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Diabetes Mellitus and Periodontal Disease: Unravelling The Two Way Relationship

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ABSTRACT

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Diabetes and chronic periodontitis are common chronic diseases affecting adults in all population groups. Periodontitis is the second common cause of dental disorder. Diabetes mellitus affects a high segment of adults especially in later life. Periodontitis is the sixth common cause of disease in Diabetes patients. This article examines the interrelationship between these common diseases.

Keywords: Periodontitis, Periodontal Disease, Diabetes and Disease Mechanisms

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INTRODUCTION

Diabetes mellitus and chronic periodontitis are common chronic diseases in adults in the world population. Periodontal disease is chronic inflammatory disease of the tissues that support and attach the teeth to the jaws.[1] They are caused by gram-negative bacterial infections and are, for the most part, asymptomatic, although much of the actual destructive tissue changes observed clinically are result of the inflammatory host response. Periodontal disease is the second main cause of oral cavity disorders affecting the population due to its high prevalence.[2]

Diabetes mellitus is a complex disease with both metabolic and vascular components, characterized by hyperglycemia due to defects in insulin secretion, insulin action or both.[3] Persons with diabetes mellitus are at greater risk of developing periodontal diseases. Periodontal disease is now considered the sixth complication of diabetes mellitus.[4] Not only is it more prevalent in this population, but also the progression of symptoms, in a more aggressive and more rapidly setting mode. The main reasons for this situation are the scarce information on the importance of oral hygiene, poor metabolic control and the irregularity in visiting dentists, among others.

Patients suffering from diabetes mellitus are known to have increased susceptibility to certain infections. The interrelationship between periodontitis and diabetes provide an example of systemic disease predisposing to oral infections, and once that infection is established, the oral infections exacerbate systemic disease. Diabetic patients are commonly encountered in the dental office. Proper patient management requires close interaction between the dentist and physician. Dentists and other oral health care providers should understand the diagnostic and therapeutic methodologies used in diabetes care. Dentists must educate patients and their physicians about the interrelationships between periodontal health and glycemic control, with an emphasis on the inflammatory nature of periodontal diseases and the potential systemic effects of periodontal infection. Working with diabetic patients can be challenging and rewarding when open lines of communication are established and thorough patient education is attained.

Associations between Periodontal Disease and Diabetes

Much of the earlier literature is based on clinical observations using small convenience-based population samples rather than epidemiological populations.

In 1928, Williams[5] reported that gingivitis and periodontitis in diabetic patients have different clinical characteristics than the same diseases in nondiabetics.

Somewhat later, Glickman[6] was one of the first

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investigators to conduct a controlled experimental study on this topic. Sheppard[7] studied alveolar resorption in diabetics. He saw no bone resorption in patients under the age of 15-16 years even in the presence of severe diabetes. He observed unusually severe alveolar resorption in 20- to 40- year-old diabetics. Belting *et al.*[8] reported that diabetics have higher periodontal disease index, as compared to nondiabetics, age matched controls. However, this difference was not significant for patients over the age of 50. Cianciola *et al.*[9] also studied the prevalence of periodontal disease in insulin-dependent diabetes mellitus. They reported a 39% prevalence of periodontitis among patients 19 years and older. They also reported that periodontal disease was more related to age than duration of diabetes. By comparison, Finestone[10] compared 189 diabetics to nondiabetics and found a higher prevalence and severity of periodontal disease in diabetics across all age groups. In a more recent study, Bacic *et al.*[11] concluded that, up to the age of 34, there were no differences between diabetics and controls regarding periodontal pockets of 6 mm or more Cohen[12] completed the first longitudinal study of diabetes and periodontal disease, to examine the incidence of disease progression.

One of the largest scale studies to date were carried out in 1978 by Knowler WC *et al* in the Pima Indians of the Gila River Indian community in Arizona, who have the highest reported prevalence of type 2 DM in the world. About 50% of them above 35 years of age are affected by the disease.[13]

Sastrowijoto and co-workers[14] in 1989 found high levels of Porphyromonas gingivalis, Prevotella intermedia and Actinobacillus actinomycetemcomitans, with low levels of Capnocytophaga species, in periodontal pockets of patients with type 1 DM. In a 9-month longitudinal study on 6 type 1 DM subjects, Sastrowijoto *et al*[15] in the year 1990 reported that with intensive conventional insulin therapy, long-term metabolic control improved significantly, accompanied by a reduction in gingival redness. However, there was no effect on probing depth, attachment level, bleeding on probing and the plaque index. Thus, improvement in the glycaemic control in type 1 DM patients may not necessarily result in improvement in periodontal parameters, unless local oral hygiene is maintained.

A study by Martorelli de Lima and co-workers[16] in 2004 demonstrated that the adjunctive use of locally delivered doxycycline improved the periodontal attachment levels of diabetic patients with periodontitis as compared with controls who received scaling and root planning. In studies done by Engebretson SP *et al* in the year 2004, poorer glycaemic control was found to be associated with elevated gingival crevicular fluid interleukin-1 α (IL-1 α), which may explain the association between poor glycaemic control and more advanced periodontal disease.[17] In a very recent study by Kiran and co workers[18] in 2005, it was found that even in subjects with good glycaemic control (6% to 8%), a significant improvement in HbA1c was obtained following periodontal therapy.

A recent meta-analysis done by Khader YS *et al* in 2006, compared the periodontal status of diabetics with that of non-diabetics.[19]

The studies included in the analysis were 18 cross-sectional studies, 3 prospective cohort studies and baseline data of 2 clinical trials. The authors concluded that based on average values, diabetics had poorer oral hygiene as measured by the plaque index, more severe gingival disease as measured by the gingival index, and higher severity of periodontal disease based on probing depths and clinical attachment levels. However, when based on percentages of sites with specific values of the plaque index, the gingival index, bleeding on probing, probing depths, and clinical attachment loss, there was no difference in the extent of disease between the diabetics and non-diabetics. In summary, there is general agreement that diabetes affects the severity of periodontal disease. While most studies showed that those with poor glycaemic control had more periodontal destruction, not all studies could confirm glycaemic control was significantly correlated to periodontal status indicating that factors other than glycaemic control per se could have contributed to periodontal breakdown.

CAN SYSTEMIC DISEASES COINDUCE PERIODONTITIS?

A HYPOTHETICAL "TWO-HIT" MODEL

The connection between systemic diseases and chronic destructive periodontitis (CDP) has received increasing attention in recent years. A major unanswered question is how disease in one part of the body (e.g., the joints and skeletal tissues) can transmit signals to the periodontium to enhance or to co-induce CDP. The answer can be explained a proposed "two-hit" model of CDP (Figure 1). This was done by interpreting the results of experiments with animal models and supported by evidence from human clinical studies. This model conceptualizes how bone- and connective tissue-destructive diseases in one location (e.g., the joints in patients with rheumatoid arthritis, the skeletal system

during post-menopausal osteoporosis, and diabetes) may communicate with the tissues in the periodontium (the 2nd "hit"), together with the microbial products (e.g., endotoxin) generated by the subgingival biofilm (the 1st "hit"), to co-induce periodontitis **(Figure 1).**

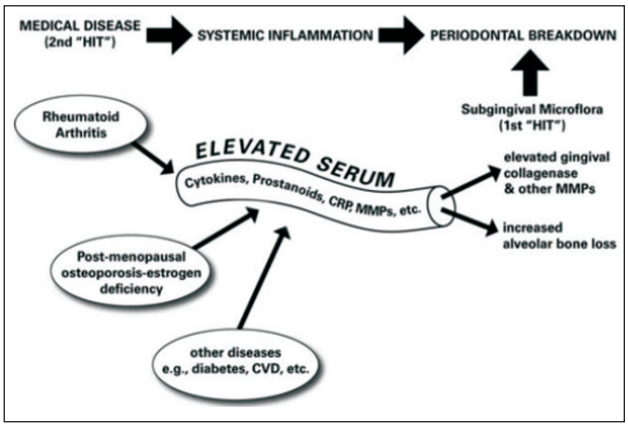

Figure 1. **A hypothetical "two-hit" model of induction of chronic destructive periodontitis. The first "hit" involves the periodontopathic subgingival biofilm and its microbial products, such as endotoxin.**

The second "hit"involves a medical systemic disease, such as (but not limited to) rheumatoid arthritis and post-menopausal osteoporosis, which increases biomarkers of systemic inflammation in the circulation, including C-reactiveprotein (CRP), cytokines (e.g., IL-6), prostanoids (e.g., PGE2), andmatrix metalloproteinases (e.g., MMP-9). CVD, cardiovascular disease.

In the first example of this hypothesis, evidence from human studies suggests that both adult rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) can increase the incidence of periodontitis (Kasser *et al.*, 1997; Miranda *et al.*, 2003). One possible link between the systemic and local diseases includes systemic osteoporosis as a complication of arthritis[20] (Greenwald and Kirkwood, 1999), which may potentiate accelerated periodontal bone loss (Payne *et al.*, 1999). Another link is the elevated levels of inflammatory mediators, both locally in the diseased synovium and systemically in the circulation. In fact, elevated levels of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α have been observed in the serum of RA and JIA patients (Vreugdenhil *et al.*, 1990; Yilmaz *et al.*, 2001). These cytokines are thought to stimulate resident cells in the synovium and the periodontium to produce MMPs mediating connective tissue destruction, and to induce the differentiation and activity of osteoclasts to destroy bone (Lotz *et al.*, 1995; McGee *et al.*, 1998).

One such cytokine in particular, TNF-α also promotes bone resorption:

(i) by up-regulating inducible nitric oxide synthase (iNOS) and the production of nitric oxide (NO) (Soory, 2002); and

(ii) by modulating the receptor activator of nuclear factor κB (NFκB) ligand (RANKL) in osteoblasts, and its antagonist osteoprotegerin (OPG), thus altering the RANKL/OPG ratio, which enhances osteoclasts activity (Hofbauer *et al.*, 2000; Haynes, 2004).

As a second example of our hypothesis, the evidence for an interaction between local inflammatory disease (periodontitis) and systemic osteoporosis has been strengthened by human clinical studies demonstrating a relationship among postmenopausal (PM) osteoporosis, tooth loss, and alveolar bone loss (Krall *et al.*, 1996). Golub and colleagues (1999), using a standard animal model of PM osteoporosis, the ovariectomized (OVX) aged rat, shed some light on potential pathways by observing increased MMP (collagenase and gelatinase) activity in the gingiva in response to ovariectomy and estrogen deficiency.[21] The increased gingival collagenase activity paralleled the increase in alveolar bone loss locally as well as trabecular bone density loss in the long bones systemically.

Finally, extensive literature published over the past several decades supports additional diseases, such as diabetes and cardiovascular disease (CVD), that share these links between biomarkers of systemic inflammation (C-reactive protein or CRP, plus other acute-phase proteins and cytokines such as IL-6 and TNF-α) and CDP. For example, Craig *et al.* (2003) reported that patients with CDP exhibited 100% higher levels of CRP in their serum than those with mild, less destructive periodontitis. Tonetti's group has also observed similar associations (D'Aiuto *et al.*, 2004). Ridker *et al.* (2002) and other cardiology groups have repeatedly demonstrated, in large-scale clinical studies, that CRP and other biomarkers, such as IL-6 and MMP-9 in plasma, are major predictors of future cardiovascular disease, including fatal heart attacks (Blankenberg *et al.*, 2003). In fact, our group recently reported that SDD, an MMP and cytokine inhibitory drug approved as adjunctive treatment for CPD, reduced these biomarkers of systemic inflammation (i.e., CRP, IL-6, and MMP-9) in the plasma of patients with cardiovascular disease [22] (Brown *et al.*, 2004).

In addition, experimentally inducing diabetes mellitus (e.g., by injecting a β-cell toxin such as alloxan or streptozotocin) in the rat has long been known to induce local biomarkers of periodontal breakdown (elevated production and activity of collagenase and gelatinase in gingiva, and severe alveolar bone loss), as well as systemic markers of both inflammation (elevated serum PGE2) and connective tissue breakdown

(elevated collagenase and collagen loss in skin, and skeletal osteoporosis). Similar changes have recently been seen in diabetic humans (Ryan *et al*., 2003).

The periodontopathic subgingival microflora, organized as a biofilm, provides one "hit" in the cascade of destructive events in chronic destructive periodontitis. An additional "hit" in this two-hit model is provided by a systemic inflammatory response (characterized by elevated biomarkers, such as CRP, IL-6, and MMP-9 in serum or plasma), induced by various medical disorders. Targeting both "hits" provides the optimal therapeutic strategy, with benefits for both the local periodontal and associated systemic medical diseases.

Current treatment approaches available to the periodontist and dentist include:

(i) antimicrobial therapy, including mechanical debridement and surgical reduction of probing depth to reduce the bacterial "load" in the periodontal pocket, combined (as needed) with topical and systemically administered antimicrobials; and

(ii) host-modulation therapy (using FDA-approved, MMP-inhibitor sub-antimicrobial-dose doxycycline by itself or, after confirmation by additional research, using other pharmaceuticals, such as non-steroidal anti-inflammatory drugs [NSAIDs] and bisphosphonates, or combinations of these).

Above all, assuming that this "two-hit" model is supported by future research, this concept could facilitate the incorporation of systemic/medical/pharmacologic treatment with the current mechanical/surgical approach in the management of chronic destructive periodontitis.

THE INFLUENCE OF DIABETES ON THE PERIODONTAL TISSUES

The pathogenesis of periodontal disease is complex because it reflects a combination of the initiation and maintenance of the chronic inflammatory process by a diverse microbial flora and its numerous bacterial products. The subsequent host response to this infection mediates a complex cascade of tissue-destructive pathways. Additional factors contributing to this multifaceted local disease process in the oral cavity include a number of systemic diseases, especially diabetes, that can exaggerate the host response to the local microbial factors (for example, endotoxin), resulting in unusually destructive periodontal breakdown **(Figure 2).**

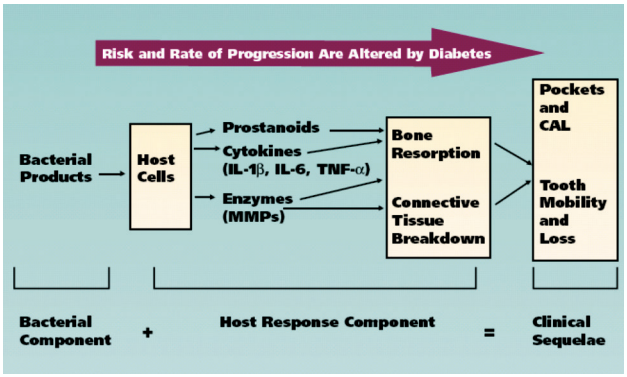

Figure 2. **Simplified schematic depicting etiologic factors and cascade of events contributing to periodontitis that are altered by diabetes. IL-1β: Interleukin-1 beta. IL-6: Interleukin-6. TNF-α: Tumor necrosis factor-alpha. MMPs: Matrix metalloproteinases. CAL: Clinical attachment loss.**

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MECHANISMS BY WHICH PERIODONTAL DISEASES MAY INFLUENCE DIABETES

Inflammation and Diabetes Mellitus

Inflammation is significantly pronounced in the presence of diabetes, insulin resistance and hyperglycemia. There is growing evidence that obesity has major pro-inflammatory effects, which cause chronic activation of the innate immune system and play an important role in alterations of glucose tolerance. Various studies have demonstrated the elevated production of inflammatory products in these patients and the association with other risk factors. Subclinical inflammation has been linked as a risk factor for cardiovascular disease. High serum levels of the acute-phase reactants fibrinogen and C-reactive protein have been found in people with insulin resistance and obesity. The inflammatory response in large vessels involves the upregulation of pro-inflammatory cytokines, such as tumor necrosis factor-α, interleukin-1, and interleukin- 6, and vascular adhesion molecules such as vascular cell adhesion molecule 1 and E-selectin. Proinflammatory cytokines amplify the inflammatory response, in part, by stimulating the expression of chemokines such as monocyte chemotactic protein 1 and macrophage inflammatory protein 1 that direct the migration of leukocytes into the vessel wall. Activation of interleukin-18 has been found to be involved in the pathogenesis of the metabolic syndrome. Interleukin-18 is a pleiotropic pro-inflammatory cytokine with important regulatory

functions in the innate immune response. Higher levels of inflammatory indexes and adhesion molecules are detected in patients with diabetes and coronary artery disease, compared with nondiabetic patients with coronary artery disease and healthy control subjects. These higher levels are implicated in the prognosis of cardiovascular disease. Patients with diabetes have elevated local arterial heat generation during coronary thermography, indicative of increased inflammation in the arterial wall, when compared to nondiabetic subjects.[23]

Insulin resistance is present in almost 70% of women with polycystic ovary syndrome. These women are often obese and hyperinsulinemia is considered to play a role in the hyperandrogenism (virilization) seen in these individuals. Polycystic ovary syndrome is a pro-inflammatory state as evidenced by elevated plasma concentrations of C-reactive protein, and low-grade chronic inflammation has been proposed as a mechanism contributing to increased risk of coronary heart disease and type 2 diabetes in these women. Obesity constitutes a low-grade chronic inflammatory state. An increased body mass index is associated with an increase in the size and number of adipocytes. Adipocytes have a high level of metabolic activity and produce large quantities of tumor necrosis factor-α and interleukin-6. In fact, about one third of the circulating level of interleukin-6 is produced in adipose tissue. Obese individuals have elevated production of tumor necrosis factor-α and interleukin-6, and these increases are important in the pathogenesis of insulin resistance. Tumor necrosis factor-α is the major cytokine responsible for inducing insulin resistance at the receptor level.

Tumor necrosis factor-α prevents auto phosphorylation of the insulin receptor and inhibits second messenger signaling via inhibition of the enzyme tyrosine kinase. Interleukin-6 is important in stimulating tumor necrosis factor- α production; therefore, elevated interleukin-6 production in obesity results in higher circulating levels of both interleukin-6 and tumor necrosis factor-α. The increased cytokine levels also lead to increased C-reactive protein production, which may impact insulin resistance as well.

Recent years have seen an increased appreciation of the role systemic inflammation plays in the pathophysiology of diabetes and its complications. Research is ongoing into the potential sources of elevated systemic inflammatory states, including the potential for inflammation in localized sites such as the periodontium to have widespread effects.

Periodontal Disease and Insulin Resistance

Inflammation has been suggested to cause increased insulin resistance.[24] To date, several molecules have been demonstrated to be responsible for inducing insulin resistance, e.g. tumor necrosis factor-α, resistin, and free fatty acid **(figure 3 & table 1).** Among these, tumor necrosis factor-α was found to be abundantly expressed in the adipose tissues of obese diabetic subjects. Mice lacking the tumor necrosis factor-α gene as well as its receptor do not develop insulin resistance even when they are fed a high-fat diet. Although tumor necrosis factor-α is one of the best-characterized inflammatory cytokines causing insulin resistance, several studies have reported that interleukin-6 also causes insulin resistance. Interestingly, interleukin-6 appears to selectively suppress insulin action in hepatocytes. Monocytes from diabetic subjects are pre-activated by hyperglycemia. These subjects tend to develop severe periodontitis as documented. Therefore, it is possible that periodontal infection

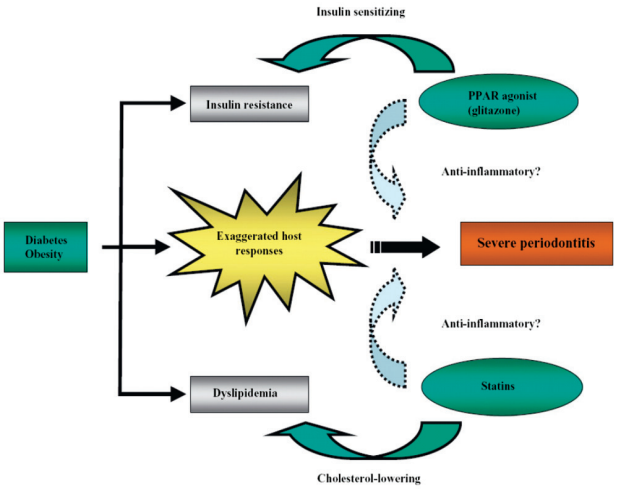

Figure 3. **Periodontal disease and insulin resistance**

Table 1. Role of Leader Genes in Periodontitis and Diabetes[26]

Gene symbol	Role in Periodontitis	Role in Diabetes
NFKBI	Increased activity beneath periodontal lesions	Probably related to microvascular complications resulting from the systemic inflammation process
RELA	Triggering of inflammation	Increased inflammation and oxidative stress
PIK3RI	Marker of severe inflammation	Control of metabolic actions of insulin
GRB2	Possible involvement in growth and differentiation in periodontal tissue, via EGFR/RAS Signaling	Control of metabolic and/or mitogenic actions of insulin, via EGFR/RAS Signaling
CBL	Possible involvement in bone resorption	Substrate of the insulin receptor kinase, activation of macrophages associated with insulin resistance

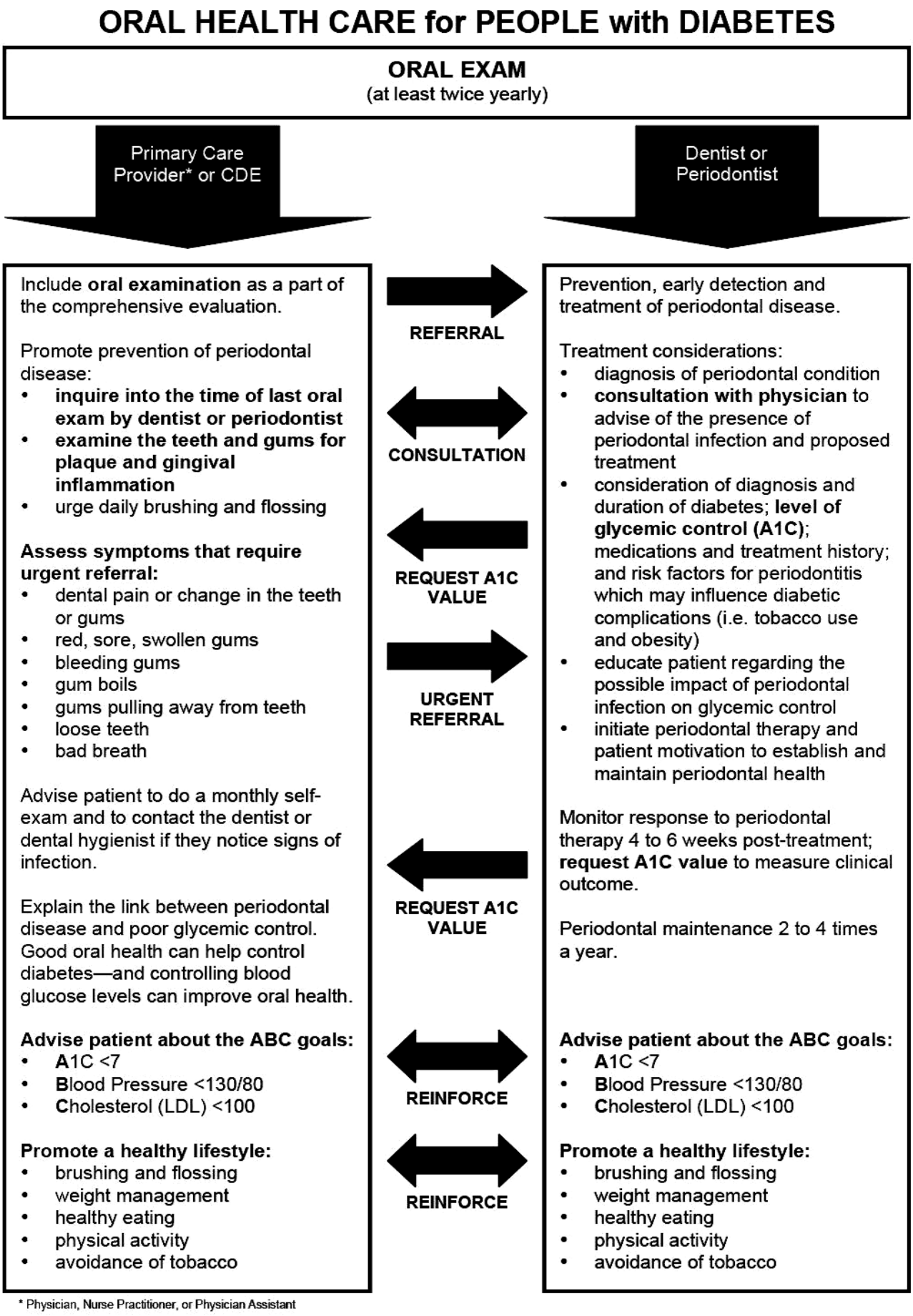

Figure 4. **Oral Health Care for People with Diabetes**

Table 2. Chart showing Periodontal Maintenance for Diabetic Patients

Patient Characteristics[a]	T3 ng/dl N=(62-179)	T4 µg/dl N=(4.5-12.5)
Diabetes well controlled		
Healthy Periodontium; no or minimal localized gingivitis	Record probing depths and bleeding score; deplaque	Annually
Healthy Periodontium, generalized gingivitis	Record probing depths and bleeding score	Annually
	Deplaque; OHI	Every 6 months
Chronic, mild to moderate periodontal disease	Record probing depths and bleeding score	Annually
	Deplaque; OHI	Every 3-4 months
Advanced attachment loss or aggressive (early onset) periodontal disease	Refer management to periodontist if possible	
	If referral not possible, monitor	Every 3 months
	Record probing depths and bleeding score	Annually
	Check probing depths and bleeding score; deplaque; OHI	At each visit
Diabetes poorly controlled		
Healthy periodontium; no or minimal localized gingivitis	Record probing depths and bleeding score	Every 6 months
	Deplaque: OHI	Every 6 months
Healthy peiodontium, generalized gingivitis	Record probing depths and bleeding score	Annually
	Deplaque: OHI	Every 4-6 months
Chronic, mild to moderate peiodontal disease	Refer if possible	
	If referral not possible, monitor	Every 3 months
	Record probing depths and bleeding score	Annually
	Check probing depths and bleeding score; deplaque; OHI	At each visit (every 3 months)
Advanced or aggressive peiodontal disease	Refer if possible	
	If referral not possible, monitor	Every 3 months
	Record probing depths and bleeding score	Annually
	Check probing depths and bleeding score; deplaque; OHI	At each visit

[a] Type 1 or type 2 diabetes
OHI = Oral hygiene Instruction

further stimulates circulating monocyte/macrophage as well as tissue-resident macrophages such as Kupffer cells. Activated circulating macrophages may be recruited to the adipose tissues as documented, and may express further increased amounts of tumor necrosis factor-α, resulting in increased insulin resistance in such subjects. Tissue-resident macrophages as Kupffer cells may also be activated by periodontal infection. Activated Kupffer cells express increased amounts of interleukin-6, leading to the stimulation of hepatocytes, which results in increased synthesis and secretion of acute-phase proteins such as C-reactive protein.[25] Activated Kupffer cells also express higher amounts of tumor necrosis factor-α, resulting in increased insulin resistance in the liver. Recently, mimicking chronic, subacute inflammation by low-level activation of nuclear factor-κβ in the liver of transgenic mice has been reported to cause insulin resistance both locally and systemically. Patients with severe periodontitis exhibit increased interleukin-6 and C-reactive protein levels, as compared with systemically and orally healthy controls. Additionally, these inflammatory markers as well as tumor necrosis factor-α levels decline with successful periodontal treatment. All these data support the fact that severe periodontal disease causes insulin resistance. The most probable target organ influenced by periodontal infection is hepatocytes, as it is well known that C-reactive protein is produced by hepatocytes. Circulating tumor necrosis factor- α may also cause insulin resistance in muscle cells and adipocytes as well. The role of circulating tumor necrosis factor-α on insulin resistance has also been reported in cases of gestational diabetes. Taken together, it is obvious that the reported beneficial effects of periodontal treatment on the metabolic control of diabetes are mediated by improved insulin sensitivity.

PERIODONTAL MANAGEMENT IN DIABETIC PATIENT

The dental practitioner is extremely likely to encounter periodontal patients who suffer from undiagnosed

or poorly controlled diabetes mellitus or others who are diagnosed and well maintained. More stringent medical standards have narrowed the criteria for good metabolic control, with the result that an increased number of periodontal patients may now fall into the inadequately controlled category. To properly evaluate periodontal patients, the dental clinician must be aware of the general and oral signs and symptoms of diabetes mellitus. Appropriate dental practice requires a thorough oral examination and an appropriate medical history. The medical history format must include questions patient's family history of diabetes mellitus and any general symptoms that may raise the practitioner's level of suspicion regarding this disease. The oral examination should identify oral features suggestive of diabetes mellitus, and the presence of any such features may indicate a need for medical consultation.[27]

CONCLUSION

Therapeutic surgery is a frequent requirement for diabetic patients and in the past has been associated with increased morbidity and mortality. Recent outcomes data are lacking, but it is likely that advances in surgical science, anesthesiology, and intensive care medicine, together with increased awareness and appropriate metabolic intervention, may have improved the perioperative fate of diabetic patients in recent times. Clinicians are encouraged to continue to give careful attention to metabolic control in surgical patients with diabetes.[28]

Diabetic patients who require surgery present special challenges in perioperative management. Special attention must be paid to prevention and treatment of metabolic derangements. Vigilance for the development of acute complications that lead to higher rates of surgical morbidity and mortality is also critical. Establishing effective measures during diagnosis, prognosis and treatment of patient having periodontal disease with diabetes will help in minimising the complications that may arise due to the depilating nature of the disease **(figure 4 & table 2).**

END NOTE

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