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REVIEW ARTICLE

Implants in Diabetic Patients

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ABSTRACT

Diabetes mellitus has become a public health problem because of its increased prevalence all over the world. Diabetes is associated with altered glucose homeostasis. Diabetics have impaired wound healing and impaired bone metabolism. Safely managing the patient with diabetes requires effective communication among multiple health care providers. Although implants are increasingly used in healthy patients, their appropriateness in diabetic patients is less equivocal. Perhaps surprisingly, the evidence of their efficacy in these groups of patients is quite sparse. It is known to impair healing which increases the risk of tissue necrosis and infection. Improvement in glycemia levels in previous studies are well suited to dental implant surgery with acceptable degree of predictability. This article review the implications of diabetes and glycemic control for the prognosis and evolution of dental implants.

Keywords: Implant, Hyperglycemia, Osseointegration, Diabetes, Wound healing, Bone metabolism.

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INTRODUCTION

Diabetes mellitus is defined as a metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism resulting from defects in insulin secretion, insulin action, or both. The World Health Organization (WHO) defines diabetes as a 'chronic, debilitating and costly disease associated with severe complications, which poses severe risks for families, countries and the entire world'. The clinical diagnosis of diabetes is often indicated by the presence of symptoms such as polyuria, polydipsia and unexplained weight loss, and is confirmed by measurement of abnormal hyperglycemia. The WHO advises that the range of blood glucose indicative of diabetes mellitus is as follows:[1]

1. Fasting venous plasma glucose (FPG) ≥7.0 mmol/l or
2. Venous plasma glucose ≥11.1 mmol/l at two hours after a 75 gm oral glucose load [oral glucose tolerance test (OGTT)]. According to Diabetes Atlas published by the International Diabetes Federation (IDF), there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. Diabetes has sometimes been considered a contraindication for the use of dental implants. The 1988 National Institute of Health Consensus Development Conference Statement on Dental Implants stopped short of explicitly stating this, but did include 'debilitating or uncontrolled disease' and 'conditions, diseases, or treatment that severely compromise healing' within its list of contraindications for dental implants. Since 1982, the worldwide market for dental implants has grown to approximate $450 million. Chronic complication of diabetes and oral manifestations of diabetes (Tables 1 and 2).

Classification of Diabetes

Diabetes is classified as types I and II.

Type I diabetes mellitus is an autoimmune disease affecting the beta cells in the pancreas that produce insulin, thus making it necessary to use exogenous insulin to ensure survival and prevent or delay the chronic complications of this illness.[2]

Type II diabetes mellitus, on the other hand, is a multifactorial disease resulting from environmental effects on genetically predisposed individuals and is related with obesity, age and a sedentary lifestyle. In these patients, there is a defect in the secretion of insulin together with a greater or lesser degree of insulinopenia. The treatment of type II

Table 1: Chronic complication of diabetes

Microvascular complication	*Macrovascular complication*	*Others*
1. Retinopathy	1. Ischemic heart disease	1. Dermatological
2. Nephropathy	2. Peripheral arterial disease	2. Rheumatological
3. Neuropathy • Peripheral • Autonomic	3. Cerebrovascular disease	3. Hepatic
4. Erectile dysfunction		
5. Periodontal disease		

Table 2: In the oral cavity, diabetes is commonly associated with oral signs and symptoms

• Burning mouth syndrome
• Candidiasis
• Dental caries
• Gingivitis
• Glossodynia
• Lichen planus
• Neurosensory dysesthesias periodontitis
• Salivary dysfunction
• Taste dysfunction
• Xerostomia

diabetics includes, in stages, measures relating to their diet and lifestyle, oral hypoglycemic drugs either alone or in combination and insulin.[3]

In both types I and II diabetes, the therapeutic goal focuses on maintaining blood glucose at normal or near-normal levels. Glycated hemoglobin (HbA1c), reflects average plasma glucose over the previous 2 to 3 months in a single measure, which can be performed at any time of the day and does not require any special preparation such as fasting, has made it a key measure for assessing glycemic control in people with established diabetes. In 2006 the WHO considered HbA1c as a candidate diagnostic tool for diabetes.

Consequences of Increased Blood Glucose Levels

If the high concentrations of extracellular glucose found in diabetes mellitus are allowed to persist, then glucose will covalently bond to macromolecules in the body. Over time, these bonds become irreversible and form advanced glycosylation end products, which inhibit normal organ function by depositing in unwanted areas, leading to nephropathies, neuropathies and retinopathies. Other pertinent comorbidities associated with diabetes include delayed wound healing and altered bone metabolism,[4] as well as microvascular abnormalities. Such issues associated with diabetes may complicate or contraindicate implant surgery. Although there has been some conflicting evidence, diabetic patients seem to be more prone to infection.[5] Healing after surgery in the diabetic patient seems to occur more slowly, exposing the tissues to complications such as tissue necrosis. Furthermore, animal studies indicate that streptozotocin-induced diabetes interferes with the process of osseointegration.[6] Periodontal disease, affects both patients with types 1 and 2 diabetes mellitus, by a factor of 3 to 4 times.[5]

Wound Healing in Diabetics

The pathophysiologic relationship between diabetes and impaired healing is complex. Vascular, neuropathic, immune function and biochemical abnormalities each contribute to the altered tissue repair.[7,8] These deficiencies can complicate the body's acceptance of an implant. There are reports of decreased or impaired growth factor production (Table 2) and decreased neutrophil and macrophage function and significant diminution in intracellular bactericidal activity in subjects with poorly controlled diabetes compared with healthy controls.[9] Complement proteins play an important role in the innate immune system. Serum complement-mediated bactericidal activity was impaired in type 2 diabetic patients, which might be a cause for delayed wound healing and repeated infections. Diabetic patients exhibit decreased and less organized granulation tissue formation, poor angiogenic response, and altered collagen. Studies involving PMNLs in diabetic patients have reported abnormalities in the adherence, chemotaxis, phagocytosis, oxidative properties and intracellular killing of these cells. Reportedly, PMNL chemotaxis is significantly lower in diabetic patients even after stimulation when compared to controls. In addition, PMNL phagocytotic and killing capacity has been found to be lower in diabetic patients, leading to a poorer ability to fight off infection. Diabetic monocytes also exhibit both impaired chemotaxis and phagocytosis most likely resulting from an intrinsic monocyte defect.[10]

Alteration in growth factors and cytokine functions are shown in Table 3.

Effect on Bone Metabolism

Studies in bone histomorphometry in type 1 diabetes have generally, but not always, shown a low turnover of bone with reduction in bone formation and, to a lesser degree, bone resorption. The decrease in bone formation is manifested by reduced serum concentrations of osteocalcin, a marker of osteoblastic activity. In comparison, resorption markers (such as serum tartrate resistant acid phosphatase and urinary hydroxyproline) are increased in some patients, perhaps related to alterations in renal function[6] (Table 4).

Results of Osseointegration of Implants in Experimental Models of Diabetes

The effect of diabetes on implants has revealed an alteration in bone remodeling processes and deficient mineralization, leading to less osseointegration.

In experimental models of diabetes, the normoglycemia levels obtained by treatment with insulin brought about growth in bone matrix and formation of osteoid similar to control subjects.[11]

Table 3: Alteration in growth factors and cytokine functions

Cytokines and growth factors	*Normal role in wound healing*	*Expression in diabetic wound healing*
IGF-1	Promotion of re-epithelialization Keratinocyte and fibroblast proliferation Endothelial cell activation	Decreased
TGF-B1	Chemoattractant (keratinocyte, fibroblast, inflammatory cells) ECM deposition Promotes angiogenesis	Decreased
PDGF	Fibroblast proliferation ECM deposition Promotes angiogenesis MMP synthesis	Decreased
EGF	ECM deposition Keratinocyte migration and proliferation	Decreased
IL-8	Keratinocyte proliferation Macrophage chemotaxis Neutrophil chemotaxis	Decreased
Angiopoietin-2	Disrupts blood vessel formation	Increased

Table 4: Effect of hyperglycemia on bone metabolism

Hyperglycemia		
Osteoblasts	*Osteoclastas*	*Osseous factors*
↓ Proliferation ↓ Matrix formation ↓ Osteocalcin	↑ Cell recruitment ↑ Cell differentiation ↑ Osteocalcin	↑ Cytokines (IL-1b,6,8,TNFα) ↑ PGE2

Although, the amount of bone formed is similar when comparing diabetes-induced animals with controls, there is a reduction in the bone-implant contact in diabetics.[12,13]

Clinical and experimental studies show, with few exceptions, that type 1 diabetes mellitus is associated with a delay in bone repair around endosseous implants. The effect of insulin in bone repair/remodeling is not completely understood.

A study was done to investigate the influence of local infiltration of insulin at the implant-bone interface after implantation in type II diabetic rats. Implant-bone contact, osteoid and osteogenic volume and the amount of newly formed bone in the diabetes mellitus group were significantly less than in the control group without diabetes mellitus. Implant-bone contact in the insulin group was less than that in the control group, but the amount of newly formed bone was greater. Therefore, although the implant-bone contact in the insulin group did not reach the control level, direct infiltration of insulin could improve implant-bone contact. Local infiltration of insulin at the implant-bone interface may have important clinical implications by naturally improving the success of oral implantation.[14]

Histological and histomorphometric analysis of bone-implant sections were performed 10 and 21 days after implant placement into the tibiae of male Wistar rats.

It was found that in rats with alloxan-induced diabetes exhibited a 50% reduction in the area of formed bone and in the surface of contact between bone and implant 21 days after implant placement values returned to normal levels in diabetic rats after insulin treatment. Presence of chondrocyte-like cells surrounded by a cartilaginous like matrix in diabetic rats suggests a delay in the process of bone repair. Ultrastructural characteristics of bone-implant interface in diabetic rats treated with insulin resembled those observed in controls.[15]

These results suggest that metabolic control is essential for osseointegration to take place, as constant hyperglycemia delays the healing of the bone around the implants.[15] Although, numerous studies have shown that insulin therapy allows regulation of bone formation around the implants and increases the amount of neoformed bone, it was not possible to equal the bone-implant contact when compared with nondiabetic groups.[16]

Implant Survival in Patients with Diabetes Mellitus

After reviewing the literature published in the last 10 years, the survival rate for implants in diabetic patients ranges between 88.8 and 97.3% 1 year after placement, and 85.6 to 94.6% in functional terms 1 year after the prosthesis was inserted.

In a retrospective study with 215 implants placed in 40 diabetic patients, 31 failed implants were recorded, 24 of which (11.2%) occurred in the first year of functional loading. This analysis shows a survival rate of 85.6% after 6.5 years of functional use. The results obtained show a higher index of failures during the first year after placement of the prosthesis.[17] Another study carried out with 227 implants placed in 34 patients shows a success rate of 94.3% at the time of the second surgery, prior to the insertion of

the prosthesis.[18] In a meta-analysis with two implant systems placed in edentulous jaws, failure rates of 3.2% were obtained in the initial stages, whereas in the later stages (from 45 months to 9 years), this figure increases to 5.4%.[19]

A prospective study with 89 well-controlled type 2 diabetics in whose jaws a total of 178 implants had been placed reveals early failure rates of 2.2% (4 failures), increasing to 7.3% (9 further failures) 1 year after placement, indicating a survival rate of 92.7% within the first year of functional loading. The 5-year survival rate was 90%.[20]

The fact that most failures occur after the second-phase surgery and during the first year of functional loading might indicate microvascular involvement is one of the factors implicated in implant failures in diabetic patients.[21,22]

The microvascularization alteration associated with diabetes leads to a diminished immune response and a reduction in bone remodeling processes.[20,23] Most of the articles revised conclude that, despite the higher risk of failure in diabetic patients, maintaining adequate blood glucose levels along with other measures improves the implant survival rates in these patients.[21]

A study was done to determine if type 2 diabetes represents a significant risk factor to the long-term clinical performance of dental implants. A total of 2,887 implants (663 patients) were surgically placed, restored and followed for a period of 36 months. Of these, 2,632 (91%) implants were placed in nondiabetic patients and 255 (8.8%) in type 2 patients. It was concluded that implants in type 2 patients have significantly more failures; the use of preoperative antibiotics improved survival by 4.5% in non-type 2 patients and 10.5% in type 2 patients. The use of HA-coated implants improved survival by 13.2% in type 2 diabetics (Table 5).

Consideration for Implant Placement in Diabetic Patient

Certain pre- and intraoperative measures should be taken before placing implants in diabetic implants which is as follows in Table 6.

Antibiotic Coverage

Patients with poorly controlled diabetes are at risk of developing oral complications because of their susceptibility to infection and sequelae and likely will require supplemental antibiotic therapy.[15] Anticipation of dento-alveolar surgery (involving mucosa and bone) with antibiotic coverage may help prevent impaired and delayed wound healing. Orofacial infections require close monitoring. The antibiotic selected for prophylaxis should be bactericidal and of low toxicity, e.g. penicillin or amoxicillin (Garg 1992; Sbordone et al, 1995). In cases of penicillin allergy, clindamycin, metronidazole, or a first-generation cephalosporin may be an alternative choice (Peterson 1990; Garg 1992). A first-generation cephalosporin is recommended, however, only if the patient's allergic reaction to penicillin is not anaphylactic (Peterson, 1990). If antibiotics are given for the prophylaxis of postoperative wound infection, it is highly recommended that the first dose be administered preoperatively (e.g. for penicillin VPO, 1 hour preoperative) (Burke, 1961; Dajani et al 1997), so that sufficient antibiotic tissue concentrations can be achieved during surgery. Dentists can select a more effective antibiotic based on the patient's sensitivity test results.[23]

Table 6: Pre- and intraoperative consideration

- HbA1 ≤ 7 mg%
- Baseline and preprandial glycemia (80-110 mg/dl)
- Maximum postprandial glycemia (180 mg/dl)
- Preoperative antibiotic coverage
- 0.12% chlorhexidine mouthwash

Adjustment of Insulin

Most forms of dental therapy should not interfere with the medical control of diabetes. However, dentoalveolar surgery, orofacial infections and the stress of dental procedures can increase serum glucose levels and metabolic insulin requirements. Therefore, dentists must consider modifying medical therapy in consultation with the patient's physicians. For example, patients whose condition is controlled with insulin usually will require increased insulin dosages in the presence of an acute oral infection.[24]

Medications used by dental professionals may require adjustment of diabetes-associated therapies.

For example, large amounts of epinephrine can antagonize the effects of insulin and result in hyperglycemia. Small amounts of systemic corticosteroids can severely worsen glycemic control; patients taking oral hypoglycemic

Table 5: Implant survival rate

Authors	*Type of study*	*Type of diabetes*	*No. of patients*	*No. of implants*	*Implant survival*
Shernoff et al	Prospective	Type 2	89	178	92.7
Morris et al	Retrospective	Type 2		255	92.2
		(diabetic, nondiabetic)		2632	93.2
Olson et al	Prospective	Type 2	89	178	88
Peled et al	Case study	Type 2	41	141	94.3

agents who are placed on steroid therapy may require short-term insulin therapy to maintain glycemic control. Alternatively, hypoglycemia can be promoted by aspirin, sulfa antibiotics and antidepressants.

Monitoring Glycemic Control

Two critical steps are involved in treating patients with diabetes: Establishing the diagnosis (type 1 or type 2 diabetes, and the form of therapy) and the level of disease control (well-controlled or poorly controlled). Most commonly, blood glucose or HbA1c levels will be available from the physician's office. Medical updates must be recorded in the dental record at each visit to guide the clinician's treatment decisions. The dentist should be able to use a glucometer to measure blood glucose levels rapidly from a patient's fingertip.[25] Finally, the dental office should be equipped with immediate sources of glucose in case a diabetic-induced hypoglycemic event occurs. One study determined that the risk of infections was directly related to fasting blood glucose levels. Patients with levels below 206 mg/dl had no increased risk, whereas patients with fasting blood glucose levels above 230 mg/dl had an 80% increased risk of developing infection.[26] Therefore, dentists must be familiar with the diabetic status of their patients, and make appropriate accommodations to prevent and treat effectively diabetes-associated oral and systemic disorders.

Chlorhexidine Mouthwash

Chlorhexidine mouthrinse is a well-proven antibacterial rinse that has been shown to reduce infectious complications associated with dental implants. The use of chlorhexidine rinses following implant placement resulted in a slight improvement (2.5%) in survival in non-type 2 patients and a greater improvement in type 2 patients (9.1%).[27]

Communication with Physicians

Regular communication with physicians is a critical component of safely treating patients with diabetes.

DISCUSSION

Implants represent a significantly better solution for tooth loss replacement than traditional dental appliances. Because they are anchored directly into bone, they provide complete stability, in contrast to traditional tooth-replacement alternatives such as dentures. They also minimize bone resorption and atrophy, conditions that can cause facial collapse and the resultant appearance of premature aging. As techniques for managing diabetes have evolved, evidence has accumulated that diabetic patients who effectively control their disease incur a lower risk of various health complications than uncontrolled patients. Awareness of such distinctions has resulted in a greater degree of openness to the idea that diabetic patients may be good candidates for dental implants. In 1998, Kapur et al compared 37 diabetic patients who received conventional removable mandibular overdentures *vs* 52 who were fitted with implant supported ones and concluded that implants can be successfully used in diabetic patients with even low to moderate levels of metabolic control. This article aims at justifying the placement of implants in diabetics implants. From various studies we can infer that placement in well-controlled diabetes has better success rate than diabetic patients but may not be equal to nondiabetics. Diabetes alter the bone metabolism and causes various microvascular complication which hampers the success of implant placement. Understanding the effect of diabetes on dental implants still needs further prospective studies.

CONCLUSION

Diabetes mellitus affects people of all ages. Its prevalence has been increasing all over world. The oral implants have become a mainstream treatment for the replacement of missing teeth even for patients who are medically compromised. To provide effective implant therapy for patients with diabetes requires an understanding of the disease and familiarity with its oral manifestations. Various studies shows that hyperglycemia has a negative influence on bone formation and remodeling and reduces osseointegration of implants. Soft tissue is also affected by the microvascular complications deriving from hyperglycemia, vascularization of the tissue is compromised, healing is delayed and wounds are more predisposed to infection. Although, uncontrolled diabetes has been shown to interfere with various aspects of the healing process, high success rate is achievable when dental implants are placed in diabetic patients whose disease is under control. Hence it is necessary to extend the number of prospective studies in humans in order to clarify the true impact of diabetes on the prognosis for osseointegration.

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