J Indian Prosthodont Soc (July-Sept 2013) 13(3):175–183
DOI 10.1007/s13191-012-0207-9

REVIEW ARTICLE

Rehabilitative Considerations for Dental Implants in the Diabetic Patient

Preeti Agarwal Katyayan · Manish Katyayan · Rupal J. Shah

Received: 11 September 2011 / Accepted: 18 October 2012 / Published online: 1 November 2012

Abstract Diabetes is a serious illness that affects many people, and there are many new cases diagnosed every year in all populations around the world. Dental implant is one of the restorative methods to replace missing teeth. As implants are directly anchored into bones, they provide stability, a more natural appearance, and minimize the risk of bone resorption. Thus, today, there is a high demand of dental implants and it is inevitable to meet diabetics who request implant treatment. However, Diabetes mellitus patients may pose contraindications to dental implants because of microvascular complications leading to slower healing process after surgery. Studies have shown that dental implantation failure rate in diabetic patients is much higher than that in non-diabetic patients. This article reviews the effect of diabetes on the osseointegration of implants and the soft tissue healing. It presents the factors used in assessing the severity of diabetes and its complications, as well as considerations for rehabilitation planning in these patients. In addition, the role of antibiotic prophylaxis has been reviewed since its effect on wound healing in diabetics is controversial. Integration of these factors by the dentist can dictate whether, as well as what type of implant supported prosthesis should be given to the diabetic patient.

Keywords Dental implants · Diabetes mellitus · Osseointegration · Implant prosthesis

38th Indian Prosthodontic Society Conference, Indore, India.

On 14th November 2010 as faculty paper and won best paper award.

P. A. Katyayan (✉)
Department of Prosthodontics, Government Dental College, Ahmedabad, Gujarat, India
e-mail: preeti80_a@yahoo.com; drkatyayan@ymail.com

M. Katyayan (✉)
Department of Dentistry, GMERS Medical College, Gandhinagar, Gujarat, India
e-mail: drkatyayan@ymail.com

R. J. Shah
Government Dental College, Ahmedabad, Gujarat, India

Introduction

For a long time now, diabetes mellitus has been considered a relative contraindication for implant therapy because of increased susceptibility to infection, delayed wound healing and microvascular complications in such patients. Diabetic patients endure early and excessive loss of teeth caused by periodontitis and thus need implants more often than the general population. According to the World Health Organization, more than 180 million people worldwide are suffering from diabetes mellitus, one of the most common health problems in the world, while the number of diabetes sufferers is mounting to a double by 2030 [1, 2].

Diabetes mellitus is a chronic metabolic disease, which occurs when blood glucose concentration in body is in excess. This happens usually when the production of insulin, a hormone essential to regulate blood glucose level, from pancreas is inadequate (Type 1 diabetes), or when the body cannot effectively use the insulin it produces (Type 2 diabetes). Diabetes mellitus affects the blood circulations and is associated with many complications such as retinopathy, ischaemic heart disease, nephropathy, cerebrovascular disease, neuropathy and peripheral arterial diseases [3, 4].But the most obviously apparent complication of diabetes happens to be periodontal disease which, in cases of uncontrolled diabetes, may eventually lead to

tooth loss and total or partial edentulism [5–7]. Unfortunately, these Diabetics have always posed as a contraindication to dental implants [8].

Pathways of Oral Complications in the Diabetic Patient

Alteration in Bone Healing Mechanism

Chronic hyperglycaemia has been shown to be a stimulus for bone resorption. Bone loss in diabetes does not seem to depend so much on an increase in osteoclastogenesis as in the reduction in bone formation [9]. Hyperglycaemia inhibits osteoblastic differentiation and alters the response of the parathyroid hormone that regulates the metabolism of phosphorus and calcium [10]. In addition, it produces a deleterious effect on the bone matrix and its components and also affects adherence, growth and accumulation of extra-cellular matrix [11]. Mineral homeostasis, production of osteoid and, in short, bone formation has been shown to be clearly diminished in various experimental models of diabetes [12] (Fig. 1).

Oxidative Stress Phenomenon

This phenomenon refers to a condition when hyperglycemia triggers an imbalance between production of reactive oxygen species and antioxidants, leading to tissue breakdown. Reactive oxygen species like superoxide anions, hydroxyl radicals and peroxyl radicals destroy many biologic molecules like DNA, lipids and proteins, leading to cell death [13–18].

Diabetes-Periodontitis Inter-Relationship

The degree of glycemic control is an important variable in the relationship between diabetes and periodontal diseases, with higher prevalence and severity of gingival inflammation and periodontal destruction being seen in those with poor glycemic control [19–24]. There are few differences in the subgingival microbiota between diabetic and non-diabetic patients with periodontitis, suggesting that alterations in the host immunoinflammatory response to the potential pathogens may play a prominent role [25, 26]. Diabetes may result in impairment of neutrophil adherence, chemotaxis and phagocytosis, which may facilitate bacterial persistence in the periodontal pocket and significantly increase periodontal destruction [27, 28]. While neutrophils are often hypofunctional in diabetes, these patients may have a hyper-responsive monocyte/macrophage phenotype, resulting in increased production of pro-inflammatory cytokines and mediators [29, 30]. This occurs due to the reaction between the advanced glycation end products (AGE) and their receptors (RAGE) on target cells such as macrophages. Production of matrix metalloproteinases such as collagenase increases in many diabetic patients, resulting in altered collagen homeostasis and wound healing within the periodontium [31]. On the other hand, studies have shown that diabetic patients with periodontal infection have a greater risk of worsening glycemic control over time as compared to diabetics without periodontitis [32]. Periodontal infection can induce elevated serum levels of interleukin-6 and tumour necrosis factor-α levels, and may play a similar role in obesity in inducing or exacerbating insulin resistance [33].

Thus it can be said that diabetes and periodontitis are difficult to separate and the co-occurrence of these two diseases is a serious consideration for dental implant specialists (Fig. 2).

Effect on Osseointegration

It has been shown that, although the amount of bone formed is similar when comparing diabetes induced

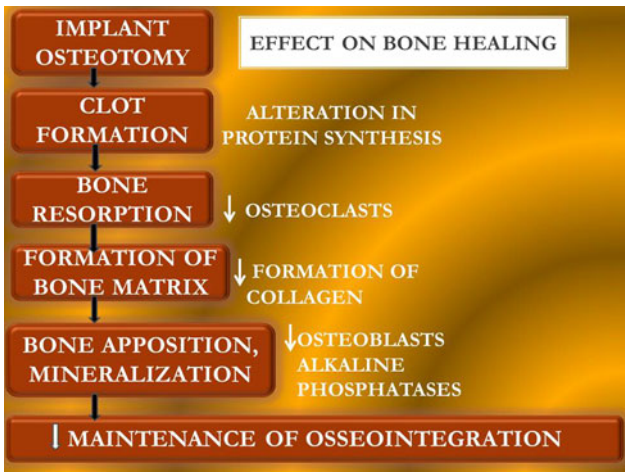

Fig. 1 Alteration in bone healing in diabetic patients

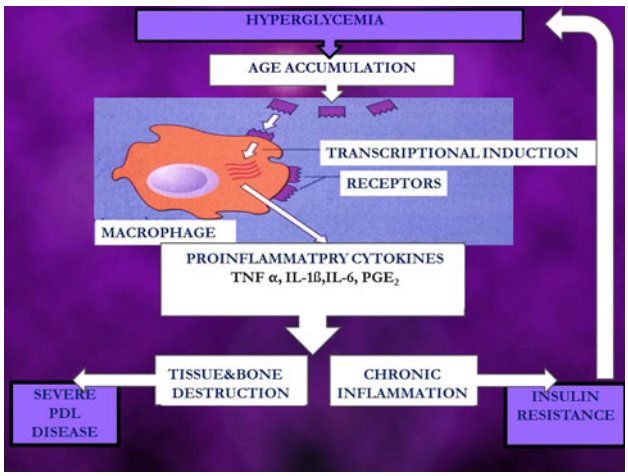

Fig. 2 Linkage between diabetes and periodontal disease severity

animals with controls, there is a reduction in the bone implant contact in diabetics [34, 35]. This confirms that diabetes inhibits osseointegration and this situation may be reversed by treating the hypoglycemia and maintaining near-normal glucose levels [36].

Survival Rate of Implants in Patients with Diabetes Mellitus

Diabetes is currently classified as a relative contraindication for implant treatment. Compared with the general population, a higher failure rate has been seen in patients with adequate metabolic control [37]. 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 85.6–94.6 % in functional terms 1 year after the prosthesis was inserted [38]. In a retrospective study [39] 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. Another study [40] 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 [40]. In a meta-analysis [41] with two implant systems placed in edentulous jaws, failure rates of 3.2 % were obtained in the initial stages, whereas in the later stages, this figure increases to 5.4 %. A prospective study [42] 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 %(four failures) increasing to 7.3 % (nine 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 % [42].

The fact that most failures occur after the second phase of surgery and during the first year of functional loading might indicate microvascular involvement is one of the factor implicated in implant failures in diabetic patients [43, 44]. The percentage of failures in these studies is shown graphically in Fig. 3. The left axis shows time elapsed since placement of implants. The right hand axis reflects the different phases from placement of implants till 1 year of functional loading after the prosthesis placement. The numbers in the columns indicate the percentages of failures in two distinct stages for each study. Early failures include up to 1 year of functional loading. Late failures have been monitored for up to 5 years. Most articles conclude that, despite the high risk of failure in diabetic patients, maintaining adequate blood glucose levels along with other measures improves implant survival rate in these patients [38, 43].

Ayson et al. [45] in an evidence based review (Table 1) [46–51] concluded that there is insufficient evidence that

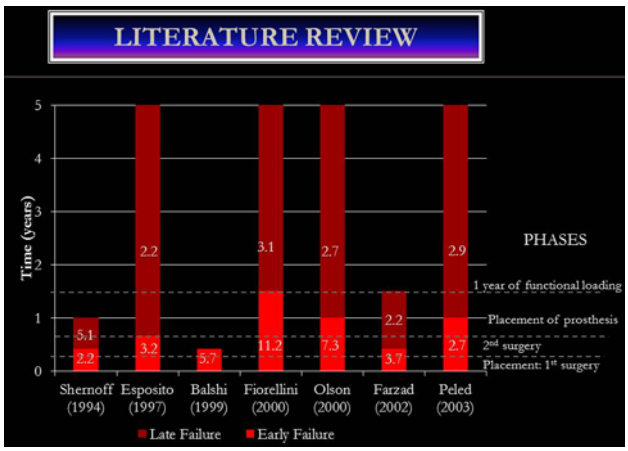

Fig. 3 Graph of percentage of failures in diabetic patients

well controlled diabetes type II is a significant risk factor on its own for implant failure. The study with the largest numbers [46] found no significant difference; however, the number of people with diabetes was not reported so it is not possible to estimate the power of the study to detect a difference. The systematic review by Klokkevold [49] on the other hand, found an absolute difference in survival of 1.5 % between those people with diabetes type II and those without (Table 1).

Which Diabetic Patient is Suitable for Implant Placement

It is estimated that in India, as many as 50 % of the people with type 2 diabetes mellitus are undiagnosed every year [52]. To increase cost effectiveness, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus recommends testing in high risk populations (Table 2) [53, 54]. Early detection and treatment might well reduce the type 2 diabetes related disease burdens such as periodontitis [55].

Disease Severity

Once the patient is confirmed to have diabetes, it is important to assess the severity of the disease. Type 1 diabetes is often characterized by severe systemic complications because of its early onset and difficult control. In this type of disease one must be extremely cautious when using dental implants [42].

Disease Duration and Treatment Regime

Disease duration is another important factor [42]. Longer duration allows more damage to accumulate systemically, in relation to the degree to which the disease has been controlled. Disease severity can also be reflected by the regimen

Table 1 Effect of diabetes on dental implant failure [24, 46–51]

Reference	Description	Numbers		Key results
		People	Implants	
Alsaadi et al. [46]	Dental implant (Brånemark system®) survival and factors related to risk of early* failure. University setting *early = before or up to abutment connection	2,004	6,946	No significant difference in risk of early failure in people with diabetes type II.
Alsaadi et al. [47]	Dental implant (MkII TiUnite™) survival and factors related to early* failure. University setting *early = before or up to abutment connection	238	720	Significantly increased failure rate in people with type I diabetes (100 %*) compared to 1.81 % failed in people without diabetes type I; $p = 0.02$ *only one implant and it failed. No significant difference in implant failures in people with type II diabetes; $p = 0.39/0.36$
Alvim-Pereira et al. [48]	Relationship between vitamin D receptor gene polymorphism and other clinical factors with dental implant failure. NEODENT™ implants University setting	217	1,376	6.6 % of 'no failure' group had diabetes compared to 1.3 % in 'failure' group ($p = 0.096$).
Klokkevold et al. [49]	Systematic review of the effect of smoking, diabetes and periodontitis on the survival or success of dental implants ($N = 14$ studies)	1,150	10,904	Diabetes: type II only survival (4 studies) Diabetics = 91.7 % (95 %CI: 89.1–94.3 %). Non-diabetics = 93.2 % (95 %CI: 92.2–94.1 %). Pooled estimate of the difference in survival rates not possible to calculate because only one study included both diabetic and non-diabetic patients. Implant success not reported in any of the studies.
Kourtis et al. [50]	Associate the causes of dental implant failure with some potential risk factors. Various implant brands. Private dental clinics (4).	405	1,692	"No statistical significance was noted among failures in people with diabetes".
Moy et al. [73]	Risk factors for implant failure. Various dental implant brands. University setting.	1,140	4,680	People with diabetes have an increased chance of implant failure: $R = 1.94$, $p = 0.003$
Mundt et al. [51]	Potential risk factors for implant failure. Tiolox dental implants. Private practice.	159	663	Reported that 'diseases' were not significantly correlated with implant failure ('diseases' included: cardiovascular diseases, allergies, blood clotting disorders, diabetes, hepatitis, tuberculosis, HIV, thyroid diseases, osteoporosis, arthritis/arthrosis, and rheumatism).

needed to control one's disease. Diabetic patients requiring insulin usually have a more advanced disease and will probably experience the most disease complications [56].

Glycemic Control

HbA_{1c} (glycosylated hemoglobin) can reflect the glucose levels in the blood over the previous 6–12 weeks prior to the test. It is expressed as a percentage of the total hemoglobin. For healthy, non-diabetic adults, the normal range is 4–8 % [57]. The HbA_{1c} allows assessment of intermediate term balance of diabetes, and the feasibility of implant supported rehabilitation should therefore be evaluated with past test results. In addition to assessing the HbA_{1c}, daily plasma glucose levels should be monitored near the time of implantation to rule out short term glucose imbalance that was not represented by it [58, 59].

Target Organ Involvement

Systemic complications are a good measure of diabetes disease severity. Diabetes attacks organs such as retina, kidneys, heart, brain etc. in the form of micro and macrovascular complications. The involvement of target organs depends on the duration of the disease and the level of its control over that time. Thus it is logical that target organ involvement will correlate with dental implant failure rates. Furthermore, a history of delayed wound healing should be sought. Previous surgical operations including dental and oral procedures are a good measure for this [56].

Table 2 Criteria for testing for type 2 DM in asymptomatic, undiagnosed individuals [45, 46]

Age >45, particularly in those who are overweight (BMI > 25 kg/m^2)
Age <45, particularly in those who are overweight (BMI > 25 kg/m^2) and have additional risk factors
a. First degree relatives with DM
b. Sedentary lifestyle
c. High risk ethnic groups: African Americans, Hispanic Americans, Native Americans, Asian Americans, Pacific Islanders.
d. Delivered a baby weighing >9 lb or have been diagnosed with gestational diabetes.
e. Hypertension (BP > 140/90 mm)
f. HDL <35 mg/dl
g. History of impaired fasting glucose or impaired glucose tolerance on previous testing.
h. History of vascular disease.

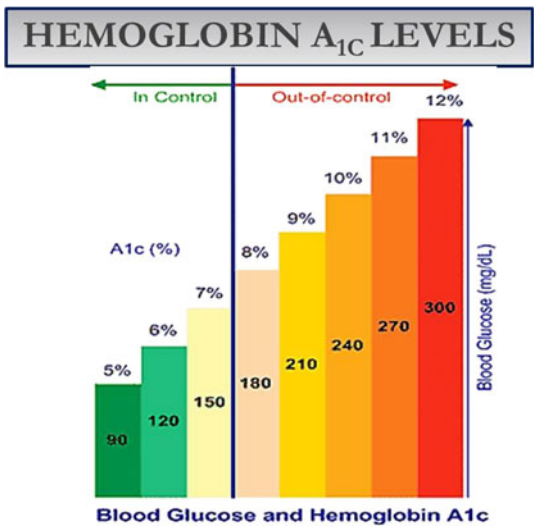

Fig. 4 Blood glucose and hemoglobin A_{1c} levels

Treatment Strategies for Placing Dental Implants in Diabetic Patients

The physiological events associated with the "stress" of a procedure can affect both diabetic control and cardiac function. Consequently, the clinician treating a patient with diabetes mellitus must develop treatment strategies that, take into consideration the patient's overall health and, in particular, the patient's cardiovascular status [60, 61].

Medical Consultation

In general, patients with good glycemic control can be managed as normal patients. It is recommended that elective treatment be deferred if the fasting blood glucose level is either <70 mg/dL or more than 200 mg/dL or when the HbA1c level is in excess of 7 %. This recommendation is based on evidence that patients with a blood glucose level of <70 mg/dL are high-risk candidates for hypoglycemic events, and that a blood glucose level of more than 200 mg/dL or an HbA1c level in excess of 7 % is indicative of poor glycemic control, and that the patients are likely to have or are developing significant microvascular and/or macrovascular disease (Fig. 4). Medical consultation is further required if the anticipated dental therapy may adversely impact good glycemic control [58, 59, 62–65].

The Timing and Length of Appointments

Patients should preferentially be treated in the morning with short appointment durations, after having taken their normal insulin or oral hypoglycemic agent and after having eaten a normal breakfast. This timing of the appointment will place the patient in the oral health care setting before the peak activity of the therapeutic agents is reached (i.e., a time of high glucose and low-insulin or oral hypoglycemic agent activity) [57].

The Use of Local Anesthetic Agents

When indicated, the local anesthesia may be supplemented with an oral benzodiazepine, nitrous oxide, or intravenous sedation. If nitrous oxide is used, the clinician should ensure adequate oxygenation (35 % nitrogen dioxide/65 % dioxygen) to avert rebound hypertension secondary to hypoxia. Issues related to the use of vasoconstrictors in local anesthetic agents, with special reference to patients with cardiovascular diseases, were extensively reviewed in recent publications [60, 61]. In patients with DM, the presence of cardiovascular risk factors in association with dental procedures and the functional capacity of the patient should be the critical determinants for the safe use of a vasoconstrictor.

The use of Antibacterial Agents

The reciprocal relationship between infection and poor glycemic control has led some to advocate the administration of antimicrobial prophylaxis prior to dental therapy, particularly in the patients with poorly controlled diabetes [66, 67]. When a patient with DM presents with significant infection, his or her primary physician should be consulted promptly, as the patient's therapeutic regimen may have to be adjusted to ensure adequate glycemic control. In addition, the patient must be instructed to practice meticulous oral hygiene, and should be recalled at regular intervals to monitor resolution of the infection and compliance with recommended preventive measures [57, 68, 69] (Table 3).

An informal survey of surgeons performing dental implant surgery indicates that the majority administrate the

Table 3 Antibiotic prophylaxis for dental implant surgery [60, 61]

A. Intraoral application
Penicillin G, 1–2 million U IV q2h
Penicillin V, 2 g po q2h
Clindamycin, 300 mg po IV q6h
B. Intraoral application: nasal or chronic sinus involvement
Amoxicillin/clavulanic acid, 500 mg po q4h
Ampocillin/sulbactam 2g1g IV/IM q3h
Clindamycin, 300 mg po IV q6h
Cephalexin, 500 mg po q4h
Cefazolin, 1 g IV/IM q4h
C. Bone-grafted or extraoral application
Same as above

antibiotic for 5–7 days postoperatively. A review and study of antibiotic prophylaxis for oral and maxillofacial surgery support the view that there is no significant reduction of postoperative wound infections when administering antibiotics for more than 1 day after surgery [68, 69].

In addition to antibiotic prophylaxis, the use of 0.12 % chlorhexidine mouthwash has shown a clear benefit by reducing the failure rates from 13.5 to 4.4 % in type 2 diabetics, during a follow-up period of 36 months. This same study observed a reduction of 10.5 % in the failure rate when antibiotics were administered pre-operatively [37, 56].

Postoperative Pain Management

Treatment strategies should also include effective postoperative pain management. Opioid-based analgesics effectively block pain and tend to contribute to cardiovascular stability [70]. Possible increased hypoglycemic effect with large doses of salicylates has been reported in patients on insulin, and increased hypoglycemia with large doses of salicylates has been reported in combination with chlorpropamide, a sulfonylurea. However, usual therapeutic doses of acetylsalicylic acid (ASA) have little effect [71]. These potential drug interactions, are not an absolute contraindication to the use of an opioid/ASA formulation for pain management in the dental setting, but rather they are another indication to monitor plasma glucose levels in the post-operative period. Indeed, since many patients with DM are taking ASA as primary or secondary therapy to prevent cardiovascular events, an opioid/ASA formulation is more appropriate than an opioid/ibuprofen formulation, which may interfere with the antiplatelet effect of ASA [72].

Implant Location

Implant success in the general population is dependent on implant location in the jaws and should be even more so in diabetic patients. Success rates are higher in the mandibular jaw and are improved when the implants are anteriorly located. The best location for implants, yielding the greatest success rate, is the symphysis area of the mandible [46, 47, 73].

Implant Selection

The same basic principles of osseointegration by Albrektsson et al. [74] apply to the diabetic patient as well. Screw shaped design, surface roughness of implant, surface purity of implant are all factors that help to achieve a better osseointegration.

Hydroxyapatite plasma-spray-coated implants have been found to have a higher survival rate than titanium implants in type 2 diabetic patients, i.e., 97.9 versus 84.7 % after 36 months [37]. This is noteworthy, since hydroxyapatite (HA) plasma-spray-coated implants are more susceptible to failure through microbial contamination, dissolution, and fracture of the HA from the titanium surface [75].

Position, Number and Length of Implant Fixtures

The most important principle is to achieve good initial stability and full coverage of the fixtures in well-vascularized, highly osteogenic bone. Bio-cortical initial stabilization should be the goal. If this is not possible, one must resort to at least monocortical fixation. For adequate load distribution to the bone and fixtures themselves, the latter should be spread well apart and placed along a curve or any arrangement other than a straight line [76]. The anterior loop of the mandibular canal and the nasopalatine duct should be avoided so as not to interfere with nerve function and osseointegration. The available bone volume in different areas can be reasonably well assessed preoperatively by palpation and, especially, by tomographic radiographs. For oral purposes, one fixture can carry one crown only, two fixtures provide minimal support for a bridge in partial edentulism, and four fixtures are the minimum for a full-arch bridge, provided they are spaced well apart along a curve. The lengths of the fixtures should be determined only after all high-speed drilling has been finished. In particular, marginal countersinking may reduce the depth of fixture site, then fixture shorter than originally anticipated must be chosen [77].

Surgical Protocol

For the diabetic patients, atraumatic tissue handling is very critical [78]

Handling of the Covering Soft Tissues

The leading surgical principle of the osseointegration method has always been the minimize trauma to the host

tissues. Incisions should be placed to reduced interference with vascularization and in areas where there is little frictional (denture) load. A crestal incision is usually preferred.

Handling of the Bone Tissue

All aspects of the process of drilling in bone should be carefully scrutinized to avoid frictional heat, and strict recommendations have been published [79]. Clinical studies in dense mandibular bone have confirmed that if these recommendations are followed, the frictional heat at the threshold level is 47 °C for 1 min [80]. Frictional heat above this level will prevent osseointegration from taking place.

Matching the Fixture to Its Bone Site

Matching the fixture to the prepared bone site should be performed with the aim of avoiding over tightening yet creating an optimal fit. Over tightening is likely to cause marginal compression ischemia, which may result in inadvertent loss of marginal bone height [81]. Finally, very loosely textured bone may create a risky situation, because even with correctly performed surgery, only a few trabeculae touch the fixture surface to provide the initial stability.

Abutment Considerations

Choice of Abutment

The longest possible abutments with regard to esthetics should be chosen to facilitate access to the periabutment area for hygiene purpose [76].

Managing Periabutment Soft Tissues

Abutments should penetrate through attached gingiva or immobile oral mucosa or skin. For oral purposes, attached gingiva may be strictly necessary only on the lingual aspect of mandibular abutments to protect the vulnerable mucosa in the floor of the mouth from frictional movements against the abutments or from excessive hygiene efforts. However, a prerequisite for healthy marginal soft tissue is always good oral hygiene and no exposed fixture threads. If stabilization of oral periabutment mucosa is needed, conventional sulcoplastics or mucosal grafts are recommended after the prosthesis is finished so that additional stabilization of healing marginal tissues can be obtained by a surgical pack [76].

Type of Implant Loading

Bone quality at the implant site also impacts the chances for osseointegration. Bone remodeling around the implants is lower and less effective in diabetic patients [37]. Since patients with diabetes have slow rate of bone remodeling, it is customary to delay implant exposure by 4–8 weeks after what is acceptable for the general population. For this reason, immediate loading of implants should be avoided in diabetic patients [56]. Conversely, according to a study by Balshi et al. [82], despite the metabolic differences seen in diabetic patients, an immediate loading protocol can be successful and result in osseointegration.

Conclusion

The factors used in assessing the severity of diabetes and its complications, as well as the considerations for rehabilitation planning in these patients have been presented. Integration of these factors by the clinician dictates whether as well as what type of implant supported restoration should be performed. Although there is a higher risk of failure in diabetic patients, experimental studies have shown that the optimization of glycaemic control improves the degree of osseointegration in the implants. Nonetheless, 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.

(1) Good glycaemic control: HbA1c <7 % baseline and pre-prandial glycaemia (mg/dL): 80–110 maximum post-prandial level of glycaemia (mg/dL): <180.
(2) Pre-operative antibiotic therapy.
(3) 0.12 % Chlorhexidine mouthwash.

Sources of Support in the Form of Grants None.

References

1. Chalmers J, Joshi R, Patel A (2008) Advances in reducing the burden of vascular disease in type 2 diabetes. Clin Exp Pharmacol Physiol 35:434–437
2. Loo WTY, Jin LJ, Cheung NB, Wang M (2009) The impact of diabetes on the success of dental implants and periodontal healing. Afr J Biotechnol 8(19):5122–5127
3. Aronson D (2008) Hyperglycemia and the pathobiology of diabetic complications. Adv Cardiol 45:1–16
4. Bianchi C, Miccoli R, Penno G, Del Prato S (2008) Primary prevention of cardiovascular disease in people with dysglycemia. Diabetes Care 31(2):S208–S214
5. American academy of periodontology (1999) Diabetes and periodontal disease (position paper). J Periodontol 70:935–949
6. Cianciola RJ, Park BH, Bruck E, Mosovich L, Genco RJ (1982) Prevalence of periodontal disease in insulin dependent diabetes mellitus (juvenile diabetes). J Am Dent Assoc 104:653–660
7. Schlossman M, Knowler WC, Pettitt DJ, Genco RJ (1990) Type 2 diabetes mellitus and periodontal disease. J Am Dent Assoc 121:532–536

8. Park JB (2007) Bone healing at a failed implant site in a type II diabetic patient: clinical and histologic evaluations: a case report. J Oral Implantol 33:28–32
9. He H, Liu R, Desta T, Leone C, Gerstenfeld LC, Graves DT (2003) Diabetes causes decreased osteoclastogenesis, reduced bone formation and enhanced apoptosis of osteoblastic cells in bacteria stimulated bone loss. Endocrinology 145:1447–1452
10. Santana RB, Xu L, Babakhanlou C, Chase HB, Amar S et al (2003) A role for advanced glycation end products in diminished bone healing in type 1 diabetes. Diabetes 52:1502–1510
11. Weiss RE, Gora A, Nimni ME (1981) Abnormalities in the biosynthesis of cartilage and bone proteoglycans in experimental diabetes. Diabetes 30:670–677
12. Nyomba BL, Verhaegue J, Tomaste M, Nyomba BL, Verhaeghe J, Thomasset M, Lissens W, Bouillon R (1989) Bone mineral homeostasis in spontaneously diabetic BB rats. Abnormal vitamin D metabolism and impaired active intestinal calcium absorption. Endocrinology 124:565–572
13. Brownlee M (2001) Biochemistry and molecular cell biology of diabetic complications. Nature 414:813–820
14. Ceriello A (2000) Oxidative stress and glycemic regulation. Metabolism 49:27–29
15. Hammes HP, Martin S, Federlin K, Geisen K, Brownlee M (1991) Aminoguanidine treatment inhibits the development of experimental diabetic retinopathy. Proc Natl Acad Sci USA 88:11555–11559
16. Mahadev K, Wu X, Zilbering A, Lawrence JT, Goldstein BJ (2001) Insulin stimulated hydrogen peroxide generated during cellular insulin stimulation is integral to activation of the distal insulin signaling cascade in 3T3-L1 adipocytes. J Biol Chem 276:48662–48669
17. Marfella R, Quagliaro L, Nappo F, Ceriello A, Giugliano D (2001) Acute hyperglycemia induces an oxidative stress in healthy subjects. J Clin Invest 108:635–636
18. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y et al (2000) Normalizing mitochondrial superoxide production blocks three pathways of hyperglycemic damage. Nature 404:787–790
19. Campus G, Salem A, Uzzau S, Baldoni E, Tonolo G (2005) Diabetes and periodontal disease: a case control study. J Periodontol 76:418–425
20. Ervasti T, Knuutilla M, Pohjamo L, Haukipuro K (1985) Relation between control of diabetes and gingival bleeding. J Periodontol 56:154–157
21. Gusberti FA, Syed SA, Bacon G, Grossman N, Loesche WJ (1983) Puberty gingivitis in insulin dependent diabetic children. J Periodontol 54:714–720
22. Karjalainen KM, Knuuttila MLE (1996) The onset of diabetes and poor metabolic control increases gingival in children and adolescents with insulin-dependent diabetes mellitus. J Clin Periodontol 23:1060–1067
23. Seppala B, Seppala M, Ainamo J (1993) A longitudinal study on insulin dependent diabetes mellitus and periodontal disease. J Clin Periodontol 20:161–165
24. Tervonen T, Oliver RC (1993) Long term control of diabetes mellitus and periodontitis. J Clin Periodontol 20:431–435
25. Sastrowijoto SH, Hillemans P, van Steenbergen TJ, Abraham-Inpijn L, De Graaff J (1989) Periodontal condition and microbiology of healthy and diseased periodontal pockets in type I diabetes mellitus patients. J Clin Periodontol 16:316–322
26. Zambon JJ, Reynold H, Fisher JG, Shlossman M, Dunford R, Genco RJ (1988) Microbiological and immunological studies of adult periodontitis in patients with non-insulin dependent diabetes mellitus. J Periodontol 59:23–31
27. Manoucher-Pour M, Spagnuolo PJ, Rodman HM, Bissada NF (1981) Comparison of neutrophil chemotactic response in diabetic patients with mild and severe periodontal disease. J Periodontol 52:410–415
28. McMullen JA, Van Dyke TE, Horoszevicz HU, Genco RJ (1981) Neutrophil chemotaxis in individuals with advanced periodontal disease and a genetic predisposition to diabetes mellitus. J Periodontol 52:167–173
29. Salvi GE, Yalda B, Collins JG, Jones BH, Smith FW, Arnold RR, Offenbacher S (1997) Inflammatory mediator response as a potential risk marker for periodontal diseases in insulin dependent diabetes mellitus. J Periodontol 68:127–135
30. Salvi GE, Yalda B, Collins JG, Arnold RR, Lang NP, Offenbacher S (1997) Monocytic TNF-α secretion patterns in IDDM patients with periodontal diseases. J Clin Periodontol 24:8–16
31. Ryan ME, Ramamurthy NS, Geolub NM (1996) Matrix metalloproteinases and their inhibition in periodontal treatment. Curr Opin Periodontol 3:85–96
32. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ (1996) Severe periodontitis and risk for glycemic control in patients with non-insulin dependent diabetes mellitus. J Periodontol 67:1085–1095
33. D'Aiuto F, Parker M, Andreou G, Suvan J, Brett PM, Ready D, Tonetti MS (2004) Periodontitis and systemic inflammation: control of local infection is associated with a reduction in serum inflammatory markers. J Dent Res 83:156–160
34. McCracken M, Lemons JE, Rahemetulla F, Prince CW, Feldman D (2000) Bone response to titanium alloy implants placed in diabetic rats. Int J Oral Maxillofac Implants 15:345–354
35. Nevins ML, Karimbux NY, Weber HP, Giannobile WV, Fiorellini JP (1998) Wound healing around endosseous implants in experimental diabetes. Int J Oral Maxillofac Implants 13: 620–629
36. Kopman JA, Kim DM, Rahman SS, Arandia JA, Karimbux NY, Fiorellini JP (2005) Modulating the effects of diabetes on osseointegration with aminoguanidine and doxycycline. J Periodontol 76:614–620
37. Morris HF, Ochi S, Winkler S (2000) Implant survival in patients with type 2 diabetes: placement to 36 months. Ann Periodontol 5:157–165
38. Valero AM, García JC, Ballester AH (2007) Effects of diabetes on the osseointegration of dental implants. Med Oral Patol Oral Cir Bucal 12:E38–E43
39. Fiorellini JP, Chen PK, Nevins M, Nevins ML (2000) A retrospective study of dental implants in diabetic patients. Int J Periodontics Restorative Dent 20:366–373
40. Balshi TJ, Wolfinger GJ (1999) Dental implants in the diabetic patient: a retrospective study. Implant Dent 8:355–359
41. Esposito M, Hirsch JM, Lekholm U, Thomsen P (1997) Failure patterns of four osseointegrated oral implant systems. J Mater Sci Mater Med 8:843–847
42. Olson JW, Shernoff AF, Tarlow JL, Colwell JA, Scheetz JP, Bingham SF (2000) Dental endosseous implant assessments in a type 2 diabetic population: a prospective study. Int J Oral Maxillofac Implants 15:811–818
43. Farzad P, Andersson L, Nyberg J (2002) Dental implant treatment in diabetic patients. Implant Dent 11:262–267
44. Peled M, Ardekian L, Tagger-Green N, Gutmacher Z, Machtei EE (2003) Dental implants in patients with type 2 diabetes mellitus: a clinical study. Implant Dent 12:116–122
45. Ayson M, leichter J, Lyons K (2006) Dental implants: patient selection factors. An evidence based review. MSc thesis, University of Otago, School of Dentistry
46. Alsaadi G, Quirynem M, Komarek A, Van Steenberghe D (2008) Impact of local and systemic factors on the incidence of late oral implant loss. Clin Oral Implants Res 19:670–676
47. Alsaadi G, Quirynem M, Komarek A (2007) Impact of local and systemic factors on the incidence of late oral implant failures,

up to abutment connection. Int J Oral Maxillofac Implants 34:610–617
48. Alvim-Pereira F et al (2008) Analysis of association of clinical aspects and vitamin D receptor gene polymorphism with dental implant loss. Clin Oral Implants Res 19(8):786–795
49. Klokkevold PR, Han TJ (2007) How do smoking, diabetes, and periodontitis affect outcomes of implant treatment? Int J Oral Maxillofac Implants 22(Suppl):173–202; erratum appears in Int J Oral Maxillofac Implants. 2008;23(1):56
50. Kourtis SG et al (2004) Private practice results of dental implants. Part I: survival and evaluation of risk factors—Part II: surgical and prosthetic complications. Implant Dent 13(4):373–385
51. Mundt T et al (2006) Private practice results of screw-type tapered implants: survival and evaluation of risk factors. Int J Oral Maxillofac Implants 21(4):607–614
52. Harris MI, Hadden WC, Knowler WC, Bennett PH (1987) Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in the U.S. population aged 20–74 years. Diabetes 36:523–534
53. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (2003) Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 26:S5–S20
54. American Diabetes Association (2004) Screening for type 2 diabetes. Diabetes Care 27:S11–S14; S5–S20
55. Klein MI (1995) Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care 18:258–268
56. Michaeli E, Weinberg I, Nahlieli O (2009) Dental implants in the diabetic patient: systemic and rehabilitative considerations. Quintessence Int 40:645–649
57. Miley DD, Terezhalmy GT (2005) The patient with diabetes mellitus: etiology, epidemiology, principles of medical management, oral disease burden, and principles of dental management. Quintessence Int 36:779–795
58. Knowler WC (1994) Screening for NIDDM: opportunities for detection, treatment and prevention. Diabetes 17:445–450
59. Peters AL, Davidson MB, Schriger DL, Hasselblad V (1996) A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. Meta-Analysis Research Group on the Diagnosis of Diabetes using Glycated Hemoglobin Levels. JAMA 276:1246–1252
60. Steinhauer T, Bsoul SA, Terezhalmy GT (2005) Risk stratification and dental management of the patient with cardiovascular diseases. Part I: etiology, epidemiology, and principles of medical management. Quintessence Int 36:119–137
61. Steinhauer T, Bsoul SA, Terezhalmy GT (2005) Risk stratification and dental management of the patient with cardiovascular diseases. Part II: the oral disease burden and principles of dental management. Quintessence Int 36:209–227
62. McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Knowler WC, Bennet PH (1994) Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ 308:1323–1328; Erratum in BMJ 309:841
63. Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, Badran A, Sous ES, Ali MA (1997) Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes: diagnostic criteria and performance revisited. Diabetes 20:785–791
64. Jackson CA, Yudkin JS, Forrest RD (1992) A comparison of the relationships of the glucose tolerance test and the glycated hemoglobin assay with diabetic vascular disease in the community: the Islington Diabetes Survey. Diabetes Res Clin Pract 17:111–123
65. Beks PJ, Mackay AJC, de Neeling JND, De Vries H, Bouter LM, Heine RJ (1995) Peripheral arterial disease in relation to glycaemic level in elderly Caucasian population: the Hoorn Study. Diabetologia 38:86–96
66. Lockhart PB, Schmidtke MA (1994) Antibiotic considerations in medically compromised patients. Dent Clin North Am 38:381–402
67. Hall EH, Sherman RG, Emmons III, Naylor GD (1994) Antibacterial prophylaxis. Dent Clin North Am 38:707–718
68. Heydman JC, Nelson CL (1986) Short term preventive antibiotics. Clin Orthop Relat Res 205:184
69. Conver MA, Kaban LB, Mulliken JB (1985) Antibiotic prophylaxis for major maxillocraniofacial surgery. J Oral Maxillofac Surg 43:865
70. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE (2002) ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). J Amn Coll Cardiol 39:542–553
71. Kim RB (ed) (2003) The medical letter handbook of adverse drug interactions. The Medical Letter Inc., New Rochelle, p 142
72. Kim RB (ed) (2003) The medical letter handbook of adverse drug interactions. The Medical Letter Inc., New Rochelle, p 143
73. Moy PK, Medina D, Shetty V, Aghaloo TL (2005) Dental implant failure and associated risk factors. Int J Oral Maxillofac Implants 20:569–577
74. Albrektsson T, Brånemark P-I, Hansson H-A, Lindström J (1981) Osseointegrated titanium implants. Requirements for ensuring a longlasting, direct bone-to-implant anchorage in man. Acta Orthop Scand 52:155–170
75. Johnson BW (1992) HA-coated dental implants: long-term consequences. J Calif Dent Assoc 20:33–41
76. Salak R (1985) Aspect of biomechanical considerations. In: Brånemark PI, Zarb GA, Albrektsson T (eds) Tissue-integrated prostheses. Osseointegration in clinical dentistry. Quintessence Publishing Company, Chicago; Chapter 5
77. Marchand F, Raskin A, Dionnes-Hornes A, Barry T, Dubois N, Valéro R, Vialettes B (2012) Dental implants and diabetes: conditions for success. Diabetes Metab 38(1):14–19
78. Palmer R, Palmer P, Floyd P (1999) Dental implants: basic implant surgery. Br Dent J 187:415–421
79. Ericsson RA (1984) Heat-induced bone tissue injury. Thesis, Department of anatomy, University of Gothenburg, Sweden
80. Ericsson RA, Adell R (1986) Temperatures during drilling for the placement of implants using the osseointegration technique. J Oral Maxillofac Surg 44:4–7
81. Röstlund T, Carlsson L, Albrektsson B, Albrektsson T (1989) Osseointegrated knee prostheses. An experimental study in rabbits. Scand J Plast Reconstr Surg Hand Surg 23:43–46
82. Balshi SF, Wolfinger GJ, Balshi TJ (2007) An examination of immediately loaded dental implant stability in the diabetic patient using resonance frequency analysis (RFA). Quintessence Int 38(4):271–279