] 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.[21] Adiponectin is another secretary product from adipose tissue that may be involved in the development of type-2 diabetes in susceptible obese individuals.[22] 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.[23] 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.[24] 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.[25] Behavioral therapy programs generally resulted in modest weight loss.[24]

Obesity is claimed to be significantly associated with periodontal disease through the pathway of insulin resistance.[26] The pro-inflammatory cytokine, serum TNF-α produced from adipose tissues in obese patients is known to play a predominant role in inducing insulin resistance.[27] Conditions associated with obesity such as the metabolic syndrome may exacerbate periodontitis.[28] Obesity has a significant association with periodontitis in terms of BMI, body fat, and maximum oxygen consumption.[29] However, the association is limited to younger obese populations with increased prevalence of periodontal disease,[30] and periodontal disease is positively associated with total cholesterol and low density lipoprotein cholesterol.[31] Long term observational studies also showed increased weight and obesity to be positively associated with progression of periodontal disease[32] and severity of probing pocket depths.[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.[34]

Psychological factors

Depression and psychosocial factors are considered as risk factors for both type-2 DM[35] and periodontal disease.[36] Older women seem to suffer more from depression than men.[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.[38] Prolonged negative events may disturb the optimal functioning of host defenses, consequently individuals experiencing stress have the potential to develop chronic diseases.[39]

Stress and depressive symptoms have been shown to be predictive regarding incidence of type-2 diabetes.[36] The possible mechanisms include influence of depressive symptoms on behaviors such as physical activity and diet[40] or their influence on the activity of hypothalamic-pituitary-adrenal axis and sympathetic nervous systems.[41] The odds of type-2 diabetes increased by about 13% with addition of each negative stressful life event.[42] It was also reported that stressful life events related to finance and work are indicators of poor metabolic health.[43]

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,[44] or may affect the development of the disease through lifestyle factors such as smoking.[45] Increased work and psychological stress is associated with poor oral health status.[46] 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.[39] Dental anxiety is also associated with periodontal attachment loss[47] and numbers of teeth with probing depths more than 6mm, and furthermore satisfaction with life is reported to be associated with flossing frequency.[48] Chronic job and financial strain, depression and inadequate coping are all associated with risk of increased clinical attachment loss.[37] This associated between stress and depression is mediated largely through the behavioral and physiologic mechanisms.[49] Psychological stress is also associated with periodontal disease resistant to periodontal treatment,[50] whereas depression is associated with tooth loss and chronic conditions associated with pain.[51]

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.[52] 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.[53]

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.[54, 55] Study following up such collaborative comprehensive care have confirmed that favorable DM management outcomes can be achieved.[56] 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.[57]

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.[6] Physical activity is positively associated with tooth brushing behavior, while alcohol consumption and smoking correlated negatively with proper oral health behavior.[58]

The frequency of tooth brushing is negatively correlated with sugar consumption among adolescents[58] and is a predictive indicator of general health behavior.[59] Poor oral health behaviors affected the periodontal status through the accumulation of plaque and calculus deposits.[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.[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.[61] Nevertheless, systemically healthy non-diabetic periodontitis subjects were reported to have a significantly higher mean fasting blood glucose level.[62]

Serum inflammatory factors

A few inflammatory mediators or related serum molecules such as interleukin-1 beta (IL-1β), IL-6, TNF-α, 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-α, is involved in the development of obesity linked insulin resistance[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-α is 0.72 ±0.28 pg/ml. In diabetes mellitus, TNF-α production was found to be increased[63] and TNF-α plasma levels seems to be positively associated to metabolic control.[11] High levels of serum TNF-α in patients with insulin resistance may be due

to high levels of fasting insulin.[64] The production and activity of serum TNF-α is modulated by several oral anti-diabetic agents.[65] 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.[66] This increase in serum TNF-α levels with aging may be due to age associated increase in percentage of body fat.[67] The levels of serum TNF-α were observed to become lower with weight loss.[68]

More recently, the cause and effect relation between pro-inflammatory cytokines such as IL-1, TNF-α and periodontal attachment loss has been established.[69] 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.[70] The increased serum TNF-α in turn may exacerbate preexisting periodontal conditions by stimulating fibroblasts to synthesize matrix degrading enzymes,[71] or by stimulating osteoclasts to activate bone resorption.[72] 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[73] and over production of serum TNF-α.[70] Further synergistic action with IL-1 can enhance bone resorption.[74] Successful periodontal management decreases circulating serum TNF-α.[75] 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.[76]

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.[77] Probing pocket depths and clinical attachment loss are also linearly associated with impaired fasting glucose levels before development of type-2 diabetes.[78] 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.[79]

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),[80] while dissatisfaction of mouth and teeth and feeling of dry mouth were report to be affecting the HRQoL of type-2 DM subjects.[5] 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.[81] The negative impact of advanced periodontal attachment loss in poor OH-QoL, however, was established.[82] Based upon the fact that type-2 DM subjects would experience more periodontitis,[83] 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[84] and diabetes mellitus is considered as risk factor for periodontal disease.[85] 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[86] as compared to the other belief of unidirectional association,[87] in which severe periodontitis is considered as a risk of poor glycemic control.[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[89] or alternatively a common pathologic defect which results in a host susceptible to either or both diseases.[90]

The prevalence of diabetes in patients with periodontitis is double (12.5%) that seen in non-periodontitis patient (6.3%),[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.[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.[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.[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.[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.[93] Diabetic men have poorer periodontal status

than non-diabetic men.[94] Diabetic women have poorer periodontal status than non-diabetic women.[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.[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.[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.[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.[97] Surgical periodontal treatment responses in diabetics were no different to those in age and sex matched non-diabetics.[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.[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)[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.

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References

1. Ervasti T, Knuuttila M, Pohjamo L, Haukipuro K. Relation between control of diabetes and gingival bleeding. *J Periodontol* 1985;56:154-7.
2. Oliver RC, Tervonen T. Periodontitis and tooth loss: comparing diabetics with the general population. *J Am Dent Assoc*, 1993;124:71-6.
3. 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;30:182-92.
4. Kawamura M, Tsurumoto A, Fukuda S, Sasahara H. Health behaviors and their relation to metabolic control and periodontal status in type 2 diabetic patients: a model tested using a linear structural relations program. *J Periodontol* 2001;72:1246-53.
5. Sanberg GE, Wikblad KF. Oral health and health-related quality of life in type 2 diabetic patients and non-diabetic controls. *Acta Odontol Scand* 2003;61:141-8.
6. Payne BJ, Locker D. Relationship between dental and general health behaviors in a Canadian population. *J Public Health Dent* 1996;56:198-204.
7. Kusaka Y, Kondou H, Morimoto K. Healthy lifestyles are associated with higher natural killer cell activity. *Prev Med* 1992;21:602-15.
8. Chaturvedi N, Stephenson JM, Fuller JH. The relationship between socioeconomic status and diabetes control and complications in the EURODIAB IDDM Complications Study. *Diabetes Care* 1996;19:423-30.
9. Dean K, Colomer C, Perez-Hoyos S. Research on lifestyles and health: searching for meaning. *Soc Sci Med* 1995;41:845-55.

10. Larsson D, Lager I, Nilsson PM. Socio-economic characteristics and quality of life in diabetes mellitus--relation to metabolic control. *Scand J Public Health* 1999;27:101-5.

11. Nilsson PM, Johansson SE, Sundquist J. Low educational status is a risk factor for mortality among diabetic people. *Diabet Med* 1998;15:213-9.

12. Leung WK, Movva LR, Wong MCM, Corbet EF, Siu SC, Kawamura M. Health behaviour, metabolic control and periodontal status in medically treated Chinese with type 2 diabetes mellitus. *Ann R Australas Coll Dent Surg* 2008;19:102-10.

13. Al-Zahrani MS, Borawskit EA, Bissada NF. Increased physical activity reduces prevalence of periodontitis. *J Dent* 2005;33:703-10.

14. Troiano RP, Frongillo Jr. EA, Sobal J, Levitsky DA. The relationship between body weight and mortality: a quantitative analysis of combined information from existing studies. *Int J Obes Relat Metab Disord* 1996;20:63-75.

15. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. *J Am Med Assoc* 2001;286:1195-200.

16. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. *Arch Intern Med* 2000;160:898-904.

17. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001;345**:**790-7.

18. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, et al. Diabetes trends in the U.S.: 1990-1998. *Diabetes Care* 2000;23**:**1278-83.

19. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol* 1997;146: 214-22.

20. Everhart JE, Pettitt DJ, Bennett PH, Knowler WC. Duration of obesity increases the incidence of NIDDM. *Diabetes* 1992;41:235-40.

21. Hotamisligil GS, Spiegelman BM. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. *Diabetes* 1994;43:1271-8.

22. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J Clin Endocrinol Metab* 2001;86:1930-5.

23. Albu JB, Raja-Khan N. The management of the obese diabetic patient. *Primary Care* 2003;30:465-91.

24. Wing RR, Epstein LH, Paternostro-Bayles M, Kriska A, Nowalk MP, Gooding W. Exercise in a behavioural weight control programme for obese patients with Type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1988;3:902-9.

25. Hamby S, Goodyear L, Horton E. Diet and exercise in type 2 diabetes mellitus. *Endocrinol Metab Clin North Am* 2001;30:883-907.

26. 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(Suppl 11):2075-84.

27. Nishimura F, Murayama Y. Periodontal inflammation and insulin resistance-lessons from obesity. *J Dent Res* 2001;80:1690-4.

28. Saito T, Shimazaki Y, Sakamoto M. Obesity and periodontitis. *N Engl J Med* 1998;339:482-3.

29. Wood N, Johnson RB, Streckfus CF. Comparison of body composition and periodontal disease using nutritional assessment techniques: Third National

Health and Nutrition Examination Survey (NHANES III). *J Clin Periodontol* 2003;30:321-7.

30. Al-Zahrani MS, Bissada NF, Borawskit EA. Obesity and periodontal disease in young, middle-aged, and older adults. *J Periodontol* 2003;74**:**610-5.

31. Katz J, Flugelman MY, Goldberg A, Heft M. Association between periodontal pockets and elevated cholesterol and low density lipoprotein cholesterol levels. *J Periodontol* 2002; 73:494-500.

32. Gorman A, Kaye EK, Apovian C, Fung TT, Nunn M, Garcia RI. Overweight and obesity predict time to periodontal disease progression in men. *J Clin Periodontol* 2012;39:107-14.

33. Saito T, Shimazaki Y, Kiyohara Y, Kato I, Kubo M, Iida M, et al. Relationship between obesity, glucose tolerance, and periodontal disease in Japanese women: the Hisayama study. *J Periodontal Res* 2005;40:346-53.

34. Morita I, Okamoto Y, Yoshii S, Nakagaki H, Mizuno K, Sheiham A, et al. Five-year incidence of periodontal disease is related to body mass index. *J Dent Res* 2011; 90:199-202.

35. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Depressive symptoms and occurrence of type 2 diabetes among Japanese men. *Diabetes Care* 1999;22:1071-6.

36. Ng SKS, Leung WK. A community study on the relationship between stress, coping, affective dispositions and periodontal attachment loss. *Community Dent Oral Epidemiol* 2006;34:252-66.

37. Minicuci N, Maggi S, Pavan, Enzi MG, Crepaldi G. Prevalence rate and correlates of depressive symptoms in older individuals: the Veneto Study. *J Gerontol A Biol Sci Med Sci* 2002;57:M155-61.

38. Patten SB, Sedmak B, Russell ML. Major depression: prevalence, treatment utilization and age in Canada. *Can J Clin Pharmacol* 2001;8:133-8.

39. Clarke NG, Hirsch RS. Personal risk factors for generalized periodontitis. *J Clin Periodontol* 1995;2:136-45.

40. Padgett DK. Sociodemographic and disease-related correlates of depressive morbidity among diabetic patients in Zagreb, Croatia. *J Nerv Ment Dis* 1993;181:123-9.

41. Plotsky PM, Owens MJ, Nemeroff CB. Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. *Psychiatr Clin North Am* 1998;21:293-307.

42. Vitaliano PP, Scanlan JM, Zhang J, Savage MV, Hirsch IB, Siegler IC. A path model of chronic stress, the metabolic syndrome, and coronary heart disease. *Psychosom Med* 2002;64:418-35.

43. Pyykkonen AJ, Raikkonen K, Tuomi T, Eriksson JG, Groop L, Isomaa B. Stressful life events and the metabolic syndrome: the prevalence, prediction and prevention of diabetes (PPP)-Botnia Study. *Diabetes Care* 2010;33:378-84.

44. Breivik T, Thrane PS, Murison R, Gjermo P. Emotional stress effects on immunity, gingivitis and periodontitis. *Eur J Oral Sci* 1996;104:327-34.

45. Preber H, Bergstrom J. Effect of cigarette smoking on periodontal healing following surgical therapy. *J Clin Periodontol* 1990;17**:**324-8.

46. Deinzer R, Hilpert D, Bach K, Schawacht M, Herforth A. Effects of academic stress on oral hygiene--a potential link between stress and plaque-associated disease? *J Clin Periodontol* 2001;28:459-64.

47. Ng SKS, Leung WK. A community study on the relationship of dental anxiety with oral health status and oral health-related quality of life. *Community Dent Oral Epidemiol* 2008;36:347-56.

48. Dumitrescu AL, Kawamura M. Involvement of psychosocial factors in the association of obesity with periodontitis. *J Oral Sci* 2010;52:115-24.

49. Rosania AE, Low KG, McCormick CM, Rosania DA. Stress, depression, cortisol, and periodontal disease. *J Periodontol* 2009;80:260-6.

50 Axtelius B, Soderfeldt B, Nilsson A, Edwardsson S, Attstrom R. Therapy-resistant periodontitis. Psychosocial characteristics. *J Clin Periodontol* 1998;25:482-91.

51. Persson GR, Persson RE, MacEntee CI, Wyatt CC, Hollender LG, Kiyak HA. Periodontitis and perceived risk for periodontitis in elders with evidence of depression. *J Clin Periodontol* 2003;30:691-6.

52. Colagiuri S. Optimal management of type 2 diabetes: the evidence. *Diabetes Obes Metab* 2012;14(Suppl. 1):3-8.

53. Clinical Guidelines Task Force. Global Guideline for Type 2 Diabetes. *International Diabetes Federation*, Brussels, 2005; http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf.

54. Centers for Disease Control and Prevention. A Guide for Pharmacists, Podiatrists, Optometrists, and Dental Professionals. *National Center for Chronic Disease Prevention and Health Promotion*, Atlanta, Georgia, U.S., Department of Health and Human Services, Public Health Service, 2004; www.caldiabetes.org.

55. Harris P, Mann L, Phillips P, Bolger-Harris H, Webster C, editors. Diabetes management in general practice. Guidelines for Type 2 Diabetes 2011/12 17th edition, *Diabetes Australia*, 2011; http://www.racgp.org.au/Content/NavigationMenu/ClinicalResources/RACGPGuidelines/Diabetesmanagement/201107diabetesmanagementingeneralpractice.pdf.

56. Grimmer-Somers K, Dolejs W, Atkinson J, Worley A. Integrated GP and allied health care for patients with type 2 diabetes. *Aust Fam Physician* 2008;37:774–9.

57. Skamagas M, Breen TL, LeRoith D. Update on diabetes mellitus: prevention, treatment, and association with oral diseases. *Oral Dis* 2008;14:105-14.

58. Rajala M, Honkala E, Rimpela M, Lammi S. Toothbrushing in relation to other health habits in Finland. *Community Dent Oral Epidemiol* 1980;8:391-5.

59. Tada A, Matsukubo T. Relationship between oral health behaviors and general health behaviors in a Japanese adult population. *J Public Health Dent* 2003;63:250-4.

60. Nutbeam D, Aar L, Catford J. Understanding childrens' health behaviour: the implications for health promotion for young people. *Soc Sci Med* 1989;29:317-25.

61. Commisso L, Monami M, Mannucci E. Periodontal disease and oral hygiene habits in a type 2 diabetic population. *Int J Dent Hyg* 2011;9:68-73.

62. Lö sche W, Karapetow F, Pohl A, Pohl C, Kocher T. Plasma lipid and blood glucose levels in patients with destructive periodontal disease. *J Clin Periodontol* 2000;27:537–41.

63. Lechleitner M, Herold M, Dzien-Bischinger C, Hoppichler F, Dzien A. Tumour necrosis factor-alpha plasma levels in elderly patients with Type 2 diabetes mellitus-observations over 2 years. *Diabetic Med* 2002;19:949-53.

64. Mishima Y, Kuyama A, Tada A, Takahashi K, Ishioka T, Kibata M. Relationship between serum tumor necrosis factor-alpha and insulin resistance in obese men with Type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2001;52:119-23.

65. Desfaits AC, Serri O, Renier G. Normalization of plasma lipid peroxides, monocyte adhesion, and tumor necrosis factor-alpha production in NIDDM patients after gliclazide treatment. *Diabetes Care* 1998:21:487-93.

66. Taha W, Paz-Priel I, Anhalt H. Are tumor necrosis factor-alpha receptor 2 levels associated with age? *Diabetes Care* 2000;23:1713-5.

67. Garthwaite SM, Cheng H, Bryan JE, Craig BW, Holloszy JO. Ageing, exercise and food restriction: effects on body composition. *Mech Ageing Dev* 1986;36:187-96.

68. Dandona P, Weinstock R, Thusu K, Abdel-Rahman E, Aljada A, Wadden T. Tumor necrosis factor-alpha in sera of obese patients: fall with weight loss. *J Clin Endocrinol Metab* 1998;83:2907-10.

69. Delima AJ, Oates T, Assuma R, Schwartz Z, Cochran D, Amar S, et al. Soluble antagonists to interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibits loss of tissue attachment in experimental periodontitis. *J Clin Periodontol* 2001;28:233-40.

70. Assuma R, Gates T, Cochran D, Amar S Graves DT. IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis. *J Immunol* 1998;160:403-9.

71. Brenner DA, O'Hara M, Angel P, Chojkier M, Karin M. Prolonged activation of jun and collagenase genes by tumour necrosis factor-alpha. *Nature* 1989;337:661-3.

72. Kobayashi K, Takahashi N, Jimi E, Udagawa N, Takami M, Kotake S, et al. Tumor necrosis factor alpha stimulates osteoclast differentiation by a mechanism independent of the ODF/RANKL-RANK interaction. *J Exp Med* 2000;191:275-86.

73. Pfizenmaier K, Wajant H, Grell M. Tumor necrosis factors in 1996. *Cytokine Growth Factor Rev* 1996;7:271-7.

74. Stashenko P, Dewhirst FE, Peros WJ, Kent RL, Ago JM. Synergistic interactions between interleukin 1, tumor necrosis factor, and lymphotoxin in bone resorption. *J Immunol* 1987;138:1464-8.

75. Iwamoto Y, Nishimura F, Nakagawa M, Sugimoto H, Shikata K, Makino H, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. *J Periodontol* 2001;72:774-8.

76. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *J Am Med Assoc* 2001;286:327-34.

77. Choi YH, McKeown RE, Mayer-Davis EJ, Liese AD, Song KB, Merchant AT. Association between periodontitis and impaired fasting glucose and diabetes. *Diabetes Care* 2011;34:381-6.

78. Kim JB, Jung MH, Cho JY, Park JW, Suh JY Lee JM. The influence of type 2 diabetes mellitus on the expression of inflammatory mediators and tissue inhibitor of metalloproteinases-2 in human chronic periodontitis. *J Periodontal Implant Sci*, 2011;41:109-16.

79. Lee AJ, Morgan CL, Morrissey M, Wittrup-Jensen KU, Kennedy-Martin T, Currie CJ. Evaluation of the association between the EQ-5D (healthrelated utility) and body mass index (obesity) in hospital-treated people with type 1 diabetes, type 2 diabetes and with no diagnosed diabetes. *Diabetic Med* 2005;22:1482-6.

80. Busato IM, Ignácio SA, Brancher JA, Moysés ST, Azevedo-Alanis LR. Impact of clinical status and salivary conditions on xerostomia and oral health-related quality of life of adolescents with type 1 diabetes mellitus. *Community Dent Oral Epidemiol* 2012;40:62-9.

81. Ng SKS, Leung WK. Oral health-related quality of life and periodontal status. *Community Dent Oral Epidemiol* 2006;34:114-22.

82. Leung WK, Siu SC, Chu FCS, Wong KW, Jin LJ, Sham ASK, et al. Oral health status of low-income, middle-aged to elderly Hong Kong Chinese with type 2 diabetes mellitus. *Oral Health Prev Dent* 2008;6:105-18.

83. Lö e H. Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* 1993;16:329-34.

84. Salvi GE, Yalda B, Collins JG, Jones BH, Smith FW, Arnold RR, et al. Inflammatory mediator response as a potential risk marker for periodontal diseases in insulin-dependent diabetes mellitus patients. *J Periodontol* 1997;68:127-35.

85. Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. *Ann Periodontol* 2001;6:99-112.

86. Soskolne WA, Klinger A. The relationship between periodontal diseases and diabetes: an overview. *Ann Periodontol* 2001;6:91-8.

87. 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;67:1085-93.

88. Yalda B, Offenbacher S, Collins JG. Diabetes as a modifier of periodontal disease expression. *Periodontol 2000* 1994;6:37-49.

89. Mealey BL Oates TW. Diabetes mellitus and periodontal diseases. *J Periodontol* 2006;77:1289-303.

90. Soskolne WA. Epidemiological and clinical aspects of periodontal diseases in diabetics. *Ann Periodontol* 1998;3:3-12.

91. Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin-dependent diabetes mellitus. *J Periodontol* 1991;62:123-31.

92. 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;24:505-10.

93. Novaes Jr. AB, Gutierrez FG, Novaes AB. Periodontal disease progression in type II non-insulin-dependent diabetes mellitus patients (NIDDM). Part I--Probing pocket depth and clinical attachment. *Braz Dent J* 1996;7:65-73.

94. Bridges RB, Anderson JW, Saxe SR, Gregory K, Bridges SR. Periodontal status of diabetic and non-diabetic men: effects of smoking, glycemic control, and socioeconomic factors. *J Periodontol* 1996;67:1185-92.

95. Cohen DW, Friedman LA, Shapiro J, Kyle GC, Franklin S. Diabetes mellitus and periodontal disease: two-year longitudinal observations. I. *J Periodontol* 1970;41:709-12.

96. Almas K, Al-Lazzam S, Al-Quadairi A. The effect of oral hygiene instructions on diabetic type 2 male patients with periodontal diseases. *J Contemp Dent Pract* 2003;4:24-35.

97. Liew A, Punnanithinont N, Lee YC, Yang J. Effect of non-surgical periodontal treatment on HbA1c: a meta-analysis of randomized controlled trials. *Aust Dent J* 2013;58:350-7.

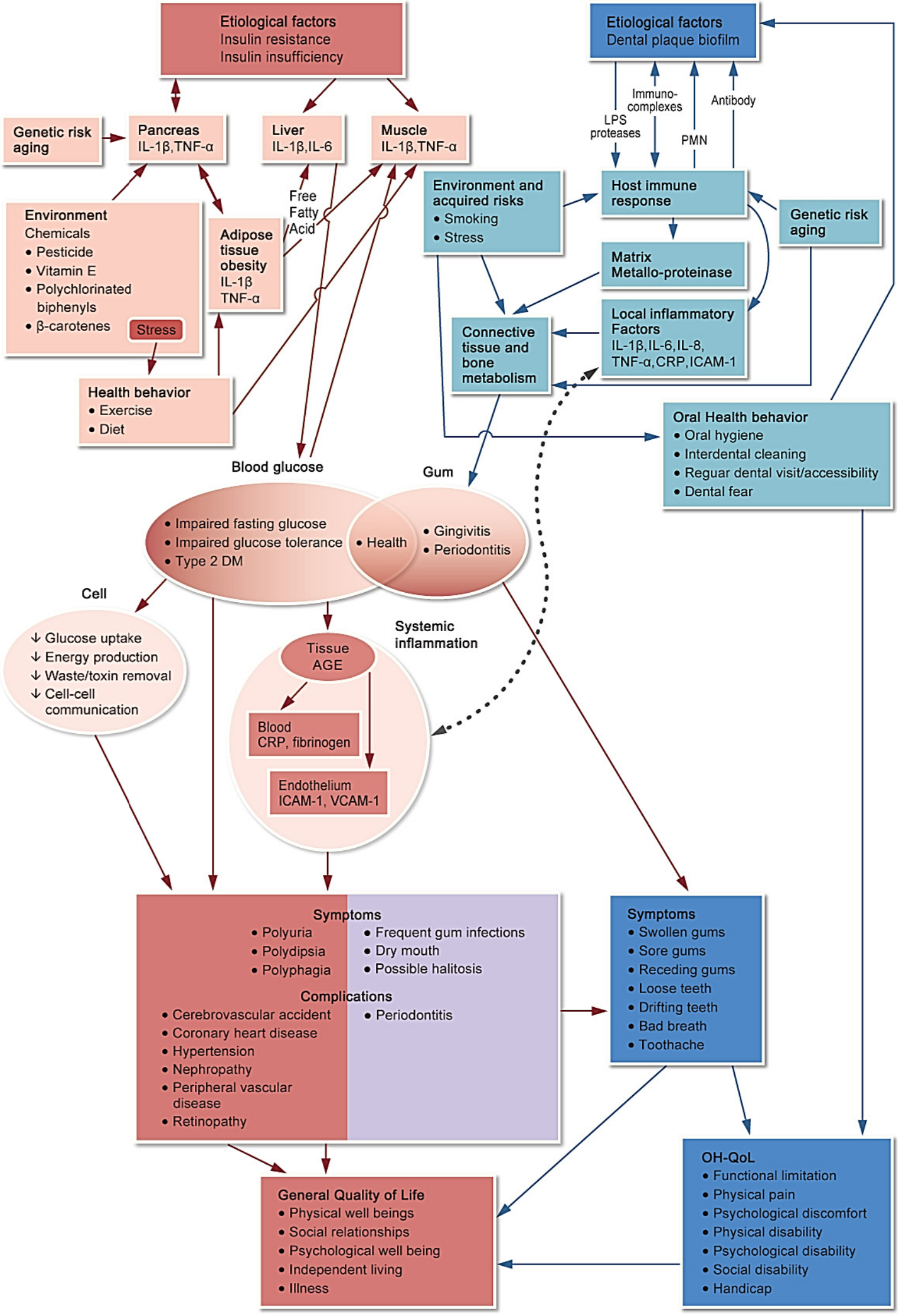
98. Westfelt E, Rylander H, Blohme G, Jonasson P, Lindhe J. The effect of periodontal therapy in diabetics. Results after 5 years. *J Clin Periodontol* 1996;23:92-100.

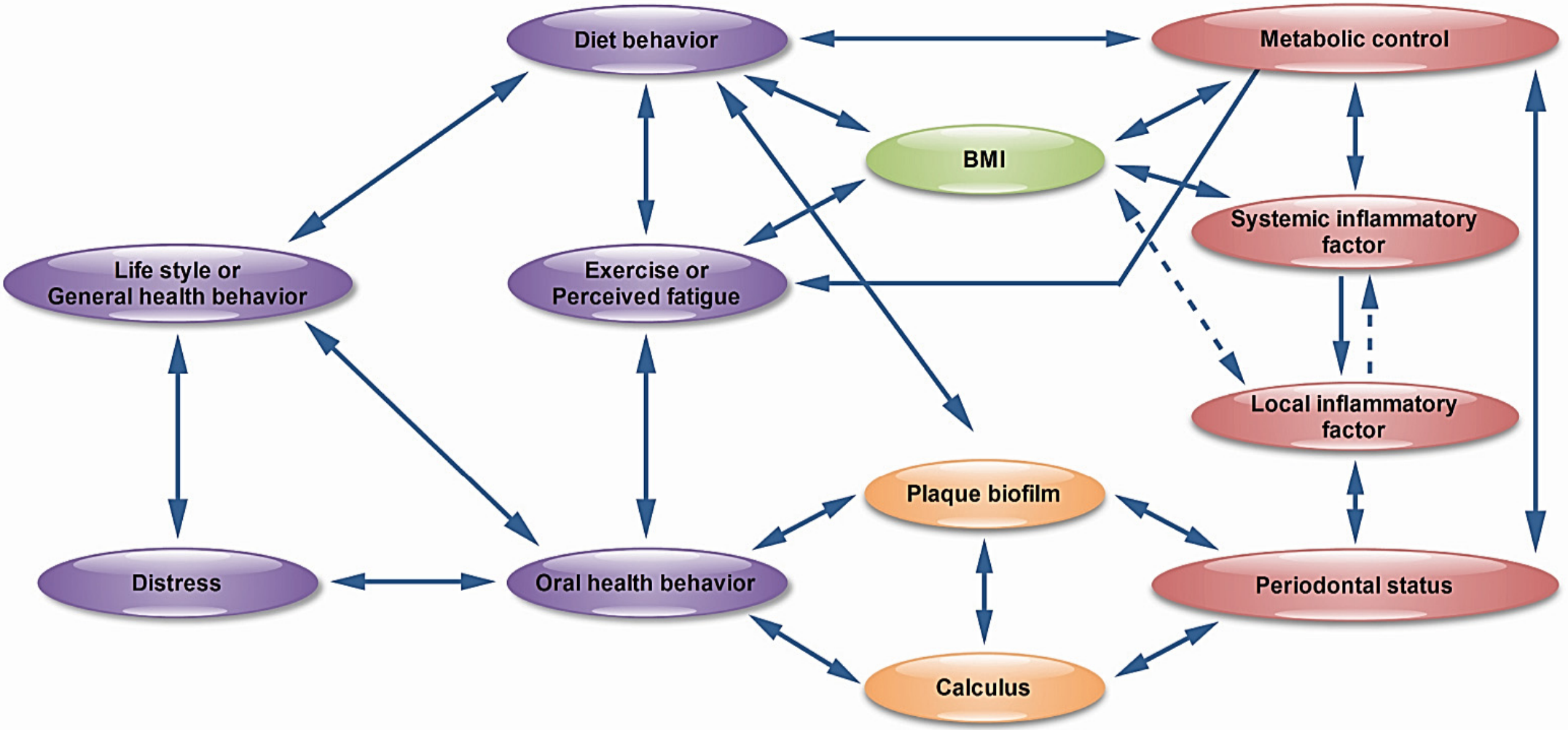
99. Katagiri S, Nitta H, Nagasawa T, Izumi Y, Kanazawa M, Matsuo A, et al. Effect of glycemic control on periodontitis in type 2 diabetic patients with periodontal disease. *J Diabetes Investig* 2013;4:320-5.

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.


Etiological factors
Insulin resistance
Insulin insufficiency
Genetic risk aging
Pancreas
IL-1β,TNF-α
Liver
IL-1β,IL-6
Muscle
IL-1β,TNF-α
Environment
Chemicals
• Pesticide
• Vitamin E
• Polychlorinated biphenyls
• β-carotenes
Stress
Adipose tissue obesity
IL-1β
TNF-α
Free Fatty Acid
Health behavior
• Exercise
• Diet
Blood glucose
Etiological factors
Dental plaque biofilm
LPS proteases
Immuno-complexes
PMN
Antibody
Environment and acquired risks
• Smoking
• Stress
Host immune response
Genetic risk aging
Matrix Metallo-proteinase
Local inflammatory Factors
IL-1β,IL-6,IL-8,
TNF-α,CRP,ICAM-1
Connective tissue and bone metabolism
Oral Health behavior
• Oral hygiene
• Interdental cleaning
• Reguar dental visit/accessibility
• Dental fear
Gum
• Impaired fasting glucose
• Impaired glucose tolerance
• Type 2 DM
• Health
• Gingivitis
• Periodontitis
Cell
↓ Glucose uptake
↓ Energy production
↓ Waste/toxin removal
↓ Cell-cell communication
Systemic inflammation
Tissue AGE
Blood
CRP, fibrinogen
Endothelium
ICAM-1, VCAM-1
Symptoms
• Polyuria
• Polydipsia
• Polyphagia
• Frequent gum infections
• Dry mouth
• Possible halitosis
Complications
• Cerebrovascular accident
• Coronary heart disease
• Hypertension
• Nephropathy
• Peripheral vascular disease
• Retinopathy
• Periodontitis
Symptoms
• Swollen gums
• Sore gums
• Receding gums
• Loose teeth
• Drifting teeth
• Bad breath
• Toothache
General Quality of Life
• Physical well beings
• Social relationships
• Psychological well being
• Independent living
• Illness
OH-QoL
• Functional limitation
• Physical pain
• Psychological discomfort
• Physical disability
• Psychological disability
• Social disability
• Handicap


Diet behavior
Metabolic control
BMI
Systemic inflammatory factor
Life style or General health behavior
Exercise or Perceived fatigue
Local inflammatory factor
Plaque biofilm
Distress
Oral health behavior
Periodontal status
Calculus