Diabetes and Periodontitis: A two-way Relationship

Review Article

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Abstract

Diabetes mellitus and periodontitis are both common, chronic diseases. It is generally accepted that the inter-relationship between diabetes mellitus and periodontitis is a two- way relationship, i.e. the presence of one condition tends to increases the risk and severity of the other, and vice versa. Mechanisms for this two-way relationship are largely unknown. Hyperlipidemia is a group of disorders characterized by an excess of lipids in the bloodstream. Hyperlipidemia increases the risk of diabetes and peridontitis. On the other hand, diabetes and periodontitis could result in hyperlipidemia. The purposes of this review were: (1) examine the two-way relationship between diabetes mellitus and periodontitis; (2) discuss the potential synergistic interactions of hyperlipidemia to both diabetes mellitus and periodontitis; and (3) explore the mechanisms through which hyperlipidemia affects the development of both diseases. The effects of hyperlipidemia on insulin secretion and pro-inflammatory cytokines production (TNF-a, IL-1b) play an important role on the path- ogenesis of diabetes and periodontitis. The purpose of this article is to express the two way relationship between diabetes and chronic periodontitis.

Key words: Diabetes mellitus, Hyperlipidemia, Periodontitis

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycaemia caused by defects in insulin secretion, insulin action, or both. There are two main forms of diabetes. Type 1 diabetes is caused by destructive autoimmune process of the insulin-producing pancreatic b cells leading to insufficient insulin secretion. A more common form, type 2 diabetes, is due to a combination of insulin resistance and impaired insulin secretion. In adults, about 90–95% of all diagnosed cases of diabetes are type 2 diabetes. Diabetes mellitus is associated with a range of complications including cardiovascular disease, neuropathy, nephropathy, retinopathy, bunions, osteoporosis, Alzheimer's disease, and cancer. During the last two decades, periodontal disease has been recognized as one of the "classic" complications of diabetes.

Periodontitis was traditionally considered to be a localised oral infection that only affected the periodontium, but is now regarded as a chronic localised infection of the oral cavity that can trigger the host inflammatory immune response at both local and systemic level, and can also be a source of bacteraemia. Nowadays, it is known that periodontitis affects the pathogenesis of certain systemic diseases, and that it can increase their risk of presentation, which has led to the emergence and development of "Periodontal Medicine".

The association between diabetes mellitus and periodontitis has been reported in numerous studies. It is generally accepted that the inter-relationship between diabetes mellitus and periodontitis is a two-way relationship.

In this review, we update studies on the two-way relationship between diabetes mellitus and periodontitis. As hyperlipidaemia is associated with both diabetes mellitus and periodontitis, we attempt to explore the mechanistic role of hyperlipidaemia in the interrelationship between these two highly prevalent chronic inflammatory disorders.

Effect of Diabetes Mellitus and Periodontitis

The relationship between glycaemic control and periodontitis was reported in both cross-sectional and longitudinal studies. Though some studies failed to observe the association between the degree of glycaemic control and periodontitis, most studies generally support good glycaemic control decreases the severity of periodontitis, while poor glycemic control increases the risk of periodontitis. A study in Japan examined the effect of improved glycemic control by intervention therapy on periodontitis in type 2 diabetic patients. Effective glycemic control with reduced HbA1c over the 6-month period improved BOP (bleeding on probing) lesions without periodontal treatment. On the other hand, other studies have reported that

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diabetic patients who had poor glycemic control had increased risk of deep periodontal pockets, severe attachment loss, and progressive bone loss, compared to well-controlled diabetic patients.

It is generally accepted that production of advanced glycation end products (AGEs) is one of the mechanisms by which diabetes appears to affect the periodontal condition. AGEs are irreversible products of non-enzymatic glycation and oxidation of proteins and lipids that accumulate in diabetic plasma and tissue. Binding of AGEs to the cell membrane receptor, RAGEs, activates host cells such as monocytes/macrophages and endothelia cells, resulting in release of pro-inflammatory cytokines such as IL-1b, TNF-a and IL-6. Exacerbated inflammatory response triggered by AGEs contribute to destruction of gingival tissues and tooth supporting bone. On the other hand, blockade of RAGEs significantly suppressed alveolar bone loss in diabetic mice infected with periodontal pathogens. In humans, it has been shown that subjects with both type 2 diabetes and periodontitis had higher expression level of RAGEs compared to that in non-diabetic subjects with periodontitis.

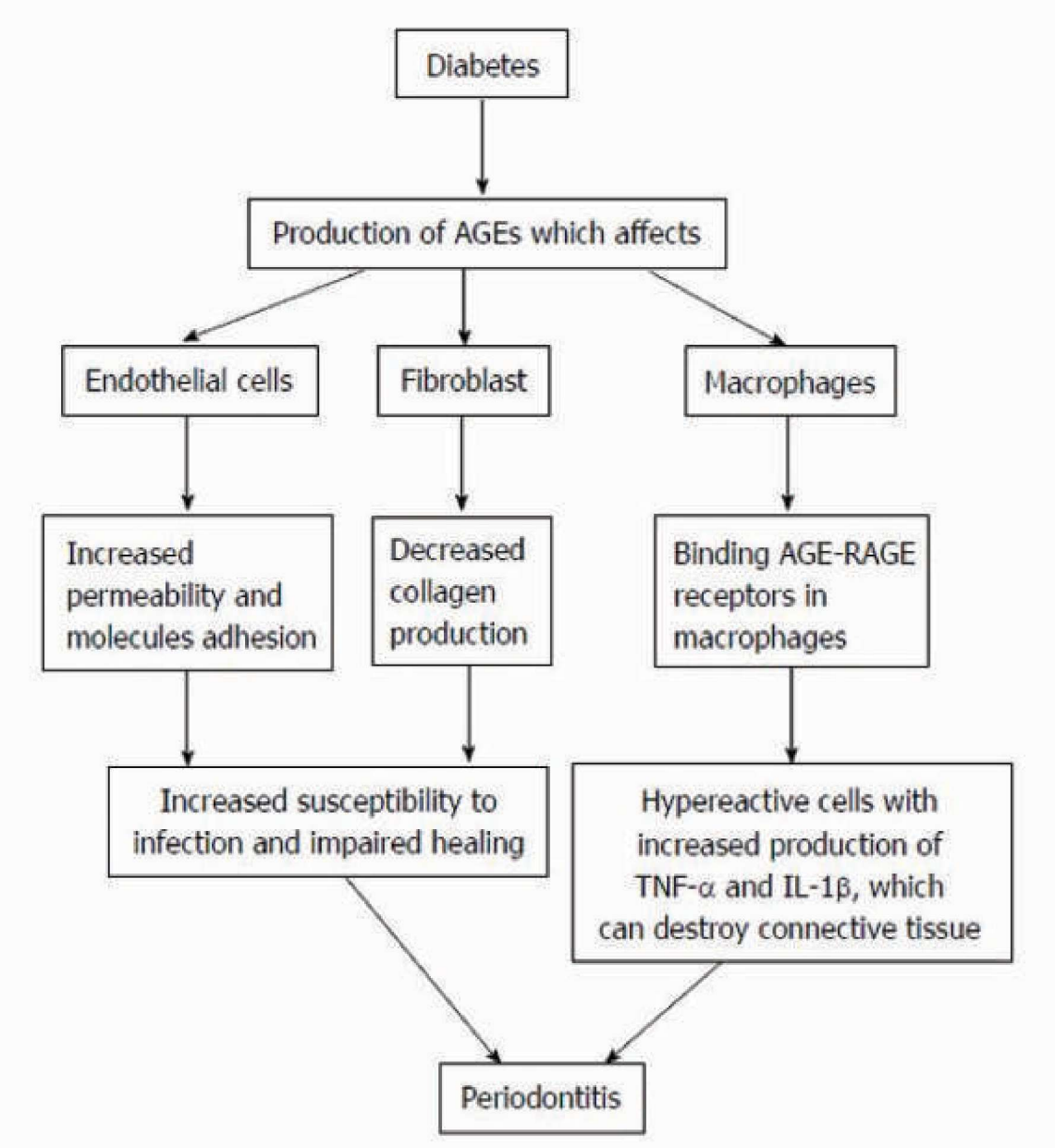

Fig. 1 Effects of diabetes on periodontium

Impact of Periodontitis on Diabetes Mellitus

There is a two-way relationship between diabetes mellitus and periodontitis, i.e. not only is diabetes a risk factor for periodontitis, but periodontitis could adversely affect diabetes mellitus. As inflammation can promote insulin resistance and dysregulated glycemia, it is hypothesized that periodontitis may affect glycaemic control in diabetic patients. Data from the longitudinal study of residents of the Gila River Indian Community revealed that severe periodontitis at baseline was associated with an increased risk of poor glycaemic control (HbA1c > 9%) during a 2-year follow-up period.

However, even hyperglycaemia may manifest its low grade systemic inflammation in periodontium and the causal impact of periodontal infection on incidence of diabetes is still uncertain. Periodontal therapies, including scaling, root planning, localized gingivectomy, dental extractions, were all shown the potentials to improve glycaemic control.

Mechanisms for the impact of periodontitis on diabetes mellitus have been explored by experimental studies, which suggest that pro-inflammatory cytokines may involve in the development of diabetes mellitus when periodontitis presents. In periodontitis, concentrations of pro-inflammatory cytokines TNF-a, IL-1b, IFN-g increased not only in periodontal tissues, but also in serum.

Though increase of serum pro-inflammatory cytokines may related to the spill over from local periodontal tissues, such increase is more like a reflex of host response during hyper-inflammatory state.

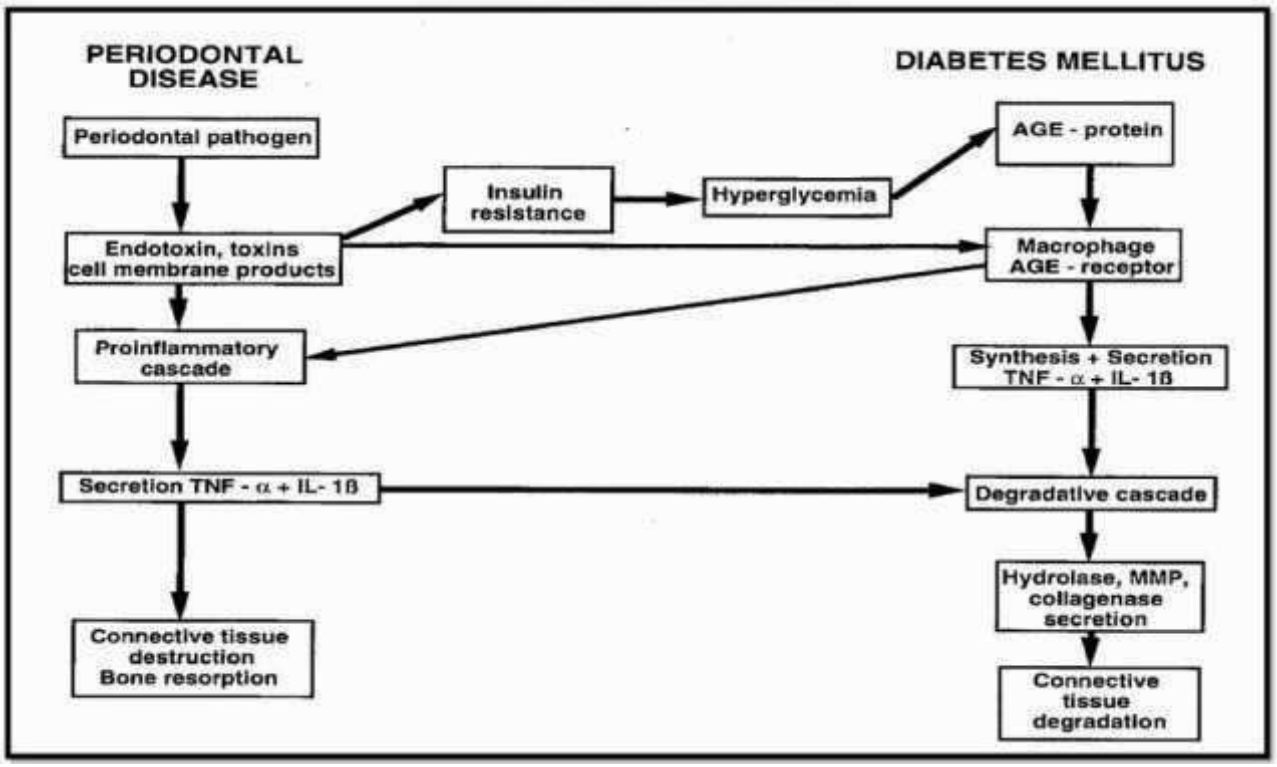

Fig 2 Two way relationship between periodontal disease and diabetes

Diabetes Mellitus and Hyperlipidemia

Hyperlipidemia is a group of disorders characterized by an excess of lipids in the bloodstream. Patients with hyperlipidemia often manifest marked elevations of low-density lipoprotein (LDL), triglycerides (TRG), and omega-6 free fatty acids.49 Elevation of omega-6 polyunsaturated acids in turn contributes to formation of LDL/TRG. Hyperglycemia is often accompanied by hyperlipidemia in both type 1 and type 2 diabetes. A number of studies have reported increased total cholesterol, TRG, LDL, and decreased HDL in diabetic patients.

The nature of fatty acids within the phospholipid bilayer determines the physical properties of membranes due to their effects on receptor responses and operation of membrane- bound enzyme. In diabetic patients, the conversion of omega-6 polyunsaturated fatty acids to active metabolites is impaired because of the inhibition of 6-desaturase enzyme activity caused by insulin deficiency. Cellular functions are affected as less active metabolites are produced, which are key components of cell membrane structure. Like hyperglycemia, hyperlipidemia is also thought to be responsible for impairments in a variety of cell types and development of some diabetic complications.

Large amount of pro-inflammatory cytokines, e.g. IL-1b and TNF-a, are released in diabetic patients due to an exaggerated inflammatory response to Gram-negative bacterial lipopolysaccharide (LPS), especially Porphyromonas gingivalis LPS. Evidences suggest that hyperlipidemia may be related to the hyper-responsive monocytic phenotype in diabetic patients. It has been shown that a 4-week high-fat diet in mice chronically increased plasma LPS concentration two to three times with the increase of the weight of adipose tissue. Cytokines exhibited several biological functions that are related to periodontitis, diabetes, and lipid metabolism: (1) high levels of pro-inflammatory cytokines in periodontal tissues are associated with the risk of periodontits because of their tissue destructive effects. Cytokines are associated with insulin resistance and the risk of diabetes. Cytokines exert effects on lipid metabolism by affecting production of other cytokines, resulting in elevated levels of free fatty acid, LDL, and TRG. The serum lipid elevation effects are due to increased hepatic TRG production and/or decreased TRG clearance.

Periodontitis and hyperlipidemia

Similar to the animal studies, a number of human studies support the positive association between periodontitis and hyperlipidemia. Patients with periodontitis had higher levels of TRG, total cholesterol, and LDL than periodontally healthy controls. On the other hand, patients with hyperlipidemia had higher values of periodontal parameters compared to normolipidemic individuals, indicating that patients with hyperlipidemia are more prone to periodontal disease. Taken all together, current evidences suggest that the association between periodontitis and hyperlipidemia is a bi-directional relationship.

Obesity has a deleterious effect on the lipid profile, leading to increased levels of TRG, total cholesterol, and LDL. The effects of obesity on periodontits have been reported in animals and humans. In animals with periodontits, greater alveolar bone loss has been observed in obese mice and rats than non-obese animals. In humans, an association between obesity and periodontitis was first reported by Saito et al. The study enrolled 241 apparently healthy dentulous Japanese subjects, among them had periodontitis, 145 had no periodontitis. The adjusted relative risk of periodontitis was 3.4 in persons with a BMI of 25–29.9 kg/m2 and 8.6 in those with a BMI 30 kg/m.

The hyperlipidemia axis uniting diabetes and periodontitis and its clinical implications

The two-way relationship between diabetes mellitus and periodontitis has been well documented. Hyperlipidemia is a common risk factor for both diabetes and periodontits. Current evidence suggests a bidirectional relationship between hyperlipidemia and diabetes, and between hyperlipidemia and periodontitis. Thus, hyperlipidemia may serve as a possible mechanistic link for the association between diabetes and periodontitis.

A proposed model linking hyperlipidaemia to diabetes and periodontitis is presented in Fig.3. Diabetes may affect periodontitis by the following potential mechanisms: diabetes is characterized by hyperglycaemia, which is associated with the increased levels of FFA, LDL, and TRG. In hyperlipidaemia status, the production of serum pro-inflammatory cytokines, e.g. IL-1b and TNF-a, are increased due to an exaggerated inflammatory response to Gram-negative bacterial lipopolysaccharide (LPS), especially P. gingivalis LPS. Hyperglycaemia can also directly induce the production of pro-inflammatory cytokines by activating the pro-inflammatory transcription factor nuclear kB (NF-kB). Elevated levels of serum pro- inflammatory cytokines result in

similarly increased levels of pro-inflammatory cytokines in gingival crevicular fluid be- cause this fluid is a serum transudate. Furthermore, the release of pro-inflammatory cytokines from host cells in periodontal tissues is induced by AGE/RAGE pathway during the inflammatory response, leading to destruction of gingival tissues and tissue supporting bone. On the other hand, periodontitis may affect diabetic status via the following potential mechanisms: in periodontitis patients, serum pro-inflammatory cytokines, IL-1b and TNF-a, are significantly increased due to a cytokine cascade caused by bacteraemia and/or endotoxemia. Cytokines induce the elevation of serum levels of FFA, LDL, and TRG by increasing hepatic TRG production and/or decreasing TRG clearance. Infection with P. Gingivalis or other Gram-negative periodontal pathogens may directly increase serum levels of FFA, LDL, and TRG, which has been reported in animal studies. High levels of lipids and/or pro-inflammatory cytokines contribute to insulin resistance by inhibiting insulin signalling or destruction of pancreatic b cells, and increase the risk of diabetes.

Due to the two-way relationship between diabetes and periodontitis, patients with diabetes or periodontitis need to be informed of the increased risk of another disease. As has been shown in this review, hyperlipidemia interacts with diabetes and periodontits, and increases risks of both diseases. Thus, for the clinical management of diabetes and periodontitis, effects of hyperlipidemia need to be considered as part of the treatment regimes. Efforts to develop therapeutic strategies aimed at limiting hyperlipidemia should be advocated. It has been well documented that diet and exercise are both effective in the management of hyperlipidemia. Key recommendations for the management of hyperlipidemia include: reduce intake of saturated fats and trans fats; increase intake of poly- and monounsaturated fats, omega-3 fatty acids, soluble fibre, soy protein, plant stanols and sterols; follow a Mediterranean diet, and regular aerobic exercise. Besides diet and exercise, other treatment strategies aimed at limiting hyperlipidemia may be developed in diabetic patients, especially those of high risk of periodontitis. The importance of maintaining optimal lipid profile in these patients should be emphasized when developing treatment plans.

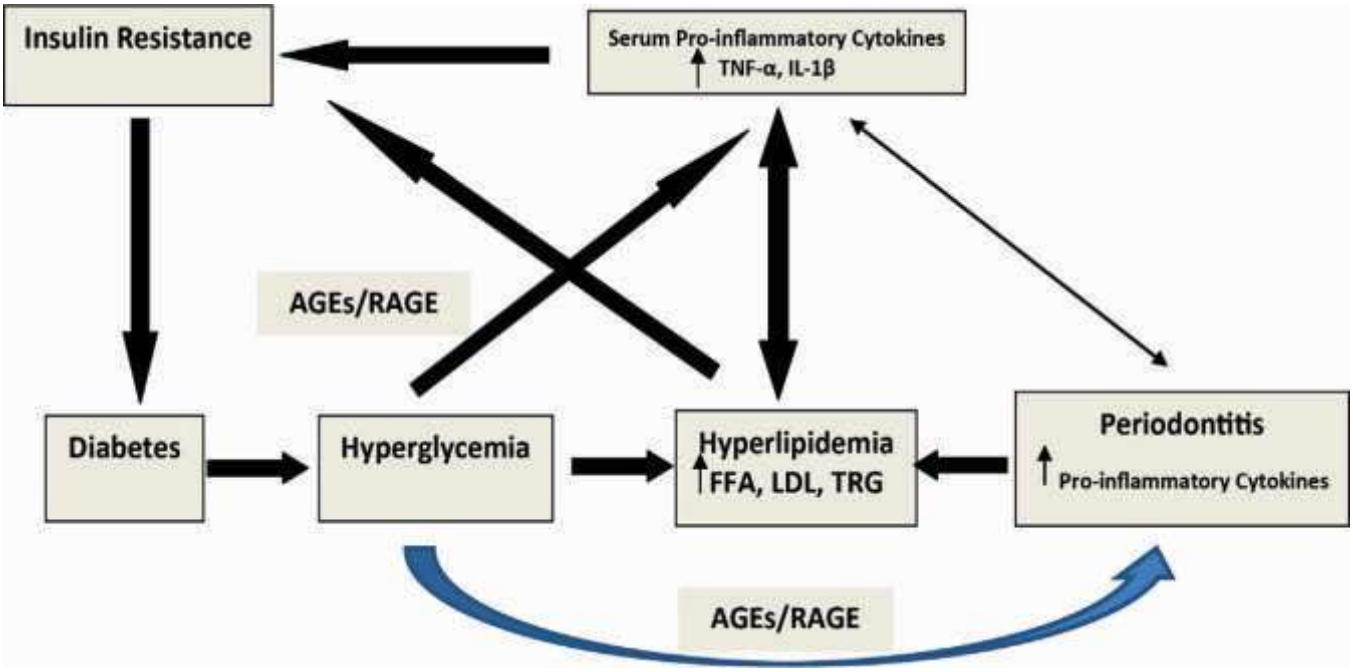

Fig. 3 – A proposed model linking hyperlipidemia to diabetes and periodontitis. Diabetes is associated with the increased levels of FFA, LDL, and TRG. In hyperlipidemia status, the production of pro-inflammatory cytokines, e.g. IL-1b and TNF-a, is increased. Release of pro-inflammatory cytokines from host cells in periodontal tissues is induced by AGE/RAGE pathway during the inflammatory response, leading to destruction of gingival tissues and tissue supporting bone. In periodontitis patients, levels of pro-inflammatory cytokines, IL-1b and TNF-a, are significantly increased. Infection with P. gingivalis or other Gram-negative periodontal pathogens may also directly increase serum levels of FFA, LDL, and TRG. High levels of lipids and/or pro-inflammatory cytokines contribute to insulin resistance by inhibiting insulin signalling or destruction of pancreatic b cells, and increase the risk of diabetes.

Conclusion

In conclusion, hyperlipidemia plays an important role on the pathogenesis of diabetes and periodontitis via its effects on insulin secretion and pro-inflammatory cytokines production (TNF-a, IL-1b). A model is proposed suggesting the possible mechanistic role of hyperlipidemia as a link between diabetes and periodontitis. As our understanding of the inter- relationship between hyperlipidemia, diabetes, and periodontitis, therapeutic strategies aimed at limiting hyperlipidemia should be advocated for the clinical management of diabetes and periodontitis.

References

1. Nelson RG, Shlossman M, Budding LM, Pettitt DJ, Saad MF, Genco RJ, et al. Periodontal disease and NIDDM in Pima Indians. Diabetes Care 1990;13:836–40.

2. Fernandes JK, Wiegand RE, Salinas CF, Grossi SG, Sanders JJ, Lopes-Virella MF, et al. Periodontal disease status in gullah african americans with type 2 diabetes living in South Carolina. J Periodontol 2009;80:1062–8.

3. Preshaw PM, Alba AL, Herrera D, Jepsen S, Konstantinidis A, Makrilakis K, Taylor R. Periodontitis and diabetes: a two-way relationship. Diabetologia. 2012 Jan;55(1):21-31.

4. Matthews DC. The relationship between diabetes and periodontal disease. Journal-Canadian Dental Association. 2002 Mar 1;68(3):161-4.

5. Bascones-Martinez A, Munoz-Corcuera M, Bascones-Ilundain J. Diabetes and periodontitis: A bidirectional relationship. Medicina Clínica (English Edition). 2015 Jul 6;145(1):31-5.

6. Zhou X, Zhang W, Liu X, Zhang W, Li Y. Interrelationship between diabetes and periodontitis: role of hyperlipidemia. Archives of Oral Biology. 2015 Apr 1;60(4):667-74.