CLINICAL REVIEW

Diabetes and Oral Implant Failure: A Systematic Review

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ABSTRACT

The aim of this systematic review and meta-analysis was to investigate whether there are any effects of diabetes mellitus on implant failure rates, postoperative infections, and marginal bone loss. An electronic search without time or language restrictions was undertaken in March 2014. The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Eligibility criteria included clinical human studies. The search strategy resulted in 14 publications. The I^2 statistic was used to express the percentage of total variation across studies due to heterogeneity. The inverse variance method was used for the random effects model when heterogeneity was detected or for the fixed effects model when heterogeneity was not detected. The estimates of an intervention for dichotomous outcomes were expressed in risk ratio and in mean difference in millimeters for continuous outcomes, both with a 95% confidence interval. There was a statistically significant difference (p = .001; mean difference = 0.20, 95% confidence interval = 0.08, 0.31) between diabetic and non-diabetic patients concerning marginal bone loss, favoring non-diabetic patients. A meta-analysis was not possible for postoperative infections. The difference between the patients (diabetic vs. non-diabetic) did not significantly affect implant failure rates (p = .65), with a risk ratio of 1.07 (95% confidence interval = 0.80, 1.44). Studies are lacking that include both patient types, with larger sample sizes, and that report the outcome data separately for each group. The results of the present meta-analysis should be interpreted with caution because of the presence of uncontrolled confounding factors in the included studies.

KEY WORDS: diabetes mellitus, blood glucose, dental implants, infection, periodontal bone loss, meta-analysis.

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A supplemental appendix to this article is published electronically only at http://jdr.sagepub.com/supplemental.

INTRODUCTION

Dental implant survival is initially dependent on successful osseointegration following placement. Any alteration of this biological process by excessive surgical trauma, infection, or metabolic upset may adversely affect treatment outcomes (Accursi, 2000). Subsequently, as an implant is restored and placed into function, bone remodeling becomes a critical aspect of implant survival in responding to the functional demands placed on the implant restoration and supporting bone. The critical dependence on bone metabolism for implant survival may be heightened in patients with diabetes (Oates *et al.*, 2013). Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin that it produces. The number of people with diabetes increased from 153 million (95% uncertainty interval = 127, 182) in 1980 to 347 million (95% uncertainty interval = 314, 382) in 2008 (Danaei *et al.*, 2011). These trends highlight the urgency for a better understanding of diabetes as well as for improving the care of patients with diabetes.

Diabetic patients have increased frequency of periodontitis and tooth loss (Khader *et al.*, 2006), and diabetes has been considered a risky condition for dental implants with the fact that it is associated with delayed wound healing (Rothwell and Richard, 1984), prevalence of microvascular disease (Frantzis *et al.*, 1971), and impaired response to infection (McMahon and Bistrian, 1995). Accordingly, diabetes remains a relative contraindication for implant therapy (Michaeli *et al.*, 2009); that is, well-controlled diabetic patients may be considered appropriate for implant therapy, while diabetic patients lacking good glycemic control may be denied the benefits of implant therapy (Oates *et al.*, 2013). Decreased levels of implant osseointegration have been demonstrated in hyperglycemic animals consistent with untreated type 1 diabetes (Siqueira *et al.*, 2003; de Morais *et al.*, 2009). However, the subject is contradictory, since numerous studies offer indirect evidence for diabetes patients benefiting from oral rehabilitation based on dental implant therapy.

The ability to anticipate outcomes is an essential part of risk management in an implant practice. Recognizing conditions that place the patient at a higher risk of failure will allow the surgeon to make informed decisions and refine the treatment plan to optimize the outcomes (Chrcanovic *et al.*, 2014). The use of implant therapy in special populations requires consideration of potential benefits to be gained from the therapy. To better appreciate this potential, we conducted a systematic review and meta-analysis of published clinical studies to investigate whether dental implant placement in diabetic *vs.* non-diabetic patients yields any detrimental effects on implant failure rates, postoperative infection, and marginal bone loss. The present study presents a more detailed and profound analysis of the influence of diabetes on implant

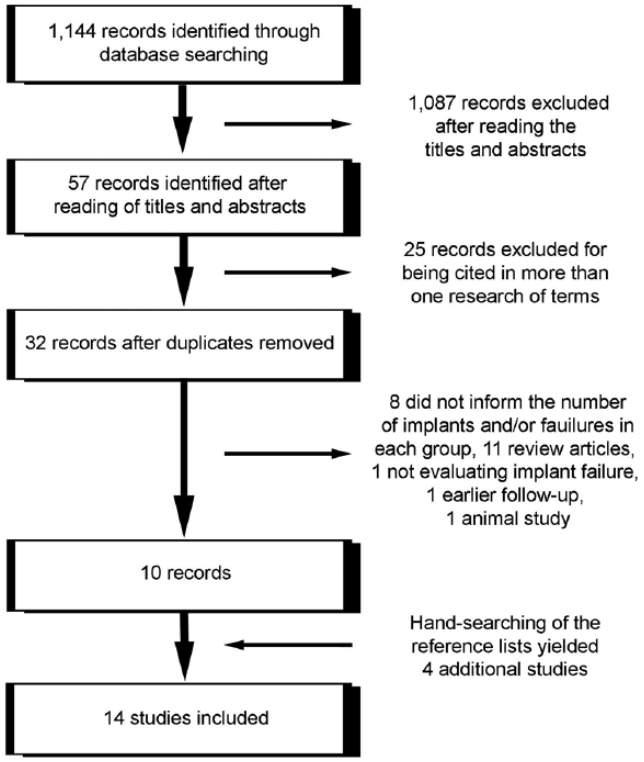

Figure 1. Study screening process.

failure rates previously assessed in a published systematic review (Chrcanovic *et al.*, 2014).

MATERIALS & METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Moher *et al.*, 2009). A review protocol does not exist. For the objective, search strategies, inclusion and exclusion criteria, study selection, and quality assessment, see the Appendix.

Data Extraction and Meta-analysis

From the studies included in the final analysis, the following data were extracted (when available): year of publication, study design, unicenter or multicenter study, number of patients, patients' age, follow-up, days of antibiotic prophylaxis, mouth rinse, implant healing period, failed and placed implants, postoperative infection, marginal bone loss, and implant surface modification. Contact with authors for possible missing data was performed.

Implant failure and postoperative infection were the dichotomous outcomes measures evaluated. Weighted mean differences were used to construct forest plots of marginal bone loss, a continuous outcome. The statistical unit for "implant failure" and "marginal bone loss" was the implant, and for "postoperative infection," it was the patient. Whenever outcomes of interest were not clearly stated, the data were not used for analysis. The I^2 statistic was used to express the percentage of the total variation across studies due to heterogeneity, with 25%, 50%, and 75% corresponding to low, moderate, and high heterogeneity. The inverse variance method was used for random or fixed effects model. Where statistically significant ($p < .10$) heterogeneity is detected, a random effects model was used to assess the significance of treatment effects. Where no statistically significant heterogeneity is found, analysis was performed with a fixed effects model (Egger and Smith, 2003). The estimates of an intervention for dichotomous outcomes were expressed in risk ratio and for continuous outcomes in mean difference in millimeters, both with a 95% confidence interval. Only if there were studies with similar comparisons reporting the same outcome measures was meta-analysis attempted.

A funnel plot was drawn (*i.e.*, plot of effect size *vs.* standard error). Asymmetry of the funnel plot may indicate publication bias and other biases related to sample size, although the asymmetry may also represent a true relationship between trial size and effect size.

The data were analyzed with the statistical software Review Manager (version 5.2.8, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark, 2014).

RESULTS

For the literature search, see Figure 1 and the Appendix.

Description of the Studies

Detailed data of the 14 included studies are listed in Tables 1 and 2. The meta-analysis included 7 controlled clinical trials (Morris *et al.*, 2000; van Steenberghe *et al.*, 2002; Dowell *et al.*, 2007; Alsaadi *et al.*, 2008a; Tawil *et al.*, 2008; Levin *et al.*, 2011; Grandi *et al.*, 2013) and 7 retrospective analyses (Keller *et al.*, 1999; Accursi, 2000; Doyle *et al.*, 2007; Alsaadi *et al.*, 2008b; Anner *et al.*, 2010; Bell *et al.*, 2011; Le *et al.*, 2013). The study of Grandi *et al.* (2013) was a randomized clinical trial for immediately *vs.* early loaded implants but not for diabetic *vs.* non-diabetic patients. Thus, here it was considered a controlled clinical trial.

From the studies with available data of patients' age, 3 included nonadult patients (Keller *et al.*, 1999; Accursi, 2000; van Steenberghe *et al.*, 2002). Three studies did not inform of the patients' ages (Morris *et al.*, 2000; Alsaadi *et al.*, 2008b; Bell *et al.*, 2011). Four studies included only patients with diabetes type 2 (Keller *et al.*, 1999; Morris *et al.*, 2000; Dowell *et al.*, 2007; Tawil *et al.*, 2008); 5 studies included patients with type 1 and type 2 diabetes (Accursi, 2000; van Steenberghe *et al.*, 2002; Doyle *et al.*, 2007; Alsaadi *et al.*, 2008a; Alsaadi *et al.*, 2008b); and 4 studies did not offer such information (Anner *et al.*, 2010; Bell *et al.*, 2011; Levin *et al.*, 2011; Le *et al.*, 2013). Two studies (Dowell *et al.*, 2007; Tawil *et al.*, 2008) provided information about the patients' glycemic control through the estimation of glycosylated hemoglobin (HbA1c). Only 2 studies (Accursi, 2000; Tawil *et al.*, 2008) provided information about marginal bone loss. Three studies provided information about postoperative infection (Dowell *et al.*, 2007; Tawil *et al.*, 2008; Bell *et al.*, 2011), with 15 occurrences among 780 patients receiving 1,471 implants. In one study (Bell *et al.*, 2011), all implants were inserted in fresh extraction sockets, whereas another one (Le *et al.*, 2013) inserted only short implants (≤9 mm) restored with single-unit nonsplinted restorations, and

Table 1. Detailed Data of the Included Studies

Study	Design[a]	Patients, *n*	Age,[b] yr	Follow-up	Implants		p^c	Infection[d]
					Failed / Placed, *n*	Failure Rate, %		
Keller *et al.*, 1999	RA	54 (2, G1; 52, G2)	15-73 (28-59)	12 y	0 / 11 (G1), 33 / 237 (G2)	0 (G1), 13.92 (G2)	NM	NM
Accursi, 2000	RA	45 (15, G1; 30, G2)	42-83 (57.2, G1), 15-77 (55.7, G2)	1-17 y	4 / 59 (G1), 7 / 111 (G2)	6.78 (G1), 6.31 (G2)	.905	NM
Morris *et al.*, 2000	CCT	663 (NM)	NM	36 mo	20 / 255 (G1), 180 / 2632 (G2)	7.84 (G1), 6.84 (G2)	NM	NM
van Steenberghe *et al.*, 2002	CCT	399 (NM)	15-80 (50)	NM	0 / 31 (G1), 27 / 1232 (G2)	0 (G1), 2.19 (G2)	NM	NM
Dowell *et al.*, 2007	CCT	35 (25, G1; 10, G2)	51-81 (NM, G1), 29-61 (45.7, G2)	4 mo	0 / 39 (G1), 0 / 11 (G2)	0 (G1), 0 (G2)	NM	0 (G1), 0 (G2)
Doyle *et al.*, 2007	RA	171 (3, G1; 168, G2)[e]	NM (47.5)	At least 1 yr	0 / 3 (G1), 12 / 193 (G2)[e]	0 (G1), 6.22 (G2)	NM	NM
Alsaadi *et al.*, 2008a	CCT	283 (NM)	18-86 (56.2)	6 mo	2 / 26 (G1), 13 / 694 (G2)	7.69 (G1), 1.87 (G2)	.02 (type 1), .39 (type 2)	NM
Alsaadi *et al.*, 2008b	RA	412 (10, G1; 402, G2)	NM	≤2 yr after abutment connection	0 / 34 (G1), 101 / 1480 (G2)	0 (G1), 6.82 (G2)	>.05	NM
Tawil *et al.*, 2008	CCT	90 (45, G1; 45, G2)	43-84 (64.7, G1)	*M* = 42.4 mo (1-12 y)	6 / 255 (G1), 1 / 244 (G2)	2.35 (G1), 0.41 (G2)	.66	7 (G1), 0 (G2)
Anner *et al.*, 2010	RA	475 (49, G1; 426, G2)	NM (52)	*M* = 31 mo (1-114)	5 / 177 (G1), 72 / 1449 (G2)	2.82 (G1), 4.97 (G2)	.2076	NM
Bell *et al.*, 2011	RA	655 (NM)	NM	*M* = 20 mo (3-93)	0 / 83 (G1), 15 / 839 (G2)	0 (G1), 1.79 (G2)	NM	8 (G1 + G2)
Levin *et al.*, 2011	CCT	717 (81, G1; 636, G2)	NM (51)	*M* = 54 mo (≤114)	10 / 263 (G1), 83 / 1996 (G2)[e]	3.80 (G1), 4.16 (G2)	NM	NM
Grandi *et al.*, 2013	RCT[f]	80 (3, G1; 77, G2)	39-65 (52-55)	3, 6, 9, 12, 18, 24, 30, 36 mo	0 / 6 (G1), 0 / 155 (G2)[e]	0 (G1), 0 (G2)	NM	NM
Le *et al.*, 2013	RA	168 (18, G1; 150, G2)	34-87 (61)	*M* = 37 mo (21-94)	2 / 18 (G1), 11 / 203 (G2)	11.11 (G1), 5.42 (G2)	.32	NM

NM, not mentioned; CCT, controlled clinical trial; RCT, randomized controlled trial; RA, retrospective analysis; G1, diabetic patients group; G2, non-diabetic patients group.
[a]All studies are unicenter, except Morris *et al.* (2000), which is multicenter.
[b]Mean, range.
[c]For failure rate.
[d]Postoperative.
[e]Unpublished information was obtained by personal communication with one of the authors.
[f]The study was an RCT for immediately *vs.* loaded implants but not for diabetic and non-diabetic patients.

in one study (Keller *et al.*, 1999), all implants were placed in grafted maxillary sinus or nasal floor with autologous inlay bone. Two studies (Dowell *et al.*, 2007; Alsaadi *et al.*, 2008a) had a follow-up to 6 mo; 6 studies had a follow-up of at least 1 yr (Keller *et al.*, 1999; Accursi, 2000; Morris *et al.*, 2000; Doyle *et al.*, 2007; Alsaadi *et al.*, 2008b; Grandi *et al.*, 2013); 5 studies (Tawil *et al.*, 2008; Anner *et al.*, 2010; Bell *et al.*, 2011; Levin *et al.*, 2011; Le *et al.*, 2013) had follow-ups ranging from a mean of 20 to 54 mo, whereas 1 study (van Steenberghe *et al.*, 2002) did not inform of the follow-up period.

Not every article provided information about the number of failed implants by group. Unpublished information concerning the number of failed implants in each group was obtained by personal communication with 1 of the authors in 2 studies (Doyle *et al.*, 2007; Levin *et al.*, 2011). From the 14 studies, a total of 1,260 dental implants were inserted in diabetic patients, with 49 failures (3.89%), and 11,476 implants were inserted in non-diabetic patients, with 555 failures (4.84%). Six studies (Keller *et al.*, 1999; Morris *et al.*, 2000; van Steenberghe *et al.*, 2002; Doyle *et al.*, 2007; Bell *et al.*, 2011; Levin *et al.*, 2011) did not inform whether there was a statistically significant difference or not for the implant failure rates between non-diabetic and diabetic patients, whereas the other 5 studies (Accursi, 2000; Alsaadi *et al.*, 2008b; Tawil *et al.*, 2008; Anner *et al.*, 2010; Le *et al.*, 2013) did not find a statistically significant difference. One study (Alsaadi *et al.*, 2008a) compared the implant failure rates for the non-diabetic patients with the type 1 and type 2 diabetic patients separately, with statistical and nonstatistical

Table 2. Further Data of Included Studies

Authors	Antibiotics / Mouth Rinse, d	Healing Period / Loading	Marginal Bone Loss, mm (Mean ± SD)	Diabetes Type (Patients, *n*)
Keller *et al.*	NM	NM	NM	2
Modification[a]	Turned (Brånemark, Nobel Biocare, Göteborg, Sweden)			
Observations	All implants placed in grafted maxillary sinus or nasal floor with autologous inlay bone; 73 in ex-smokers, 32 in smokers, 11 in patients irradiated			
Accursi	NM	NM	0.25 ± 0.07 (G1),[b] 0.06 ± 0.03 (G2)[b]	1 (2); 2 (13)
Modification	Turned (Brånemark, Nobel Biocare)			
Observations	Smokers: 53.3% (G1), 31.6% (G2)			
Morris *et al.*	Used, but details were not informed	NM	NM	2
Modification	Turned (Spectra System, Core-Vent Corporation, DBA Paragon Company, Encino, USA; *n* = 1,094), HA coated (Spectra System, Core-Vent Corporation; *n* = 1,793)			
Observations	—			
van Steenberghe *et al.*	NM	NM	NM	1 (NM) and 2 (NM)
Modification	Turned (Brånemark, Nobel Biocare)			
Observations	Graft in 4 patients, about 12% smokers			
Dowell *et al.*	7-10 (G1), 3 (G2) / NM	4 mo (no load was applied)	NM	2
Modification	Sandblasted and acid etched (SLA, Straumann, Waldenburg, Switzerland)			
Observations	Implants inserted after at least 4 mo of healing after tooth extraction; no smokers, no grafts			
Doyle *et al.*	NM	NM	NM	1 (NM) and 2 (NM)
Modification	NM			
Observations	10 smokers			
Alsaadi *et al.*	1 (for 378 implants) / NM	6 mo (no load was applied)	NM	1 (NM) and 2 (NM)
Modification	Oxidized (Mk III, TiUnite, Nobel Biocare)			
Observations	Implants: 95 in smokers, 9 inserted in fresh extraction sockets			
Alsaadi *et al.*	NM	NM	NM	1 (1) and 2 (9)
Modification	Turned (Brånemark, Nobel Biocare; *n* = 1,316), oxidized (Mk III, TiUnite, Nobel Biocare; *n* = 198)			
Observations	61 smokers (223 implants)			
Tawil *et al.*	7 / 14	Immediate (58, G1; 59, G2), "conventional" (197, G1; 185, G2)	0.3 ± 0.5 (G1),[c] 0.7 ± 0.9 (G1),[c] 0.21 ± 0.3 (G2)	2
Modification	Turned (Brånemark, Nobel Biocare; *n* = 75, G1; *n* = 104, G2), oxidized (TiUnite, Nobel Biocare; *n* = 180, G1; *n* = 140, G2)			
Observations	Some implants were placed in fresh extraction, but the exact number was not informed: 62 sinus lift (34, G1; 28, G2), 35 guided bone regeneration (20, G1; 15, G2), 40 smokers (22, G1; 18, G2)			
Anner *et al.*	NM	NM	NM	NM
Modification	NM			
Observations	63 smokers			
Bell *et al.*	1 / 1	3 months	NM	NM
Modification	Sandblasted and acid etched (SLA, Straumann)			
Observations	All implants placed in fresh extraction sockets: 123 placed in smokers, 24 in patients taking biphosphonates			
Levin *et al.*	NM	NM	NM	NM
Modification	NM			
Observations	103 smokers			
Grandi *et al.*	7 / 10	Immediate (*n* = 81), 2 mo (*n* = 80)	NM	NM
Modification	Double acid-etched (JDEvolution, JDentalCare, Modena, Italy)			
Observations	22 light smokers (less than 10 cigarettes/d)			
Le *et al.*	NM	NM	NM	NM
Modification	Sandblasted and acid etched (SLA, Straumann; *n* = 163), titanium blasted (Astra Tech, AstraTech AB, Mölndal, Sweden; *n* = 41), ? (Zimmer Dental, Warsaw, USA; *n* = 14), acid etched (3i Implant Innovations, Palm Beach Gardens, USA; *n* = 2), ? (BioHorizons, Birmingham, USA; *n* = 1)			
Observations	Only short implants (≤9 mm) restored with single-unit nonsplinted restorations: 13 implants placed in smokers, 114 in grafted sites			

NM, not mentioned; G1, diabetic patients group; G2, non-diabetic patients group.
[a]Implant surface modification (brand).
[b]First year of implant loading.
[c]Marginal bone loss observed in 2 subgroups of group G1, in this order: bleeding on probing <15% and >15%.

significant difference, respectively. There were no implant failures in 2 studies (Dowell *et al.*, 2007; Grandi *et al.*, 2013).

Two studies (Dowell *et al.*, 2007; Tawil *et al.*, 2008) included patients lacking acceptable glycemic control (through the estimation of glycosylated hemoglobin—HbA1c). Dowell *et al.* (2007) defined poorly controlled type 2 diabetes mellitus in patients having a HbA1c level >10.0%, whereas Tawil *et al.*, (2008) defined it as HbA1c level >9%. Five studies (Keller *et al.*, 1999; van Steenberghe *et al.*, 2002; Alsaadi *et al.*, 2008a; Alsaadi *et al.*, 2008b; Anner *et al.*, 2010) reported patients' diabetes as "under control" but did not mention the level of control, whereas 1 study (Doyle *et al.*, 2007) informed that assessment of diabetes control was not performed, and 4 studies (Accursi, 2000; Morris *et al.*, 2000; Bell *et al.*, 2011; Le *et al.*, 2013) did not mention any information about glycemic control.

Quality Assessment

Each trial was assessed for risk of bias, and the scores are summarized in Table 3. All studies were judged to be at high risk of bias.

Meta-analysis

The insertion of dental implants in diabetic or non-diabetic patients did not statistically affect the implant failure rates (p = .65, risk ratio = 1.07, 95% confidence interval = 0.80, 1.44; heterogeneity: I^2 = 9%, p = .36, fixed effects model; Figure 2).

Three studies (Dowell *et al.*, 2007; Tawil *et al.*, 2008; Bell *et al.*, 2011) provided information about postoperative infection; however, only 2 (Dowell *et al.*, 2007; Tawil *et al.*, 2008) informed of the number of occurrences separated by group. As only 1 (Dowell *et al.*, 2007) of these 2 studies observed occurrences of postoperative infection, a meta-analysis was not possible for this outcome.

Two studies provided information about the marginal bone loss with standard deviation, necessary for the calculation of comparisons in continuous outcomes. There was a statistically significant difference (p = .001, mean difference = 0.20, 95% confidence interval = 0.08, 0.31; random effects model, I^2 = 81%, p < .005; Figure 3) between diabetic and non-diabetic patients concerning the marginal bone loss, favoring non-diabetic patients.

Publication Bias

The funnel plot did not show asymmetry when the studies reporting "implant failure" were analyzed (Figure 4), indicating absence of publication bias.

DISCUSSION

It has been suggested that the relative contraindication for implant surgery is related to the stability of the diabetic patient's blood sugar level. Unfortunately, the application of the finding from many studies to clinical practice is limited by the lack of specific information characterizing the patient's diabetic status. While most of these studies describe the participants' diabetes as being "well controlled," the authors do not report how they assessed glycemic control (Dowell *et al.*, 2007). Of the 14 studies included in the present review, only 2 (Dowell *et al.*, 2007; Tawil *et al.*, 2008) provided true valuable information about the patients' glycemic control, through the estimation of glycosylated hemoglobin (HbA1c). Five studies (Keller *et al.*, 1999; van Steenberghe *et al.*, 2002; Alsaadi *et al.*, 2008a; Alsaadi *et al.*, 2008b; Anner *et al.*, 2010) reported that the patients' diabetes was under control, but they did not mention the level of control, whereas the other studies did not provide any information about glycemic control. In the study of Moy *et al.* (2005), even patients with controlled diabetes were almost 3 times as likely to develop implant failure compared with other patients. Unfortunately, the study did not indicate the number of implants in each group, and the failure rates were based on the number of patients in each group; therefore, its data could not be included in the present meta-analysis. Glycemic control is a primary consideration for patients with diabetes, and there is a clear correlation between glycemic control and the development of microvascular and macrovascular complications (Cohen and Horton, 2007). Tissue hyperglycemia affects every aspect of wound healing by adversely affecting the immune system, including neutrophil and lymphocyte function, chemotaxis, and phagocytosis (Goodson and Hunt, 1984). This also leads to a greater predisposition to infection of the wound. Moreover, animal studies showed negative effects of hyperglycemia, not only on bone formation, but also on bone strength and fracture healing (Lu *et al.*, 2003; Siqueira *et al.*, 2003; Kayal *et al.*, 2007). These effects are suggested to affect the osseointegration. However, a prospective evaluation of 58 patients with presumably well-controlled diabetes who received mandibular implants reported that glycemic control was not significantly related to implant success over 5 yr (Olson *et al.*, 2000). Dowell *et al.* (2007), and Tawil *et al.* (2008) also observed that compromises in glycemic control may not affect implant success in humans.

Table 3. Results of the Quality Assessment

Study	Incomplete Outcome Data Addressed
Keller *et al.*, 1999	Yes
Accursi, 2000	Yes
Morris *et al.*, 2000	No
van Steenberghe *et al.*, 2002	No
Dowell *et al.*, 2007	Yes
Doyle *et al.*, 2007	No
Alsaadi *et al.*, 2008a	Yes
Alsaadi *et al.*, 2008b	No
Tawil *et al.*, 2008	No
Anner *et al.*, 2010	No
Bell *et al.*, 2011	No
Levin *et al.*, 2011	Yes
Grandi *et al.*, 2013[a]	No
Le *et al.*, 2013	No

For all studies, sequence generation was not randomized; allocation concealment was inadequate; there was no blinding; and the estimated potential risk of bias was high.

[a]The study was a randomized clinical trial for immediately *vs.* loaded implants but not for diabetic and non-diabetic patients.

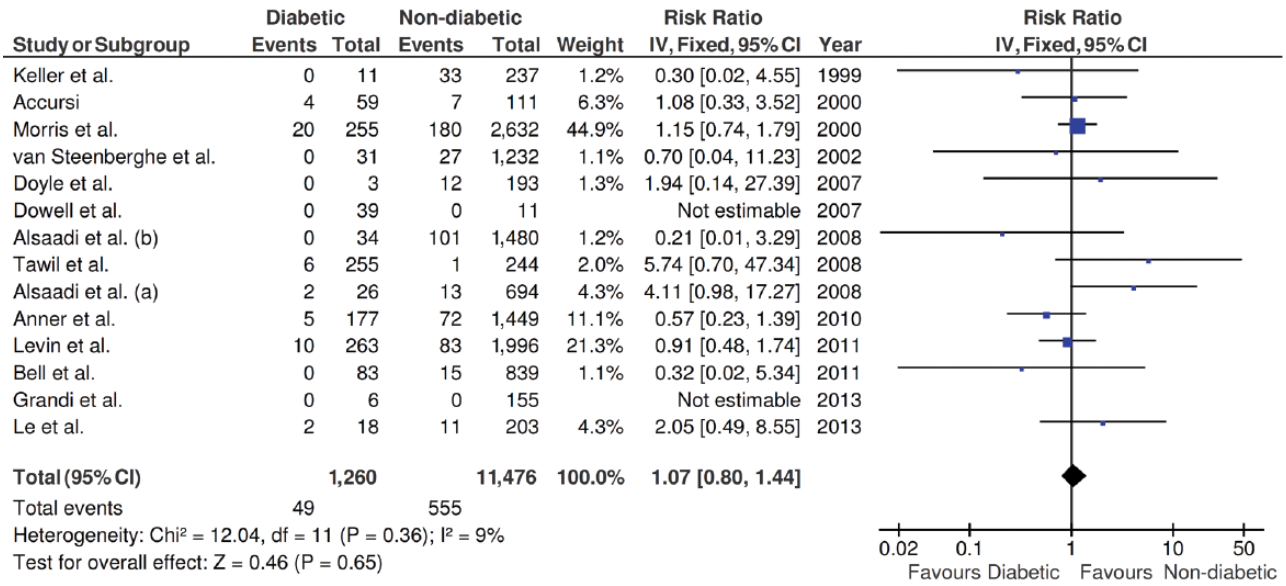

Figure 2. Forest plot for the event "implant failure."

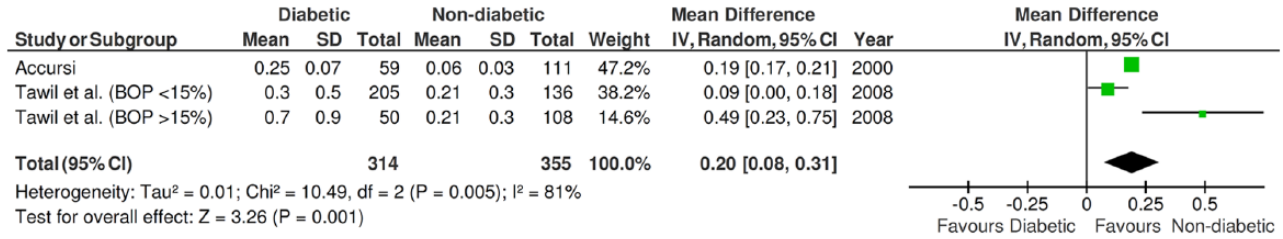

Figure 3. Forest plot for the event "marginal bone loss." BOP, bleeding on probing.

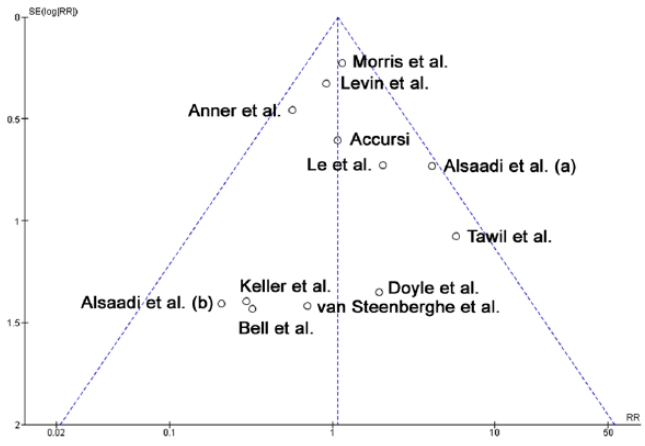

Figure 4. Funnel plot for the studies reporting the outcome event "implant failure."

Heterogeneity in eligibility criteria for implantation in different diabetic populations may explain the wide between-study variations. The true differences in metabolic effects between type 1 and type 2 diabetes remain unclear (Oates *et al.*, 2013). It has been proposed that diabetes leads to decreased bone turnover, with reductions in both resorption and formation, and that it is the difference in ages of onset of types 1 and 2 diabetes relative to bone growth patterns that leads to these distinctions in outcomes (Krakauer *et al.*, 1995). Because type 1 has an earlier onset than type 2 diabetes, one can assume that implant loss is more frequent in patients with the former form of diabetes. One possible reflection in oral implantology was observed by Alsaadi *et al.* (2008a), who detected a significant effect of diabetes type 1 on early implant failures (p = .02), with the same not happening with diabetes type 2 (p = .39). However, it is important to observe that in the study of Alsaadi *et al.* (2008a), only 1 implant was placed in the only patient with diabetes type 1 in the study and this implant failed, whereas 25 implants were inserted in patients with diabetes type 2, with only 1 failure (694 implants were placed in non-diabetic patients, with 13 failures). Prevalence is one of the possible problems in including patients with type 1 diabetes in dental implant studies: >90% of people with diabetes have type 2. Since implant outcomes for patients with type 1 diabetes may differ from those for patients with type 2 diabetes, it is important for studies that include both patient types to report the outcome data separately for each group (Klokkevold and Han, 2007). Thus, it is important to stress that as type 1 and 2 diabetes could have different responses to

implant therapy, depending on their level of control, evaluating these 2 conditions together adds an uncontrolled variable to the present meta-analysis.

Animal studies have shown that uncontrolled diabetes hinders bone formation, bone remodeling, and wound healing (Nevins *et al.*, 1998) and causes reduction in bone-to-implant contact (BIC) and bone thickness (Takeshita *et al.*, 1998), while insulin upregulates bone formation (Siqueira *et al.*, 2003) and maintains BIC (Kwon *et al.*, 2005). The effects of a hyperglycemic state have been shown to include inhibition of osteoblastic cell proliferation and collagen production during the early stages of callus development, resulting in reduced bone formation as well as diminished mechanical properties of the newly formed bone (Lu *et al.*, 2003). Reduced BIC may indicate a poorer healing response and may predict a reduced ability of the implant to withstand bacterial and load challenges. If the lack of BIC is carried to the extreme, osseointegration would be deemed to have failed, and the implant would be found to be mobile at stage 2 surgery (Accursi, 2000). Oates *et al.* (2009) demonstrated alterations in implant stability consistent with impaired implant integration for persons with type 2 diabetes mellitus in direct relation to hyperglycemic conditions. It was observed that persons with HbA1c ≥8.1% had a greater maximum decrease in stability from baseline and required a longer time for healing, which also suggests alterations in the biological integration of the implants in direct relation to glycemic control (Oates *et al.*, 2009). It seems reasonable to postulate that an implant demonstrating reduced BIC may be less able to withstand functional stresses placed on it during the healing phase. Further breakdown of the peri-implant bone could therefore ensue, and this could result in a loosening of the implant and its ultimate failure (Accursi, 2000). However, this has not yet been clinically proved, since most studies here reviewed did not indicate the times for which the implants placed in diabetic patients were loaded. The study of Tawil *et al.* (2008) was the only one in which some implants (n = 58) inserted in diabetic patients were submitted to immediate loading, but no failure was observed after a mean follow-up of 42 mo.

With respect to marginal bone loss, we did find a significant difference in favor of non-diabetic patients, with less marginal bone loss than diabetic ones. However, one has to observe that the difference was based on only 2 publications and that marginal bone loss is part of some criteria for success (Albrektsson *et al.*, 1986) but not of others (Buser *et al.*, 1990). In the light of a current and very active discussion of reasons for marginal bone loss and subsequent potential development of peri-implantitis, we find it relevant to report on the difference found, even if precise clinical conclusions may be difficult to draw at present.

Because of the small sample size in some studies (Accursi, 2000; Dowell *et al.*, 2007; Tawil *et al.*, 2008), no definite conclusions on implant survival can be drawn. Moreover, many studies (Doyle *et al.*, 2007; Alsaadi *et al.*, 2008a; Alsaadi *et al.*, 2008b; Anner *et al.*, 2010; Levin *et al.*, 2011; Le *et al.*, 2013) had a much smaller number of diabetic patients in comparison with the number of non-diabetic patients. Even though the importance of meta-analyses is to increase the sample size of individual trials to reach more precise estimates of the effects of interventions, in this particular analysis no statistically significant difference was found when implant failure rates were compared in diabetic and non-diabetic patients (p = .65). These discordant results may demonstrate our continuing need to clarify the parameters of diabetes affecting successful implant therapy.

In 2 studies (Dowell *et al.*, 2007; Alsaadi *et al.*, 2008a), the patients were followed for a short period (up to 6 mo). Thus, even though it is especially during the healing time, up to abutment surgery, that systemic factors can be most easily identified—as other risk factors that occur after abutment surgery do not apply (van Steenberghe *et al.*, 2003)—only early failures could be assessed. A longer follow-up period can lead to an increase in the failure rate. Moreover, the results found in the studies differed from one another, and this difference could be due to factors such as differences in the patients included in the study or the clinicians placing and restoring the implants. For example, Olson *et al.* (2000) observed that implant failure had a statistically significant association with an increase in years of diabetic history. The authors hypothesized that as duration of diabetes is associated with increased classic microvascular complications, this increase in microvascular disease may be postulated to have contributed to implant failure. However, Tawil *et al.* (2008) divided the patients with well-controlled diabetes into 4 groups (with reference to duration of diabetes), and the results showed no significant differences in implant survival rates among them.

The study of Morris *et al.* (2000) was the only one associating some variables to diabetes and implant failure rates. They reported improved implant survival for patients who were treated with antibiotics in comparison with those treated without prophylactic antibiotics, but the survival improvement was greater in diabetic patients (97.1% *vs.* 86.6%) than in non-diabetic patients (95.1% *vs.* 90.6%). The same happened in diabetic and non-diabetic patients when the use or nonuse of chlorhexidine rinses was evaluated.

The use of grafting in some studies (Keller *et al.*, 1999; van Steenberghe *et al.*, 2002; Tawil *et al.*, 2008; Le *et al.*, 2013) is a confounding risk factor, as well as the presence of some smokers among the patients (Keller *et al.*, 1999; Accursi, 2000; van Steenberghe *et al.*, 2002; Doyle *et al.*, 2007; Alsaadi *et al.*, 2008a; Alsaadi *et al.*, 2008b; Tawil *et al.*, 2008; Anner *et al.*, 2010; Bell *et al.*, 2011; Levin *et al.*, 2011; Grandi *et al.*, 2013; Le *et al.*, 2013), some patients taking biphosphonates (Bell *et al.*, 2011), insertion of some implants (Alsaadi *et al.*, 2008a; Tawil *et al.*, 2008) or all (Bell *et al.*, 2011) in fresh extraction sockets, insertion of only short implants (Le *et al.*, 2013), and the insertion of implants from different brands and surface treatments. Titanium with different surface modifications shows a wide range of chemical/physical properties and surface topographies/morphologies, depending on how they are prepared and handled (Chrcanovic *et al.*, 2012; Chrcanovic *et al.*, 2013), and it is not clear whether, in general, one surface modification is better than another (Wennerberg and Albrektsson, 2009; Wennerberg and Albrektsson, 2010). These variables may have affected the outcome—and not just the subjection of the insertion of implants in patients who had diabetes or not. The impact of these variables on implant survival rate is difficult to estimate if these factors are not identified separately between the 2 different procedures (*i.e.*, to perform meta-regression analysis). A greater level of

statistical significance might have been realized had the confounding variables not been present.

These findings must be viewed as preliminary in that they include relatively small numbers of patients having elevated glycemic levels and they offer only limited information on the longer term effects of diabetes on implant survival. It is also important to consider the potential for many other factors, such as technological advances in implant designs to enhance survival rates for implants in patients with diabetes.

The results of the present study should be interpreted with caution because of its limitations. First of all, all uncontrolled confounding factors may have affected the long-term outcomes and not just the fact that the implants were inserted in either diabetic or non-diabetic patients; the impact of these variables on implant survival rate, postoperative infection, and marginal bone loss is difficult to estimate if these factors are not identified separately in order to perform a metaregression analysis. The lack of control of the confounding factors limited the potential to draw robust conclusions. Unfortunately, most available data regarding diabetes as a risk factor in implant dentistry are extracted from case series. Because of conflicting data from studies with small sample sizes or case series, from groups that were not completely comparable at baseline in some studies, or from studies involving multiple surgeons, clinicians are unable to provide concrete answers to questions posed by patients seeking dental implant treatment. Second, some of the included studies had a retrospective design, and the nature of a retrospective study inherently results in flaws. These problems were manifested by the gaps in information and incomplete records. Furthermore, all data rely on the accuracy of the original examination and documentation. Items may have been excluded in the initial examination or not recorded in the medical chart (Chrcanovic *et al.*, 2010a; Chrcanovic *et al.*, 2010b).

For a more definite conclusion, we believe that future controlled studies with a larger number of patients in the diabetic group are required to determine the real effect of the condition on the dental implant outcome (*i.e.*, most studies included far fewer diabetic than non-diabetic patients).

CONCLUSION

The results of the present systematic review should be interpreted with caution because of the presence of uncontrolled confounding factors in the included studies. Within the limits of the existing investigations, the difference between the insertion of dental implants in non-diabetic and diabetic patients did not statistically affect the implant failure rates. However, the studies in the review show heterogeneity in eligibility criteria for implantation in different diabetic populations. Studies are lacking that include both patient types, with larger sample sizes, and that report outcome data separately for each group.

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