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Review Article

Effect of Periodontal Intervention on Metabolic Control of Diabetes Mellitus

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Abstract

The diabetic patient, being at a greater risk of developing periodontitis due to impaired immune responses, may not respond as well to periodontal therapy as a non-diabetic patient. A hypothesis on the basis of a direct inflammation theory in linking oral disease to systemic health is that serum levels of inflammatory mediators that cause insulin resistance may be reduced through periodontal therapies, which may improve glycemic control.

Keywords: *Diabetes Mellitus; Periodontal Diseases; Glycemic Control; Insulin Resistance*

Introduction

More research is emerging that suggests a bidirectional relationship between both types of diabetes mellitus and periodontal disease: the body responds to severe periodontitis with an increased blood glucose level, while periodontitis makes it more difficult for the diabetic to control their blood glucose level. It is accepted that the removal of periodontal pathogens can slow or arrest the progression of periodontitis by reducing local inflammation. However, the diabetic patient, being at a greater risk of developing periodontitis due to impaired immune responses, may not respond as well to periodontal therapy as a non-diabetic patient. An hypothesis on the basis of a direct inflammation theory in linking oral disease to systemic health is that serum levels of inflammatory mediators that cause insulin resistance may be reduced through periodontal therapies, which may improve glycemic control [1].

A conclusive meta-analysis by Janket., *et al*. revealed that periodontal treatment does not affect glycemic control by reducing A1c levels in diabetic patients, but recognized that the study designs impacted on the results. The variety of periodontal treatments (non-surgical with and without antibiotics) and unbalanced population samples (type 1, type 2 or mixed) lend to conflicting results, and it was therefore strongly recommended that further studies, possibly restricted to type 2 diabetics not on insulin regimens, could more accurately demonstrate the significant effects of periodontal therapies on glycemic controls in diabetics [1].

Further rigorous and controlled studies of the treatment of periodontal disease in diabetics are needed to confirm the extent to which treatment enhances glycemic control. However, there is evidence that well-controlled diabetics respond to periodontal therapies similarly as non-diabetics and diabetics continually challenged may have a less favourable outcome over the long term [1].

Effects of periodontal treatment on clinical periodontal parameters, systemic mediators, and glycaemic control were evaluated in well or poorly-controlled type 2 diabetic as well as systemically healthy periodontitis patients. The poorly-controlled diabetic group exhibited significantly decreased HbA1c levels 3 months after completion of non-surgical periodontal treatment. Increased adiponectin levels may at least partially explain the significant improvement in glycaemic control by non-surgical periodontal treatment in the DM group. These findings corroborate the previous studies demonstrating significant improvements in HbA1c levels and clinical periodontal parameters following non-surgical periodontal treatment [2].

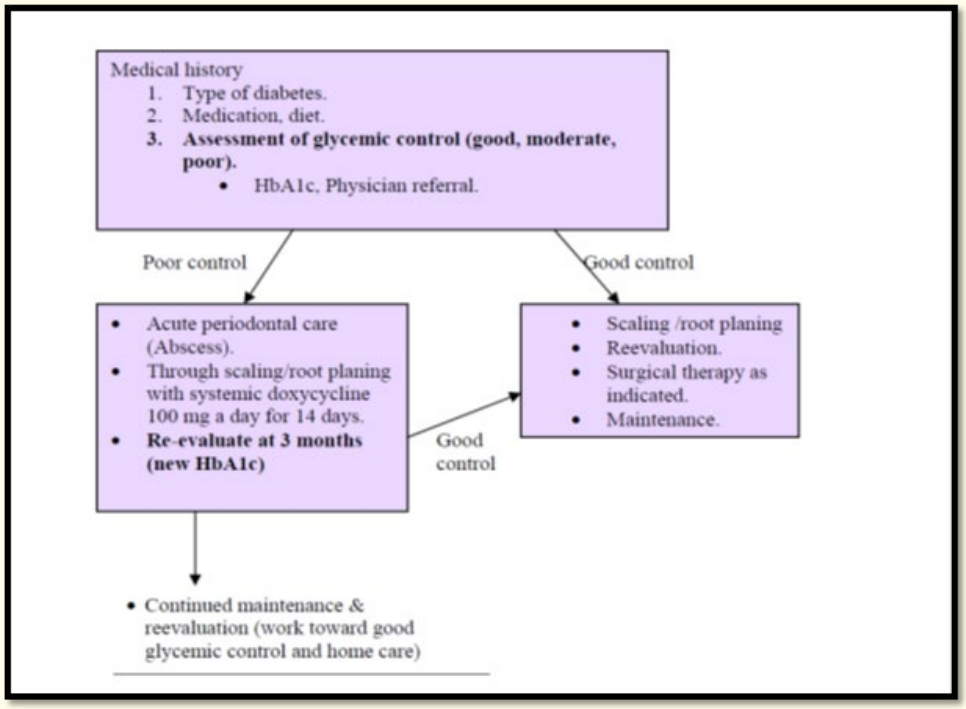

Figure 1: *Pathway of periodontal therapy for patients with diabetes mellitus (Rees and Mealey 2004).*

Almost no change in the HbA1c percentage in the well-controlled diabetics with non-surgical periodontal treatment in contrast to the significant improvement in the poorly-controlled diabetics has been reported. This may be regarded as further proof of the beneficial effects of periodontal treatment in the glycaemic control of type 2 DM. While their current medical therapies are efficient in the well-controlled diabetics, the 1.5% improvement in glycaemic control of the poorly-controlled diabetics with periodontal treatment may correspond to significant improvement in general health. It may be suggested that the deeper the baseline peritoneal dialysis is, the longer follow-up period is required for proper periodontal healing as well as significant decrease in HbA1c level. The risk of diabetic complications was strongly associated with previous hyperglycaemia in type 2 diabetics and any reduction in HbA1c is likely to reduce the risk of complications. Therefore, periodontal treatment may be regarded as a means of reducing HbA1c levels, eventually helping the overall management of diabetic patients [2].

In a study reporting better HbA1c levels in people with better tooth brushing self-efficacy, it was suggested that motivation and instruction on better oral hygiene is important in diabetic patients especially those with poor metabolic control. The importance of prevention of oral diseases for a better systemic health was also emphasised recently. Poorly-controlled diabetics have been reported to exhibit significant reductions in probing depth, peritonitis incidence (PI), and bleeding on probing (BOP) following mechanical periodontal treatment. Higher PI and BOP levels have been reported in poorly-controlled diabetics, 1 and 3 months after periodontal treatment compared to baseline. Poor glycaemic control was suggested to have contributed to higher BOP scores in the poorly controlled group. It is likely that microvascular changes due to prolonged hyperglycaemia create a tendency for bleeding in these patients despite the similar plaque scores with the well-controlled group [2].

Increased serum levels of proinflammatory cytokines like TNF-α, IL-6, C reactive protein (CRP), and sICAM-1 may play a role in insulin resistance and deteriorate glycaemic control in diabetic patients. Such an increase in serum levels of inflammatory cytokines may be one

of the mechanisms by which infection by Gram-negative bacteria promotes atherosclerosis in diabetic patients. Intervention trials suggest that periodontal therapy, which decreases the intraoral bacterial bioburden and reduces periodontal inflammation, can have a significant impact on systemic inflammatory status [2].

Reports suggest that periodontal therapy is associated with improved glycaemic control in many patients with both diabetes mellitus and periodontal diseases. TNF-α, IL-6, CRP, and sICAM-l concentrations tended to decrease in the poorly-controlled diabetics following periodontal treatment. These decreases may at least partially explain the significant improvement in HbA1c level. Recently, the possibility of a direct relationship between the severity of periodontitis and diabetic complications has been discussed in a workshop and it was concluded that moderate to severe periodontitis is associated with increased risk for macroalbuminuria, end-stage renal disease, calcification of atherosclerotic plaques, carotid intima-media thickness and cardio-renal mortality.

Moreover, the participants with the most severe periodontitis at baseline exhibited approximately 5-fold greater increase in HbA1c levels over 5 years, and they suggested that severe periodontitis predicts the progression of DM [2].

Non-diabetic patients had more healthy sextants and diabetic patients showed a higher variability in salivary-IgA levels as compared with non-diabetic patients. Serum levels of high-sensitivity CRP, TNF-α, IL-6, fasting plasma glucose, HbA1c, fasting insulin decreased and adiponectin increased 3 months after periodontal treatment in type 2 DM patients and periodontal treatment may improve glycaemic control, lipid profile, reduce serum inflammatory cytokine levels, and increase serum adiponectin levels in poorly controlled type 2 DM patients. Levels of high-sensitivity CRP and stem cell factor in serum and gingival crevicular fluid were reported to be increased in patients with periodontitis and DM [2].

Figure 2: A-Periodontal condition of a type 2 DM patient with uncontrolled diabetes mellitus
B- Same patient 3 months after extraction of hopeless teeth and periodontal treatment.

Periodontal Intervention and A1c

All studies reported absolute changes in A1c as parameter of metabolic control. Four of the five studies reported mean differences between baseline and end of trial with or without SDs [3]. Two of the five studies showed a significant improvement in metabolic control after periodontal treatment as measured by a significant decrease in A1c levels compared with that in the untreated control group. A multiple regression analysis in the study by Katagiri., et al. [4] for significant variables associated with changes of A1C levels between baseline and 6 months showed that the A1C decrease correlated with decreases in high-sensitivity CRP (hs-CRP) levels after periodontal treatment ($P \leq 0.03$) [4]. Based on this analysis, Katagiri., et al. divided the intervention group into CRP-decreased and CRP-unchanged groups. This sub analysis showed that A1c levels decreased significantly in the CRP-decreased group compared with baseline levels, but not in the CRP-unchanged group [4].

Periodontal Intervention and Other Parameters of Glycemic Control

Three studies also reported change in fasting plasma glucose (FPG) as parameter of metabolic control, and two studies showed a non-significant decrease in FPG after periodontal treatment compared with that in the control group (I-C ≤ 5.18 mg/dl, I-C ≤ 3.83 mg/dl). Notably, Katagiri., *et al*. showed a non-significant deterioration of metabolic control as reflected by a non-significant increase in FPG after periodontal treatment compared with that in the control group (I-C ≤ 22 mg/dl) [4]. In addition, Kiran., *et al*. showed a significant decrease of 2-h postprandial glucose (PPG) levels after periodontal therapy compared with baseline levels of the treatment group [5]. However, compared with that in the control group, the decrease in 2-h PPG levels was not significant.

Impact of Periodontal Therapy on Diabetic Status

The results from the earliest treatment studies are limited as they were conducted within the Pima Indian group or because of inadequate controls between groups for possible confounding variables such as age, body mass index (BMI), alcohol consumption, health motivation and behaviour, psychosocial stressors and smoking. A small sample size and/or a short follow-up time further limit the conclusions that can be drawn from some individual studies. An example of this is a study in which 13 well-controlled (HbA1c < 7 %) and 12 poorly controlled (HbA1c > 7 %) participants with type 2 diabetes mellitus and periodontitis and 15 healthy patients with periodontitis received periodontal treatment, and HbA1c decreased significantly in the poorly controlled group only, three months post-therapy. These results are similar to an earlier treatment study of 44 type 2 diabetes mellitus people re-examined after three months. Conflicting reports found a more beneficial effect of periodontal therapy on HbA1c in well-controlled diabetes mellitus patients [6].

In a larger group of 165 US veterans with poorly controlled type 2 diabetes mellitus, the group that received periodontal therapy was less likely to need an increase in insulin over four months compared with those who did not receive periodontal care. Longer follow-up periods have been employed; a small treatment study in a type 2 diabetes mellitus group (n = 10) and non-diabetes mellitus group (n = 10) reported a reduction in HbA1c within the diabetes mellitus group at six-month follow-up. The removal of all teeth and inevitable resolution of periodontitis in a type 2 diabetes mellitus group with advanced periodontitis, led to a reduction in HbA1c from 8.6 to 7.3 % after six months compared with a matched group (no treatment) in which HbA1c reduced from 7.7 to 7.5 %. However, baseline differences in HbA1c between the groups may have influenced the results. Indeed, the problem of unbalanced randomisation in which control groups had better glycaemic control at baseline was highlighted in a meta-analysis of studies conducted to January 2005. Many subsequent studies have addressed this issue [6].

In a recently published Australian randomised controlled trial (RCT), 40 people with type 2 diabetes mellitus and chronic periodontitis were matched for gender, age, periodontal and biochemical parameters (including HbA1c) and after three months HbA1c decreased in only the treatment group [6].

Another RCT assigned the 60 type 2 diabetes mellitus participants into either a periodontal treatment arm or a delayed treatment arm that received periodontal care after six months. Baseline matching for HbA1c and other confounding variables was again achieved and HbA1c levels decreased significantly more in the intervention group versus the control group. There has not been a universal improvement in fasting glucose or HbA1c within treatment studies with a few studies showing little or no improvement in glycaemic control after periodontal therapy. These conflicting results and the problem of low power within individual studies has been addressed with meta-analysis studies and a 2005 meta-analysis of 10 intervention studies reporting a weighted mean reduction in HbA1c of 0.66% in diabetes mellitus patients following periodontal therapy, although this reduction did not reach statistical significance. A second meta-analysis conducted in 2009 included 371 type 2 diabetes mellitus participants and demonstrated a weighted mean difference of HbA1c before and after therapy of -0.40%. The Cochrane Collaboration has recently reported on three studies deemed suitable for meta-analysis and also reported a mean HbA1c reduction of 0.40%, 3 - 4 months after periodontal therapy [6].

Type 1 Diabetes Mellitus

Most studies have concentrated on the relationship between type 2 diabetes mellitus and periodontitis as early studies highlighted a reciprocating relationship between these conditions. A study published in 2011 examined the effects of intensive periodontal therapy on HbA1c in 93 participants with either type 1 or type 2 diabetes mellitus and moderate periodontitis. One group received intensive periodontal therapy (IPT, n = 44) and the other received conventional periodontal therapy (CPT, n = 49) with an eight-month follow-up. After eight months, the IPT group presented with a significantly greater reduction in HbA1c than the CPT group and the difference in HbA1c was greater in individuals with type 2 diabetes mellitus compared with those with type 1 diabetes mellitus. Therefore, periodontal therapy appears to be more successful in improving glycaemic control in type 2 diabetes mellitus [6].

Impact of Periodontal Treatment on Systemic Inflammatory State and Glycemic Control

Periodontal treatment that reduces periodontal inflammation may help to restore insulin sensitivity, thereby improving glycemic control. Intervention studies showing a decrease in the level of systemic inflammatory markers and improved glycemic control following periodontal therapy would support such a hypothesis [7]. Studies of patients with both diabetes mellitus and periodontitis have shown that nonsurgical periodontal therapy with adjunctive local delivery of minocycline reduced circulating levels of TNF-α. In one of those studies, the reduction in serum levels of TNF-α was accompanied by, and strongly correlated with, a significant decrease in mean HbA1c values (from 8% to 7.1%). Conversely, a pilot study showed that serum levels of TNF-α were not significantly affected 4 weeks after mechanical periodontal therapy [8].

In the same study, systemic levels of mediators such as CRP and soluble E-selectin were significantly reduced following nonsurgical periodontal debridement. Outcomes of a meta-analysis of 10 intervention trials involving 456 patients with diabetes mellitus (type 1 or type 2) showed that following mechanical periodontal debridement, HbA1c levels decreased by an average of 0.38% over all studies, by 0.66% among patients with type 2 diabetes mellitus and by 0.71% among cases in which antibiotics were administered. However, none of these changes were statistically significant. A recent single-blind, randomized controlled trial confirmed the results of the meta-analysis, showing that periodontal therapy combined with diabetes mellitus medication had no statistically significant effect on levels of HbA1c relative to no treatment [8].

Other studies have shown significant improvements in glycemic control with periodontal therapy. These conflicting data are difficult to interpret because of the wide range of medical treatment regimens used in study populations, inadequate sample sizes, combined enrolment of patients with type 1 and type 2 diabetes mellitus, confounding by smoking and BMI, and study design (e.g., studies examining only short-term outcomes or pilot studies). Although the 0.7% improvement in HbA1c levels attributed to mechanical periodontal debridement and antibiotic therapy reported in the meta-analysis was not statistically significant, its clinical significance should not be minimized, given that the less potent class of oral glucose-lowering agents, the α-glucosidase inhibitors, reduces HbA1c level by 0.5% to 1%.

Other classes of oral agents, such as insulin secretagogues, biguanides and thiazolidinediones, as well as nutritional therapy and physical activity, improve glycemic control to a similar degree, with 1% to 2% reduction in HbA1c. Therefore, since periodontal treatment appears to have the same power to lower HbA1c as other glucose lowering therapies, it may represent an alternative or adjunctive therapy for improving insulin sensitivity and glycemic control in patients with both type 2 diabetes mellitus and periodontitis [8].

Effect of Periodontal Therapy on Glycemic Control

There are contradictory opinions in the literature concerning the appropriate time for assessing the healing response to nonsurgical periodontal therapy. Morrison., et al. and Lowenguth and Greenstein suggested a period of 1 month. Badersten., et al. found that in periodontal pockets of 4.7 mm depth most changes occur in the first 4.5 months, while in deep pockets up to 12 mm, a gradual improvement takes place over a period of 12 months. In this study, the response was evaluated after 3 months as the majority of patients showed a mean probing pocket depths around 3 mm. Patients were recalled and assessed at the end of 1 month to evaluate the response to periodontal

therapy and oral hygiene maintenance. In our study, the majority of the patients showed satisfactory oral hygiene maintenance after receiving the oral hygiene instructions. No change in the oral hygiene maintenance was seen in the control group. The results of this study show that the decrease in plaque index and gingival index were comparable in the two treatment groups [9].

As expected, there was no improvement seen in the control group. The mean probing pocket depth and clinical attachment levels also improved significantly in the treatment groups (group A and group B) compared to control group (group C). The good response of diabetics to nonsurgical therapy in the present study confirms the results of previous investigations. The results of this study suggest that following periodontal therapy there is a statistically significant improvement in glycemic control in individuals with type 2 DM when compared with a control group. At baseline, metabolic-matched diabetic patients showed similar levels of plaque accumulation, gingival inflammation, and periodontal breakdown. Fasting plasma glucose and 2-h postload plasma glucose are considered important tests for the diagnosis of diabetes mellitus [9].

In a patient with diagnosed diabetes mellitus, the HbA1C level is used to monitor the patients overall glycemic control. HbA1C reflects the mean glucose level over the preceding 2.3 months. Thus, the intervals between two consecutive HbA1C tests should be at least 2 months if any relevant changes are to be observed. There was a decrease in both fasting blood glucose and 2-h postprandial blood glucose levels in our treatment groups compared to control groups but this decrease was not significant. The significant finding of this study is the improvement in the glycated hemoglobin levels seen in the treatment groups. A more important finding is the significant change in glycated hemoglobin levels seen in group B (which received periodontal therapy and systemic doxycycline) compared to group A (which received only periodontal therapy).

This finding is in agreement with the studies by Grossi., *et al*., Miller., *et al.* and Iwamoto., *et al.* In contrast, previous studies involving periodontal treatment alone reported improvement in periodontal status only. Certain studies, like that done by Stewart., *et al.* reported a decrease in the levels of HbA1C following nonsurgical therapy of periodontitis in type 2 DM patients [9]. They also showed improvement in HbA1C levels in the control group. The authors suggest that this was possibly due to change in diabetic control in some patients. For this reason, in our present study, we did not attempt to change the diabetic control of our patients by giving any additional instructions for control of blood glucose levels. In an another study by Kiran., *et al.* there was statistically significant difference seen in HbA1C levels in the treatment group which received only scaling and root planing [9].

Here the controls were well matched and they did not show any improvement in metabolic control. The study only included patients with moderate periodontitis and the authors concluded that the improvement in HbA1C levels were due to the improvement in the gingival condition. Our study incorporates two treatment groups to compare the effect of systemic doxycycline plus scaling and root planing to scaling and root planing alone. The results of this study clearly show that patients in group B, which received adjunctive antimicrobial therapy, showed a better improvement in periodontal and metabolic parameters. A study by Iwamoto., *et al.* concluded that antimicrobial periodontal therapy reduces circulating TNF-α, which subsequently reduces circulating insulin concentration and HbA1C level. They also stated that continuous infusion of bacterial lipopolysaccharides and/or TNF-α induces severe insulin resistance in a rat model. Thus, periodontal disease may exacerbate insulin resistance in diabetic patients [9].

Dental Management of Diabetes Mellitus [10]

When a dental treatment is going to be performed, some considerations must be taken into account. These would be appreciably different depending on the type of diabetes mellitus suffered. In this paper, we analyze type 1 and 2 diabetes mellitus, the most prevalent forms.

Type 1 diabetic patients undergoing a dental procedure

Follow the considerations previously described

Non- invasive dental procedures: Well- controlled patients can be treated similarly to nondiabetic individuals. Be aware of the increased susceptibility of these patients to infections and delayed wound healing. In poorly controlled patients, delay the dental treatment if possible until they have achieved good metabolic control.

Invasive dental procedures: Patients should ask their doctor for instructions concerning their medication (normally, if they have metabolic stability, they should take half their daily dose of insulin the morning of the treatment; then, after the intervention, the whole dose should be taken with a supplement of rapid-acting insulin). Blood glucose should be measured preoperatively. If it is between 100 and 200 mg/dl, the invasive dental procedure can be performed. If blood glucose is > 200 mg/ dl, an intravenous infusion of 10% dextrose in half- normal saline is initiated, and rapid- acting insulin is administered subcutaneously. If the treatment lasts more than 1 hour, blood glucose should be measured hourly. If blood glucose is >200 mg/ dl, rapid acting- insulin should be administered subcutaneously.

Type 1 DM is considered a risk factor with regard to suffering infection. For that reason, when invasive dental procedures are going to be performed (as intra ligamentous anaesthesia, teeth extractions, biopsies, etc.), the usual guidelines for the antibiotic prophylaxis should be followed [10].

Type 2 diabetic patients undergoing a dental procedure

Follow the considerations previously described

Non- invasive dental procedures: people who control their disease well by diet and exercise require no special perioperative intervention. As in type 1 diabetic patients, be aware of their susceptibility to infections and delayed wound healing. In poorly- controlled patients, delay the dental treatment if possible until they have achieved good metabolic control.

Invasive dental procedures: patients should ask their doctor for instructions regarding their medication (normally, those patients being treated with oral hypoglycaemic agents should take their normal dose in the morning and eat their regular diet) [10].

Acute Complications [10]

Hypoglycemia is the major issue that confronts dental practitioners when treating diabetic patients, particularly if patients are fasting. The clinical presentation of hypoglycemia is very similar to hyperglycemia. If in doubt, it should be treated as a hypoglycemia. The characteristics and treatment of this complication are showed in table 1. Hypoglycemia usually appears in response to the stress experienced before, during or after the treatment, and has been shown to cause a significant increase in perioperative morbidity and mortality. The stress response is characterized by acute metabolization of carbohydrates, proteins and fats to provide increased levels of glucose, which is necessary as a major fuel source to the vital organs. In addition, resistance to the effects of insulin increase. There are no specific guidelines regarding which levels of hyperglycemia are dangerous or how it should be managed before or during the procedure, so if the patient is conscious and can follow other instructions, it is prudent to continue with the treatment.

Criteria for the Diagnosis of Diabetes		
Measurement	**Diagnostic Values for Diabetes**	**Characteristics**
Glycosylated hemoglobin (HbA1c)	≥ 6.5%	The test should be performed in a laboratory using the standarized method. It reflects average blood glucose levels over a 2- to 3-month period of time
Fasting plasma glucose	≥ 126 mg/dl (7.0 mmol/l)	Fasting is defined as no caloric intake for 8 hours
Postprandrial plasma glucose (2 hours after caloric intake)	≥ 200 mg/dl (11.1 mmol/l)	The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water
Random plasma glucose	≥ 200 mg/dl (11.1 mmol/l)	

Table 1: *Criteria for the diagnosis of diabetes mellitus (ADA 2010).*

Chronic Complications [10]

The possible cardiovascular complications of diabetes mellitus should be properly assessed before dental treatment. Autonomic neuropathy can predispose to orthostatic hypotension, respiratory arrest or hemodynamic instability. If the patient has renal complications, a dose adjustment of the drugs should be performed, using the creatinine clearance. It is recommended to associate antibiotic treatment when mechanical periodontal treatment is performed, and also administers an antibiotic prophylaxis. Osteoporosis present in type 1 DM requires great care when performing surgery, in order to prevent iatrogenic fractures. Due to the delayed healing response in diabetic patients, implant therapy is still controversial and at the moment, there is a lack of definitive guidelines. In any case, these individuals could be candidates for the placement of dental implants if they have good control of their metabolism. There is general agreement in advocating the use of prophylactic antibiotics in diabetic patients [10].

Identification and Treatment of Hypoglycemia	
Identification	
Symptoms	**Signs**
• Shakiness • Anxiety • Increased sweating • Hunger	• Tremors • Tachycardia • Altered consciousness (lethargy and obtundation or personality change) • Blood glucose level: < 60 mg/dl
Treatment	
Conscious patient	**Unconscious patient**
• Administer 15 mg of simple carbohydrates • Repeat finger- stick glucose test in 15 minutes: • Blood glucose level > 60 mg/dl: patient should be asked to eat or drink (for example, a sugar-sweetened beverage) • Blood glucose level < 60 mg/dl: repeat treatment of 15 g of simple carbohydrates and check blood glucose in 15 minutes. Continue until achieving a blood glucose level > 60mg/ dl • Ask the patient to notify his/ her physician.	**With intravenous access:** • Administer 5 to 25 g of 50% dextrose immediately • Notify the patient's physician **Without intravenous access:** • Apply glucose gel inside the mouth in a semiobtund patient or treat with 1 mg of glucagon intramuscularly or subcutaneously • Repeat the blood glucose test in 15 minutes • Establish intravenous access and notify the patient's physician

Table 2: *Identification and treatment of hypoglycaemia in the dental office.*

Conclusion

There was a decrease in both fasting and post prandial blood glucose level in treatment groups compared to control groups even though it is not significant. There was an improvement in glycated hemoglobin levels.

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