

## Review

# Impact of Diabetes Mellitus and Glycemic Control on the Osseointegration of Dental Implants: A Systematic Literature Review

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**Background:** Implant treatment is an attractive substitute to traditional fixed/removable prosthetic appliances. In patients with diabetes, dental implant therapy has been considered a contraindication. Hyperglycemia augments the severity of periodontal disease, and glycemic control is an essential variable in determining the success of dental implants in subjects with diabetes. Subjects with well-controlled diabetes may not be significantly compromised and can have high dental implant success rates compared to individuals with poorly controlled diabetes. The focused questions addressed in this systematic review were as follows: Can patients with diabetes be good candidates for dental implant therapy? And how does hyperglycemia and glycemic control influence osseointegration?

**Methods:** A systematic literature search of MEDLINE/PubMed articles published from 1982 up to and including July 2009 was independently performed by two investigators. In addition, reference lists of original and review articles were searched. The search strategy was to use the following terms in different combinations: dental implants, immediate implants, osseointegration, periodontal disease, diabetes, hyperglycemia, metabolic control, and glycemic control. The search included studies on humans and diabetes-induced animal models. The selection criteria included all levels of available evidence. Suitable variables included the implant survival rate among individuals with diabetes, effects of hyperglycemia and glycemic control on bone, and maintenance of dental implants in subjects with diabetes. Articles published only in the English language were considered, and unpublished data were not sought.

**Results:** We initially identified 33 studies. Fifteen studies, which did not fulfill the selection criteria, were excluded. The included studies reported that poorly controlled diabetes negatively affects implant osseointegration; however, under optimal serum glycemic control, osseointegration can successfully occur in patients with diabetes. Animal studies have confirmed that osseointegration can be successfully achieved in insulin-controlled rats with diabetes, whereas in uncontrolled rats with diabetes, the bone-to-implant contact appears to decrease with time. The use of antiseptic mouthrinses and oral-hygiene maintenance helps in achieving a successful dental implant osseointegration in subjects with diabetes.

**Conclusion:** A successful dental implant osseointegration can be accomplished in subjects with diabetes with good metabolic control (serum glycemic level and hemoglobin A1c in normal range) in a similar manner as in subjects without diabetes. *J Periodontol* 2009;80:1719-1730.

### KEY WORDS

Dental implants; diabetes mellitus; hyperglycemia; osseointegration; periodontal bone loss.

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The implant treatment is an attractive substitute to the traditional fixed/removable prosthesis.<sup>1-4</sup> The literature<sup>5-7</sup> contains numerous observations on the significance of systemic disorders (e.g., diabetes mellitus, osteoporosis, and human immunodeficiency virus) as contraindications to dental endosseous-implant treatment, but the justification for these statements is often apparently allegoric, and their appropriateness in medically compromised patients is less equivocal.

Diabetes is a common metabolic disorder characterized by hyperglycemia due to impaired insulin secretion, insufficient insulin action, or both.<sup>8</sup> The main types of diabetes include type 1 and type 2 diabetes. Type 1 diabetes is associated with pancreatic  $\beta$ -cell destruction and accounts for 5% to 10% of the subjects with diabetes. Type 2 diabetes is associated with a relative, rather than an absolute, insulin deficiency and accounts for 90% to 95% of all individuals with diabetes.<sup>9</sup> Chronic hyperglycemia has been related to tissue damage because endothelial cells take up glucose passively in an insulin-independent manner.<sup>10</sup> Hyperglycemia is also associated with an altered host resistance such as defective migration of polymorphonuclear leukocytes, impaired phagocytosis, and an exaggerated inflammatory response to microbial products.<sup>11</sup> Individuals with poorly controlled diabetes are more susceptible to develop complications after implant therapy compared to individuals with well-controlled diabetes.<sup>12</sup> In addition, genetic mutations have been associated with the pathogenesis of type 1 and type 2 diabetes.<sup>13</sup> The treatment of diabetes focuses on the attainment of an optimal glycemic control to impede complications. The microvascular and macrovascular complications of diabetes are summarized in Table 1.

Compared to individuals without diabetes, patients with diabetes are more susceptible to periodontal disease, which is recognized as the sixth complication of

diabetes.<sup>14-19</sup> The underlying pathophysiology that increases the risk of periodontal disease in subjects with diabetes is poorly understood; however, it has been associated with the formation and accumulation of glucose-mediated advanced glycation end products (AGEs). AGEs contribute to the pathogenesis and altered periodontal wound healing observed in patients with diabetes by activating receptors called receptors for AGEs (RAGE) located on the periodontium.<sup>20,21</sup> These end products reduce the production of matrix proteins such as collagen and osteocalcin by gingival and periodontal fibroblasts.<sup>22-27</sup> It has been suggested that the pathogenesis of diabetes and its complications are associated with an increased RAGE expression.<sup>15,28</sup> Other cell types with RAGE expression include glomerular epithelial cells (podocytes), endothelial cells, vascular smooth muscle cells, inflammatory mononuclear phagocytes, and lymphocytes.<sup>28</sup> However, genetic and epigenetic factors may play a role in the pathogenesis of periodontal disease.<sup>16</sup>

In a review,<sup>29</sup> the deleterious effects of poorly controlled diabetes on periodontal bone have been addressed; however, the benefits of blood glucose maintenance on alveolar bone should be highlighted. Because hyperglycemia may negatively affect the outcome of implant therapy, and glycemic control is an essential parameter for the success of implants in individuals with diabetes,<sup>30-32</sup> the current systematic review aims to assess the effects of diabetes and glycemic control on the osseointegration of dental implants.

## MATERIALS AND METHODS

### Focused Questions

We attempted to answer the following focused questions: Can subjects with diabetes be good candidates for dental implant therapy? And how does hyperglycemia and glycemic control influence osseointegration?

### Search Protocol (data source and search strategy)

The MEDLINE/PubMed databases of the National Library of Medicine, Bethesda, Maryland, were used to search for appropriate articles addressing the focused questions. The databases were searched for articles dating from 1982 up to and including July 2009 using the following terms in different combinations: dental implants, immediate implants, osseointegration, periodontal disease, diabetes, hyperglycemia, metabolic control, and glycemic control.

### Eligibility Criteria

The following eligibility criteria were imposed: 1) human studies (individuals with type 1 and/or type 2 diabetes); 2) experimental studies (studies on diabetes-induced [DI] animals and blood cultures);

Table 1.

### Late-Onset Complications of Diabetes

Complications of Diabetes	
Microvascular Complications	Macrovascular Complications
Neuropathy	Peripheral vascular disease
Nephropathy	Cerebrovascular disease
Retinopathy	Cardiovascular disease
Erectile dysfunction	
Periodontal disease	

3) intervention: conventional dental implants and/or immediate loading of dental implants; 4) control group: in human studies, individuals without a diagnosis of diabetes, and in DI animal studies, non-diabetic animal models; 5) reference list of potentially relevant research articles; and 6) articles published only in the English language.

Titles and abstracts of articles obtained using the above described search strategy were screened by the authors (FJ and GER) and checked for agreement. The full texts of the articles, judged by the titles and abstracts to be relevant (by either FJ or GER), were read and independently evaluated against the stated eligibility criteria. Letters to the editor, historical reviews, and unpublished articles were excluded. Any disagreements between the authors were resolved via discussion. Hand searching was not carried out.

## RESULTS

The search strategy initially yielded 33 articles. Scrutiny of the titles and abstracts reduced the number of articles to 18, as shown in Table 2.<sup>7,31,33-48</sup> Fifteen studies, which did not comply with the selection protocol, were excluded (see Appendix).

Of the 18 articles included in this systematic review, 10 studies<sup>7,31,36,37,42-46,48</sup> were clinical and were either carried out at universities or oral health-care centers. Eight studies<sup>33-35,38-41,47</sup> were experimental and were mostly carried out in DI rats. One experimental study<sup>33</sup> was carried out in monkeys, and one study<sup>35</sup> was performed on blood cultures of monocytic cells and solutions containing elevated dextrose concentrations. Most experimental studies<sup>31,35,38-41,47</sup> quantified the bone or bone-like tissues present adjacent to the dental implants using histologic and histomorphometric techniques. Some clinical studies<sup>36,45,46</sup> compared the implant survival rates between individuals with diabetes and individuals without diabetes using techniques such as resonance frequency analysis, electronic mobility testing, life-table methods, radiographs, and measurements of clinical parameters of periodontal inflammation. Three clinical studies<sup>7,31,43</sup> measured periodontal inflammatory parameters (including bleeding on probing [BOP], clinical attachment level, and probing depth [PD]) to evaluate the implant survival rates in patients with diabetes. In several studies,<sup>31,34,35,37,38,42-45,47,48</sup> serum glycemic levels were monitored using standard techniques.

Seven studies<sup>7,33,34,36,38,40,47</sup> showed that diabetes negatively affected the osseointegration of dental implants; eleven studies<sup>31,35,37,39,41-46,48</sup> reported that a successful osseointegration can be accomplished in individuals with diabetes with an optimal

serum glycemic control. Among the clinical studies included in this review, eight studies<sup>7,31,37,42-45,48</sup> were prospective, and two studies<sup>36,46</sup> were retrospective. In three clinical studies,<sup>36,43,44</sup> pre- and postoperative broad-spectrum antibiotics were administered to the patients with diabetes undergoing implant surgery to reduce the risk of infection; whereas in studies by Balshi et al.<sup>37</sup> and Olson et al.,<sup>45</sup> an antibiotic cover was not given to the patients with diabetes.

## DISCUSSION

The use of dental implants in patients with diabetes is a debatable issue due to the adverse effects of hyperglycemia on osseointegration.<sup>7,33,34,36,49-51</sup> Type 2 diabetes may increase the host inflammatory response to oral biofilm, which, in turn, may exacerbate preconditions associated with gingivitis in susceptible individuals.<sup>52</sup> Evidence is lacking to indicate that implant therapy in patients with diabetes yields long-term outcomes comparable with those of subjects without diabetes.<sup>53</sup> The results of a study by Kopman et al.<sup>40</sup> using a rat model confirmed that diabetes inhibits osseointegration as defined by marrow bone-to-implant contact. Human studies<sup>18,54</sup> have reported that there is an increased alveolar bone loss in patients with diabetes compared to individuals without diabetes. This may be explained by an increased production of proinflammatory cytokines (such as interleukin [IL]-1 $\beta$  and -6 and tumor necrosis factor-alpha [TNF- $\alpha$ ]) in the serum and gingival crevicular fluid (GCF) due to the accelerated AGE-RAGE interactions in patients with diabetes.<sup>55-57</sup> An increased expression of proinflammatory cytokines has been observed in bone tissues, thereby supporting the idea that bone, by itself, exhibits an inflammatory response in diabetes.<sup>58</sup> In general, such mechanisms would probably lead to the enhanced formation of osteoclasts and increased bone loss. Figure 1 shows the pathologic remodeling of bone observed in inflammatory disorders resulting from insufficient bone formation after resorption.

A strict glycemic control has been shown to reduce microvascular complications in diabetes.<sup>59</sup> It has been reported that maintenance of serum glycemic levels may help to improve the function of osteoblasts, and the progression of periodontal bone loss is markedly reduced in subjects with well-controlled diabetes compared to individuals with poorly controlled diabetes.<sup>60,61</sup> The serum and GCF concentrations of proinflammatory cytokines are also significantly reduced in subjects with well-controlled diabetes compared to individuals with poorly controlled diabetes.<sup>62,63</sup> In addition, metabolic control of diabetes has been related to a significant reduction in serum and urinary

**Table 2.**  
**Aim, Design, Statistical Method, Outcome, and Conclusions of Selected Studies**

Investigators, Year	Aim	Study Design	Statistical Methods	Outcome	Main Conclusions
Messer et al., 2009 <sup>33</sup>	To study the corrosion properties of titanium implants in blood, cultures of monocytic cells, and solutions containing elevated dextrose concentrations.	Experimental	ANOVA and Tukey post hoc analysis	Positive	Inflammatory stress and hyperglycemia may increase the corrosion of dental endosseous titanium-based implants.
Tawil et al., 2008 <sup>31</sup>	To investigate the effect of type 2 diabetes on implant survival and complication rate.	Clinical	For continuous data, Student <i>t</i> and Mann-Whitney tests; for comparison between baseline and follow-up data, Wilcoxon signed-rank test	Positive	Individuals with well-controlled diabetes have implant survival rates similar to that of controls without diabetes.
Hasegawa et al., 2008 <sup>34</sup>	To study the histologic and histomorphometric pattern of bone healing around titanium implants in a type 2 diabetes rat model.	Experimental	ANOVA and Student <i>t</i> -test	Positive	Type 2 diabetes impairs the osseointegration capacity of dental implants.
Casap et al., 2008 <sup>35</sup>	To assess the osseointegration of implants in the gerbil <i>Psammomys obesus</i> , a model of nutritionally induced type 2 diabetes.	Experimental	Scheffe test and Pearson product-moment correlation	Indecisive	No significant difference in osseointegration and TBV was seen between diabetic and control groups.
Alsaadi et al., 2007 <sup>36</sup>	To assess the influence of systemic and local bone and intraoral factors on the occurrence of early implant failures.	Clinical	Logistic regression	Positive	Local and systemic factors interfere with the osseointegration of dental implants.
Balshi et al., 2007 <sup>37</sup>	To evaluate the stability of 18 immediately loaded dental implants in an insulin-controlled 71-year-old patient with diabetes over the first 30 months after surgery and to correlate this data with implant stability in healthy patients.	Clinical	NA	Positive	An immediate-loading protocol can be successful and result in osseointegration in patients with diabetes.
Ferreira et al., 2006 <sup>7</sup>	To verify the prevalence of peri-implant disease and analyze possible risk variables associated with peri-implant mucositis and peri-implantitis.	Clinical	For independent variables (age, gender, and diabetes), Pearson $\chi^2$ test; for degree of association, a multinomial logistic regression model	Positive	Individuals with diabetes are more prone to develop peri-implantitis.
McCracken et al., 2006 <sup>38</sup>	To measure bone response to implants in uncontrolled and insulin-controlled rats with diabetes.	Experimental	Two-way ANOVA	Positive	Diabetes is associated with increased bone response compared to controls.

**Table 2. (continued)****Aim, Design, Statistical Method, Outcome, and Conclusions of Selected Studies**

Investigators, Year	Aim	Study Design	Statistical Methods	Outcome	Main Conclusions
Kwon et al., 2005 <sup>39</sup>	To histologically evaluate the bone-to-implant contact in uncontrolled and insulin-controlled rats.	Experimental	Unpaired <i>t</i> test and ANOVA	Positive	Bone-to-implant contacts are maintained in insulin-controlled rats with diabetes compared to rats with uncontrolled diabetes.
Kopman et al., 2005 <sup>40</sup>	To histologically evaluate the effects of aminoguanidine and doxycycline in the modification of peri-implant wound healing around endosseous implants in rats with diabetes.	Experimental	ANOVA	Positive	Diabetes inhibits osseointegration, as defined by marrow bone-to implant contact.
Siqueira et al, 2003 <sup>41</sup>	To investigate the course of histologic and ultrastructural changes of the osseointegration process under the influence of insulin.	Experimental	ANOVA and Tukey-Kramer multiple comparisons test	Positive	Bone repair around endosseous implants is regulated by insulin, and metabolic control of the patient with diabetes is essential for a successful osseointegration.
Peled et al., 2003 <sup>42</sup>	To evaluate implant success rates in patients with diabetes.	Clinical	Pearson correlation coefficient test	Positive	The clinical outcome of dental implants in patients with well-controlled type 2 diabetes is positive and encouraging.
Farzad et al., 2002 <sup>43</sup>	To investigate the outcome of dental implant treatment for patients treated at a dental clinic.	Clinical	NA	Positive	Individuals with diabetes that undergo dental implant treatment do not encounter a higher failure rate than the normal population, provided the plasma glucose level of the individual with diabetes is normal or close to normal.
Abdulwassie and Dhanrajani, 2002 <sup>44</sup>	To assess the implant survival rate in patients with diabetes.	Clinical	NA	Positive	Dental implants can be successfully used in patients with diabetes provided blood sugar levels are under control.
Olson et al., 2000 <sup>45</sup>	To assess the success of two-stage endosseous root-form implants (three different implant systems) in subjects with type 2 diabetes.	Clinical	Regression analysis	Positive	There was no difference in failure rates between the three different implant systems used. This study supports the use of dental implants in patients with type 2 diabetes.

**Table 2. (continued)****Aim, Design, Statistical Method, Outcome, and Conclusions of Selected Studies**

Investigators, Year	Aim	Study Design	Statistical Methods	Outcome	Main Conclusions
Balshi and Wolfinger, 1999 <sup>46</sup>	To report the results of placing dental implants in patients with diabetes.	Clinical	NA	Positive	Screening for diabetes and trying to ensure that implant candidates are in metabolic control are recommended to increase the chances of successful osseointegration.
Nevins et al., 1998 <sup>47</sup>	To identify the effects of streptozotocin-induced diabetes on osseointegration.	Experimental	ANOVA and Bonferroni test	Positive	The process of osseointegration is affected by streptozotocin-induced diabetes.
Shernoff et al., 1994 <sup>48</sup>	To assess the survival rates of dental implants placed in individuals with type 2 diabetes.	Clinical	NA	Positive	Patients with type 2 diabetes can be considered for dental implant therapy.

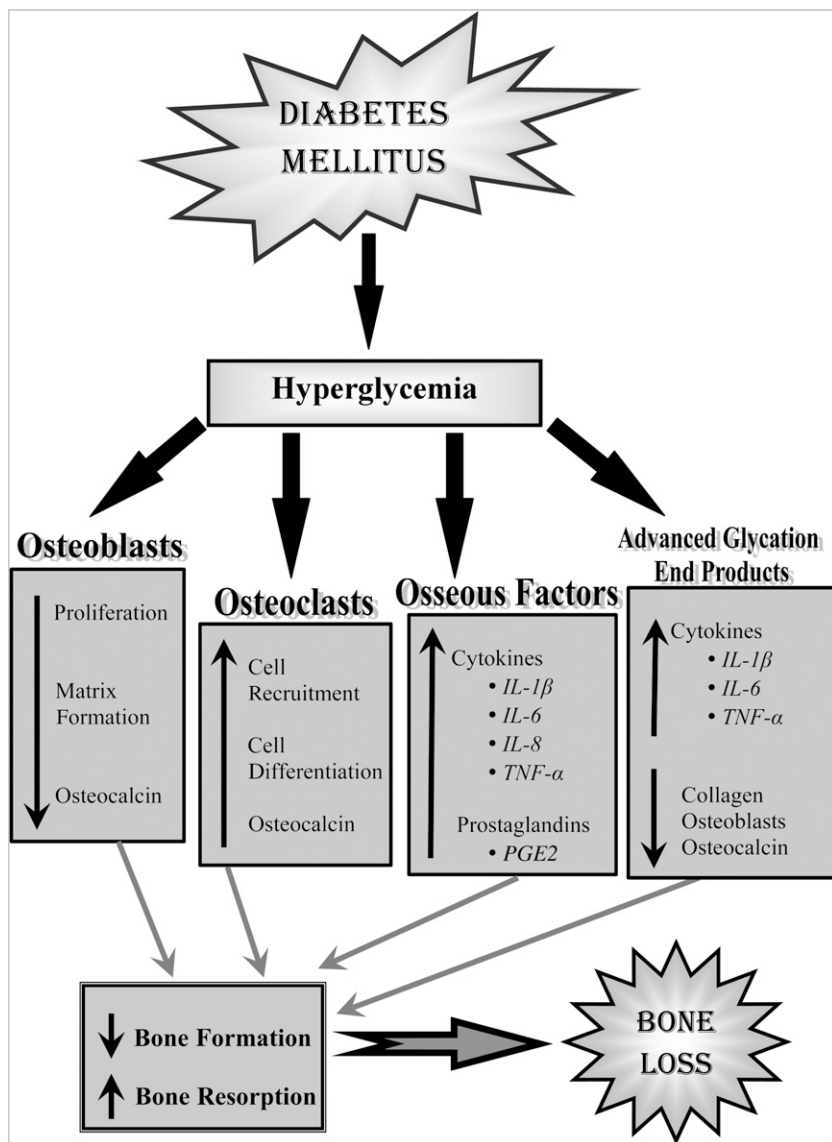
ANOVA = analysis of variance; TBV = trabecular bone volume; NA = not available.

bone-resorption parameters, such as osteocalcin, pyridinoline, and bone-specific alkaline phosphatase.<sup>64</sup> Therefore, under optimal glycemic control, subjects with diabetes can have a periodontal bone height similar to that of healthy individuals.

Studies<sup>14,35</sup> on DI rat models have shown that insulin therapy is able to upregulate bone formation around implants. Furthermore, the results of Kwon et al.<sup>39</sup> showed that osseointegrated dental implants in insulin-controlled rats with diabetes maintained bone-to-implant contacts over a 4-month period, whereas in uncontrolled rats with diabetes, the bone-to-implant contact appeared to decrease with time.<sup>39</sup> Likewise, clinical studies have shown that dental implant therapy can be offered to patients with diabetes. In a study by Shernoff et al.,<sup>48</sup> 178 implants were placed in 89 patients with diabetes; the results demonstrated a success rate of 92.7% over a year. Farzad et al.<sup>43</sup> placed a total of 136 implants in 25 individuals with diabetes (aged 47 to 79 years), and the implant survival rate was 96.3% and 94.1% during the healing period and 1 year after surgery, respectively. Tawil et al.<sup>31</sup> reported no significant difference in the implant survival rate between individuals with well-controlled (hemoglobin A1c [HbA1c] <7%) diabetes and controls without diabetes; the overall implant survival rate for individuals with and without diabetes was similar, that is, 97.2% and 98.8%, respectively. However, Dowell et al.<sup>65</sup> found no evidence of compromise in implant success in subjects with poorly

controlled diabetes compared to controls without diabetes. In general, it is accepted that individuals with well-controlled diabetes have similar rates of success for dental implants as individuals without diabetes.<sup>42,66</sup>

Immediate functional loading of dental implants is possible, and studies<sup>67-72</sup> have shown that immediate loading of dental implants (with light forces) does not negatively affect the bone-healing pattern. A histologic and histomorphometric investigation<sup>73</sup> of human-retrieved implants after immediate loading showed evidence of osseointegration and the presence of dense lamellar bone at the interface. Studies<sup>31,43,74</sup> have shown that successful osseointegration of immediately loaded dental implants can be achieved in patients with diabetes provided their plasma glucose levels are under the normal range. A case report<sup>37</sup> investigated the stability of 18 immediately loaded dental implants in a 71-year-old patient with well-controlled type 1 diabetes. The results showed that all 18 implants remained functional after 2.5 years of follow-up, and the implant stability increased. The study concluded that immediate loading can successfully osseointegrate implants in subjects with well-controlled diabetes.<sup>37</sup> Another study<sup>31</sup> showed that immediately loaded implants can be successfully osseointegrated in individuals with type 2 diabetes provided their serum glycemic levels are controlled. This may be explained by results from Javed et al.<sup>18</sup> that showed that periodontal bone loss



**Figure 1.**  
Impact of hyperglycemia on bone.

is markedly reduced in individuals with diabetes with optimal glycemic control compared to patients with poorly controlled diabetes.

The influence of age and duration of diabetes on the success of dental implants has been investigated.<sup>31,74,75</sup> Studies<sup>31,74</sup> involving patients with diabetes have shown that there is no association of age with the survival rates of dental implants. Tawil et al.<sup>31</sup> compared the implant survival rates between subjects with diabetes and subjects without diabetes aged ≤60 years and >60 years; the results showed no effect of age on the survival rate of dental implants. Similar results were reported by Morris et al.,<sup>74</sup> as shown in Figure 2. However, in a recent study,<sup>75</sup> the mean age of healthy subjects experiencing implant

loss was reported to be 51.7 years at the time of insertion. To evaluate the influence of duration of diabetes on implant survival rate, Tawil et al.<sup>31</sup> divided the patients with diabetes into four groups (with reference to duration of diabetes), and the results showed no significant differences in implant survival rates between the groups (Fig. 3). All patients with diabetes participating in the study<sup>31</sup> had well-controlled diabetes. Therefore, it may be postulated that the duration of diabetes does not negatively influence the implant survival rate under optimal serum glyce-mic control.

Although maintenance of serum glycemic levels plays a pivotal role in a successful osseointegration, there are other factors that may assist in enhancing implant survival rates in patients with diabetes. It is essential to maintain a periodontal healthy environment for successful dental implant treatment. It has been reported that inflammatory periodontal diseases may increase insulin resistance in a way similar to obesity, thereby aggravating glycemic control.<sup>76</sup> Dental plaque contains microbes, such as *Porphyromonas gingivalis* (*P. gingivalis*), which significantly contribute to periodontal destruction.<sup>77</sup> Dental plaque is a major etiologic factor in periodontal destruction, and studies<sup>18,78</sup> have reported higher scores of the plaque index, BOP, and PD in patients with diabetes compared to controls without diabetes. Inflammatory reactions in the peri-implant tissues have been associated with the presence of dental plaque around implants.<sup>79,80</sup> An in vitro study showed that bacterial adhesion on implant surfaces has a strong influence on the healing and long-term prognosis of dental implants.<sup>81</sup> Periodontal therapy has been shown to improve glycemic control in patients with diabetes.<sup>82</sup> Effective treatment of periodontal infection and reduction of periodontal inflammation have been associated with a reduction in the level of glycosylated hemoglobin, but a confirmatory study with a larger sample size and controlled diet is necessary.<sup>83,84</sup> In high-fat fed rats with diabetes, periodontitis accelerated the onset of severe insulin resistance and impaired glucose homeostasis.<sup>85</sup> Thus, control and treatment of periodontal infections should be an important part of the overall

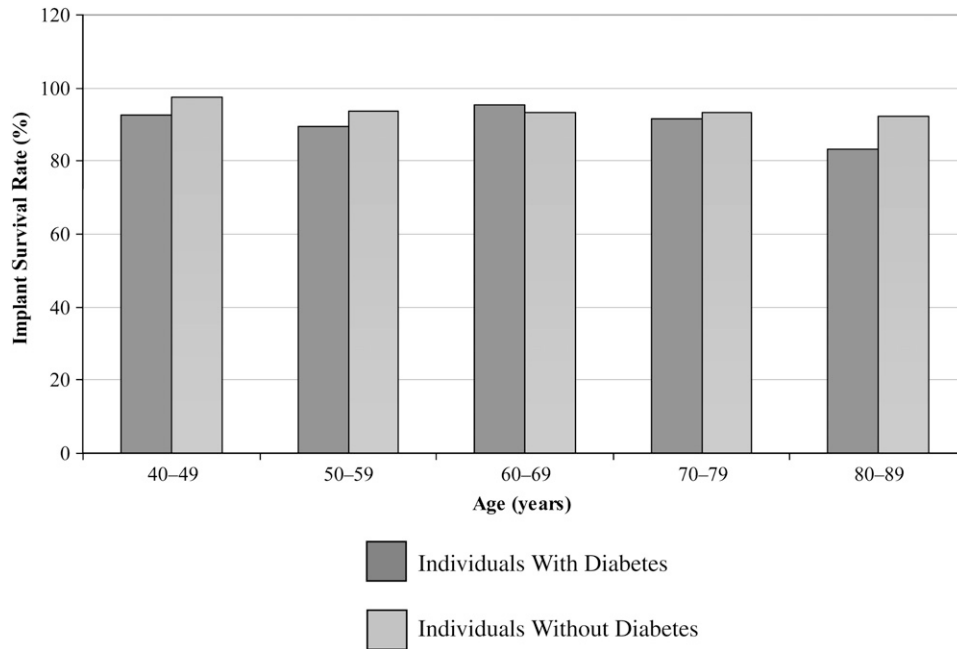
management of patients with diabetes and, consequently, could play an important role in successful implant therapy.

It has been reported that the use of chlorhexidine mouthrinse is effective at reducing the viability of *P. gingivalis* infection and peri-implant mucositis.<sup>77,86,87</sup> A twice daily use of an antiseptic mouthwash has been suggested for the maintenance of dental implants.<sup>88</sup>

**CONCLUSIONS**

A successful dental implant osseointegration and high implant survival rates can be accomplished in subjects with diabetes with good metabolic control (serum glycemic level and HbA1c in the normal range) in a similar manner as subjects without diabetes. The use of antiseptic mouthrinses and oral hygiene maintenance helps in achieving a successful dental implant osseointegration in subjects with diabetes.

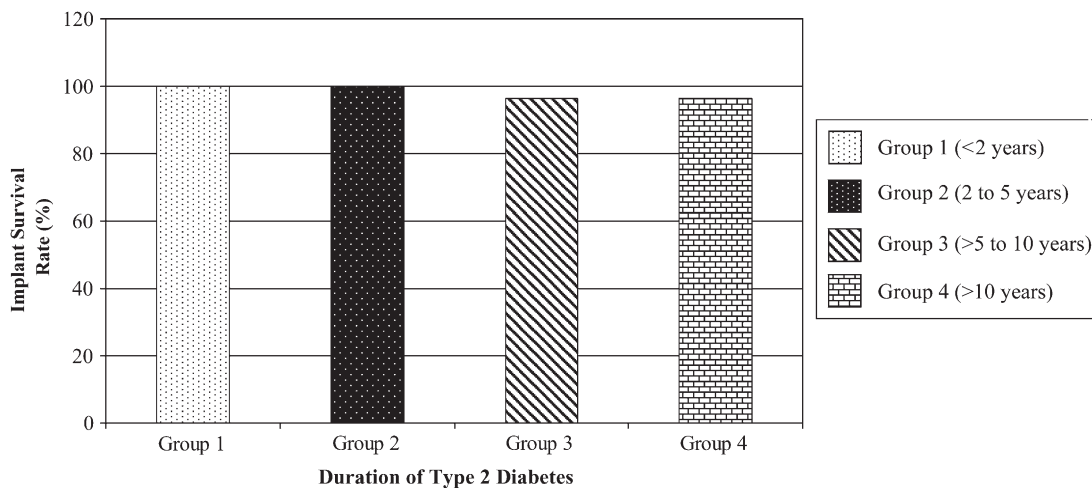
Thus, control and treatment of periodontal infections should be an important part of the overall management of patients with diabetes mellitus and consequently could play an important role in successful implant therapy. However, dental implant therapy remains contraindicated in subjects with diabetes without good metabolic control, which is frequently associated with obesity and cardiovascular disease, because of the negative effects of hyperglycemia associated with microangiopathy and AGE accumulation on peri-implant hard and soft tissues.



**Figure 2.** Effect of age on the survival rates of dental implants in patients with diabetes (dark gray) compared to those without diabetes (light gray) (modified from Morris et al.<sup>74</sup>).

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**Figure 3.** Effect of duration of diabetes on implant survival rate (based on data from Tawil et al.,<sup>31</sup> with permission from Quintessence Publishing Co., Inc.).



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#### APPENDIX: EXCLUDED STUDIES

The following studies were excluded because they did not present the variables preestablished in the selection strategy:

1. Bugea C, Luongo R, Di Iorio D, Cocchetto R, Celletti R. Bone contact around osseointegrated implants: Histologic analysis of a dual-acid-etched surface implant in a diabetic patient. *Int J Periodontics Restorative Dent* 2008;28:145-151.
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