Cover Story

Impact of hyperglycemia on the rate of implant failure and peri-implant parameters in patients with type 2 diabetes mellitus

Systematic review and meta-analysis

Ren Shang, Dr. med. dent. (candidate); Limin Gao, PhD

ABSTRACT

Background. The impact of hyperglycemia on dental implant therapy remains unclear. In this systematic review and meta-analysis, the authors compared the rates of implant failure and peri-implant bleeding on probing (BOP), probing depth (PD), and peri-implant bone loss (PIBL) among patients with type 2 diabetes mellitus and nondiabetic patients. The authors performed subgroup analyses based on glycemic level to evaluate whether patients with higher glycemic levels were more prone to peri-implant inflammation.

Type of Studies Reviewed. The authors searched 4 databases for original clinical studies. Studies in which the researchers provided information on the rate of implant failure or peri-implant parameters were included.

Results. Nine clinical studies were identified on the basis of the inclusion criteria. No significant differences were found in rates of implant failure ($P = .46$) and PD ($P = .1$) between diabetic and nondiabetic patients. Significant differences in BOP ($P < .00001$) and PIBL ($P = .02$), favoring nondiabetic patients, were observed. Results of subgroup analyses indicated that the increase in glycemic level did not significantly influence BOP, PD, and PIBL values among diabetic patients.

Conclusions and Practical Implications. Patients with type 2 diabetes mellitus seem to be able to achieve a rate of implant survival similar to that of healthy patients. Regarding peri-implant parameters, BOP and PIBL were higher in patients with type 2 diabetes mellitus, indicating that hyperglycemia is an important risk factor for peri-implant inflammation. No association was found between peri-implant parameters and glycemic level among patients with type 2 diabetes mellitus, providing oral hygiene was strictly maintained.

Key Words. Type 2 diabetes mellitus; dental implant failure; peri-implant parameters.

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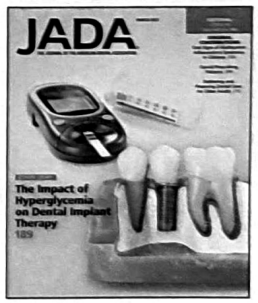


Hyperglycemia enhances infection in periodontal tissues and leads to destructive marginal bone loss via accumulating advanced glycation end products.[1] High glycemic status also disturbs the differentiation of pluripotent mesenchymal cells into osteoblasts, thereby hindering bone repair and compromising implant stability.[2] Therefore, glycemic level is viewed as an important consideration for determining eligibility for dental implant therapy. Dentists tend to believe that when glycemic level is well controlled, implant therapy is safe and predictable, with a complication rate similar to that of healthy patients, whereas diabetic patients with poorly controlled glycemic levels are considered to have a higher incidence rate of peri-implant complications. However, this belief was not confirmed in several clinical trials in which researchers found a 0% rate of implant failure in patients with poorly controlled glycemic levels during a follow-up period of up to 36 months.[3-6] Moreover, researchers found that poorly controlled glycemic status had no association with implant survival and no effect on implant stabilization.[4,7,8] In a 7-year follow-up clinical observation study, researchers reported that even patients with poorly controlled glycemic levels had rates of implant failure similar to those of nondiabetic patients.[9]

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.

In several systematic reviews, researchers focused on rejecting or accepting the hypothesis that higher glycemic levels could lead to a higher incidence rate of peri-implant complications.[10-13] However, only a few systematic reviews had high methodologic quality.[14] In 2 high-quality reviews, researchers observed no significant difference in rates of dental implant failure between diabetic patients with well-controlled glycemic levels and those with poorly controlled glycemic levels.[10,11] Lagunov and colleagues[12] found significant differences in bleeding on probing (BOP), probing depth (PD), and peri-implant bone loss (PIBL) between diabetic patients and nondiabetic patients; however, only patients with well-controlled glycemic levels were enrolled in this study. In a 2020 systematic review, researchers reported a statistically higher BOP in patients with poorly controlled glycemic levels compared with patients with well-controlled glycemic levels.[13] However, patients who had smoking habits and underwent bone augmentation surgery were enrolled in their study, which made the explanation of the impact of hyperglycemia on peri-implant inflammation tentative. Moreover, 2 cross-sectional observational studies were included in their work, which might not be adequate to establish cause (hyperglycemia) and effect (peri-implant complications) relations. Systematic reviews with more robust control of significant confounding factors are needed.

In our systematic review and meta-analysis, we aimed to assess the rate of implant failure and peri-implant parameters (BOP, PD, PIBL) in both diabetic and nondiabetic patients. To evaluate whether diabetic patients with higher glycemic levels are more prone to peri-implant inflammation, we performed subgroup analyses based on glycemic levels. To obtain more compelling evidence, more stringent exclusion criteria were used in our study to control for confounding factors.

METHODS

Our work followed the 2015 Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[15] The research question was as follows: Do patients with type 2 diabetes mellitus (T2DM) have a higher rate of implant failure and higher peri-implant parameters (BOP, PD, and PIBL) than nondiabetic (ND) patients? The question was formulated on the basis of the PICO (population, intervention, comparison, and outcome) process.

Search strategy

The literature search was performed in April 2020 and is shown in the Appendix (available online at the end of this article).

Study identification and selection

Two reviewers (R.S., L.G.) screened the titles and abstracts of retrieved studies independently. The eligibility criteria were human clinical studies with a follow-up period of no fewer than 12 months, enrolled diabetic patients who had received a clinical diagnosis of T2DM, both diabetic and nondiabetic patients were present in the same study, patients received dental implant therapy, glycemic levels (glycated hemoglobin [HbA_{1c}]) of diabetic patients were clearly described (HbA_{1c} levels > 6% for patients with T2DM and ≤ 6% for nondiabetic patients), bone dimensions were adequate for implant placement without the need for bone augmentation, healthy periodontal conditions, and clinical outcomes included the number of placed and failed implants or at least 1 of the peri-implant parameters (BOP, PD, PIBL).

Studies were excluded from analysis if participants were smokers or had bone metabolic diseases, untreated periodontal diseases, or cardiovascular diseases; had undergone bone augmentation surgery; had received radiation treatment in the head and neck region or had taken bisphosphonates within the past 90 days; or had implants with special surface modifications (such as laser ablation or coatings with proteins, drugs, and growth factors). Letters, review articles, laboratory studies, animal experiment studies, case reports, and cross-sectional observation trials were also excluded.

Data extraction

The following information was extracted: authors and publication year; study type and length of follow-up period; mean age and sex of the enrolled participants; glycemic status, although the

ABBREVIATION KEY

- **BOP:** Bleeding on probing.
- **CHX:** Chlorhexidine digluconate.
- **HbA_{1c}:** Glycated hemoglobin.
- **ND:** Nondiabetic.
- **NM:** Not mentioned.
- **PC:** Poorly controlled.
- **PCS:** Prospective cohort study.
- **PD:** Probing depth.
- **PIBL:** Peri-implant bone loss.
- **T2DM:** Type 2 diabetes mellitus.
- **WC:** Well-controlled.

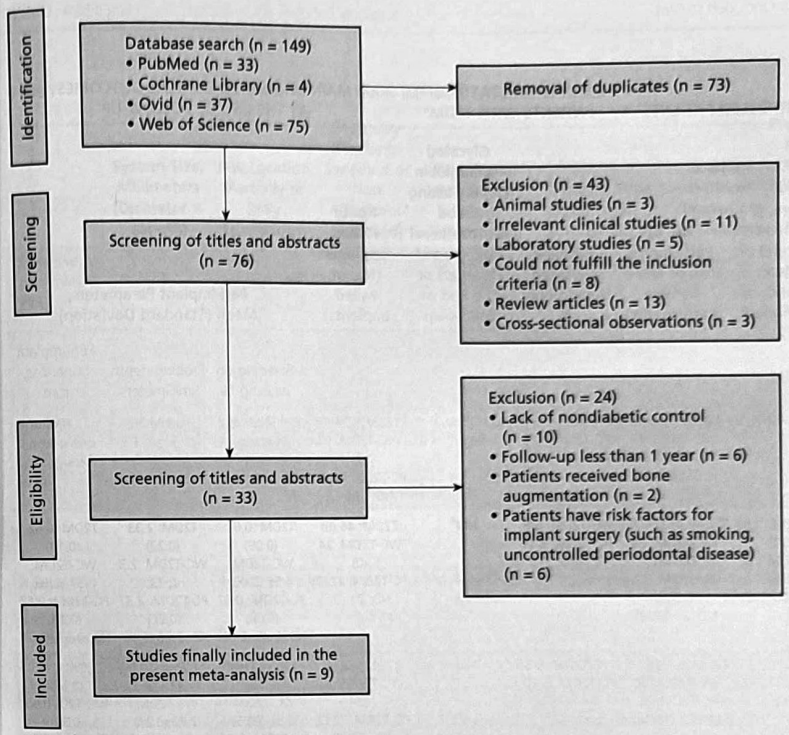


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of the screening and selection process.[15]

recommended range for defining well-controlled glycemic status is generally considered 6.5% through 7%,[16] HbA_{1c} levels greater than 8% had the highest risk of developing clinical complications[17,18] and, therefore, we classified diabetic patients as having well-controlled glycemic levels (WC-T2DM) (HbA_{1c}, 6%-8%) or poorly controlled glycemic levels (PC-T2DM) (HbA_{1c}, > 8%); periodontal status before implant therapy; number of placed and failed implants and peri-implant parameters (BOP, PD, PIBL); implant characteristics; and pre- and postoperative treatments. The median and range of continuous variables were calculated and transferred into the mean (standard deviation) using the formulas of Hozo and colleagues.[19]

Quality assessment

The modified Newcastle-Ottawa Scale was used to assess risk of bias. We allotted a score of 0 through 9 (allocated as stars) for each study. Studies with 5 or more stars on the modified Newcastle-Ottawa Scale were considered to be of high quality.

Statistical analysis

Meta-analysis was performed in line with recommendations from the Cochrane Collaboration and Quality of Reporting of Meta-Analysis guidelines.[15] The I^2 statistic describes the percentage of the total variation due to heterogeneity. I^2 values of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity, respectively. If there is little or moderate variation between trials, a fixed-effects model is appropriate. A high I^2 value indicates high variation between clinical trials, and a random-effects model is appropriate. Subgroup analyses were performed on the basis of the glycemic status of diabetic patients to assess heterogeneity. Graphical exploration with funnel plots was used to assess publication bias. Egger linear regression was used to test bias statistically. The analysis was

Table 1. Main characteristics of the included studies.

STUDY	STUDY DESIGN/ FOLLOW-UP, MO	ENROLLED PATIENTS		GLYCEMIC STATUS OF PATIENTS WITH T2DM*		MAIN INTERESTED CLINICAL OUTCOMES AT THE END OF FOLLOW-UP			
		Age, y, Mean (Range) or Mean (Standard Deviation)	No. of Participants (No. of Male/ Female Participants)	Baseline Glycated Hemoglobin, %	Glycated Hemoglobin (%) or Fasting Blood Glucose Level (Milligrams/ Deciliter) at The End of Follow-up	No. of Placed Implants (No. of Failed Implants)	Peri-Implant Parameters, Mean (Standard Deviation)		
							Bleeding on probing %	Probing depth, millimeters	Peri-implant bone loss, mm
Oates and Colleagues,[7] 2014	PCS 12†	64 (NM)	T2DM: 76 (NM) WC-T2DM: 47 PC-T2DM: 20 ND: 50 (NM)	WC-T2DM: 6-8 PC-T2DM: > 8	WC-T2DM: 6-8 PC-T2DM: > 8	T2DM: 134 (9) WC-T2DM: 94 (7) PC-T2DM: 40 (2) ND: 100 (7)	NM	NM	NM
Gómez-Moreno and Colleagues,[6] 2015	PCS 36†	WC-T2DM‡: 59 (8.1) PC-T2DM§: 62 (6.8) ND¶: 60 (7.2)	T2DM: 46 (24/22) WC-T2DM: 24 (11/13) PC-T2DM: 22 (13/9) ND: 21 (9/12)	WC-T2DM: 6-8 PC-T2DM: 8.1-10	NM#	T2DM: 46 (0) WC-T2DM: 24 (0) PC-T2DM: 22 (0) ND: 21 (0)	T2DM: 0.61 (0.09) WC-T2DM: 0.56 (0.07) PC-T2DM: 0.67 (0.08) ND: 0.45 (0.06)	T2DM: 2.33 (0.23) WC-T2DM: 2.3 (0.23) PC-T2DM: 2.37 (0.22) ND: 2.26 (0.19)	T2DM: 0.62 (0.18) WC-T2DM: 0.57 (0.16) PC-T2DM: 0.67 (0.18) ND: 0.53 (0.17)
Aguilar-Salvatierra and Colleagues,[22] 2016	PCS 24	T2DM: 58.7 (3.7) ND: 59.2 (2.3)	T2DM: 52 (26/26) WC-T2DM: 30 PC-T2DM: 22 ND: 33 (18/15)	WC-T2DM: 6-8 PC-T2DM: 8-10	NM	T2DM: 52 (5) WC-T2DM: 30 (2) PC-T2DM: 22 (3) ND: 33 (0)	T2DM: 0.61 (0.12) WC-T2DM: 0.51 (0.05) PC-T2DM: 0.74 (0.05) ND: 0.44 (0.07)	T2DM: 3.17 (0.57) WC-T2DM: 2.79 (0.24) PC-T2DM: 3.68 (0.48) ND: 2.67 (0.14)	T2DM: 1.38 (0.57) WC-T2D: 0.98 (0.27) PC-T2DM: 1.92 (0.38) ND: 0.72 (0.27)
Al-Amri and Colleagues,[21] 2016	PCS 24	WC-T2DM: 50.1 (46-55) PC-T2DM: 50.5 (45-59) ND: 48.5 (45-52)	T2DM: 61 (NM) WC-T2DM: 30 PC-T2DM: 31 ND: 30 (NM)	WC-T2DM: 6-8 PC-T2DM: > 8	WC-T2DM: 6-8 PC-T2DM: 6-8	T2DM: 61 (0) WC-T2DM: 30 (0) PC-T2DM: 31 (0) ND: 30 (0)	T2DM: 0.62 (0.06) WC-T2DM: 0.62 (0.07) PC-T2DM: 0.62 (0.05) ND: 0.4 (0.06)	T2DM: 2.3 (0.45) WC-T2DM: 2.3 (0.15) PC-T2DM: 2.3 (0.62) ND: 1.6 (0.05)	T2DM: 0.59 (0.18) WC-T2DM: 0.58 (0.15) PC-T2DM: 0.59 (0.2) ND: 0.46 (0.16)
Ghiraldini and Colleagues,[8] 2016	PCS 12	WC-T2DM: 54.91 (13.95) PC-T2DM: 56.38 (13.69) ND: 51.58 (7.74)	T2DM: 32 (18/14) WC-T2DM: 16 (9/7) PC-T2DM: 16 (9/7) ND: 19 (10/9)	WC-T2DM: 6-8 PC-T2DM: > 8	NM	T2DM: 32 (0) WC-T2DM: 16 (0) PC-T2DM: 16 (0) ND: 19 (0)	NM	NM	NM
Al-Amri and Colleagues,[23] 2017‖	PCS 24	T2DM: 42.4 (40-46) ND: 41.8 (39-44)	T2DM: 23 (23/0) ND: 22 (22/0)	6-8	6-8	T2DM: 23 (0) ND: 22 (0)	NM	NM	T2DM: 0.2 (0.04) ND: 0.23 (0.08)
Al-Amri and Colleagues,[25] 2017‖	Prospective controlled clinical trial 36	NM	T2DM: 45 (45/0) ND: 42 (42/0)	6-8	6-8	T2DM: 45 (0) ND: 42 (0)	T2DM: 23.48 (2.54) ND: 20.79 (2.8)	T2DM: 2.28 (0.3) ND: 2.43 (0.28)	T2DM: 0.26 (0.1) ND: 0.31 (0.08)
Alsahhaf and Colleagues,[20] 2019	Retrospective cohort study 36	T2DM: 52.7 (45-58) ND: 43.4 (33-49)	T2DM: 38 (23/15) ND: 40 (25/15)	6-8	6-8	T2DM: 65 (0) ND: 52 (0)	T2DM: 0.53 (0.07) ND: 0.21 (0.06)	T2DM: 2.39 (0.18) ND: 2.18 (0.18)	T2DM: 0.69 (1.37) ND: 0.51 (1.3)
Al-Shibani and Colleagues,[24] 2019	Prospective controlled clinical trial 36	T2DM: 45.2 (37-49) ND: 41.6 (30-50)	T2DM: 42 (NM) ND: 44 (NM)	6-8	6-8	T2DM: 42 (0) ND: 44 (0)	T2DM: 27.22 (3.07) ND: 19.55 (3.05)	T2MD: 2.41 (0.31) ND: 2.52 (0.29)	T2MD: 0.32 (0.14) ND: 0.21 (0.08)

* T2DM: Type 2 diabetes mellitus. † PCS: Prospective cohort study. ‡ WC-T2DM: Well-controlled T2DM. § PC-T2DM: Poorly controlled T2DM. ¶ ND: Nondiabetic.
# NM: Not mentioned. ** There are 2 different 2017 clinical trials from Al-Amri and colleagues.

Table 2. Additional characteristics of the included studies.

STUDY	MAIN IMPLANT CHARACTERISTICS							PRE- OR POSTOPERATIVE TREATMENT
	System Size, Millimeters (Diameter × Length)	Jaw Location (Partially or Fully Edentulous)	Geometry (Platform-Switched or Non–Platform-Switched)	Periodontal Conditions Before Implantation	Healing Type (Submerged or Nonsubmerged)	Loading Protocol (Immediate or Delayed)	Protocol Used For Fixing Prosthesis (Cement or Screw-Retained)	
Oates and Colleagues,[7] 2014	Straumann (4.1 × 8-12)	Mandible: anterior (fully)	NM*	Sufficient oral hygiene	NM	Delayed	NM	Pretreatment: NM Posttreatment: 500 milligrams of amoxicillin or 150 mg of clindamycin 3 times per day, 7 d; 0.12% CHX† twice per day, 2 wk
Gómez-Moreno and Colleagues,[6] 2015	Straumann (3.3-4.1 × 10-14)	Maxilla: anterior (partially)	NM	Sufficient oral hygiene	Submerged	Delayed	NM	Pretreatment: NM Posttreatment: 875 mg of amoxicillin and 125 mg of clavulanic acid twice per day, 7 d; 600 mg of ibuprofen when necessary; 0.12% CHX twice per day, 2 wk
Aguilar-Salvatierra and Colleagues,[22] 2016	Straumann (3.3-4.1 × 10-14)	Maxilla: anterior (partially)	NM	Sufficient oral hygiene	Submerged	Immediate	NM	Pretreatment: NM Posttreatment: amoxicillin plus clavulanic acid 7 d; 600 mg of ibuprofen when needed; 0.12% CHX twice per day, 2 wk
Al-Amri and Colleagues,[21] 2016	Straumann (3.3-4.1 × 10-14)	Maxilla: anterior (partially)	NM	Sufficient oral hygiene	Nonsubmerged	Immediate	NM	Pretreatment: NM Posttreatment: 500 mg of amoxicillin 3 times per day, 7 d; 600 mg of ibuprofen when needed; 6-mo periodontal and peri-implant maintenance
Ghiraldini and Colleagues,[8] 2016	Sistema de Implante Nacional S.A. (3.75 × 8.5, 11.5)	NM (partially)	NM	Sufficient oral hygiene	Nonsubmerged	Delayed	Screw-retained	Pretreatment: calculus removal, supragingival plaque control and subgingival debridement; 2 grams per liter of amoxicillin Posttreatment: 500 mg of sodic-dipyrone every 6 h for 2 d; 0.12% CHX, 7 d
Al-Amri and Colleagues,[23] 2017‡	Straumann (3.5 × 10-14)	Mandible: posterior (NM)	Platform-switched	Sufficient oral hygiene	Submerged	Delayed	NM	Pretreatment: full-mouth scaling; 2 g of amoxicillin 60 min before operation; 600 mg of clindamycin if allergy against penicillin Posttreatment: NM
Al-Amri and Colleagues,[25] 2017‡	Osseospeed (4 × 6-8 or 11)	Mandibular: posterior (partially)	Platform-switched	NM	NM	NM	NM	Pretreatment: NM Posttreatment: 500 mg of amoxicillin 3 times per day, 7 d; 600 mg of ibuprofen; essential oil–based mouthrinse

* NM: Not mentioned. † CHX: Chlorhexidine digluconate. ‡ There are 2 different 2017 clinical trials by Al-Amri and colleagues.

Table 2. Continued

STUDY	MAIN IMPLANT CHARACTERISTICS							PRE- OR POSTOPERATIVE TREATMENT
	System Size, Millimeters (Diameter × Length)	Jaw Location (Partially or Fully Edentulous)	Geometry (Platform-Switched or Non–Platform-Switched)	Periodontal Conditions Before Implantation	Healing Type (Submerged or Nonsubmerged)	Loading Protocol (Immediate or Delayed)	Protocol Used For Fixing Prosthesis (Cement or Screw-Retained)	
Alsahhaf and Colleagues,[20] 2019	NM	Maxilla and mandible (NM)	NM	Sufficient oral hygiene	Nonsubmerged	NM	Screw-retained	Pretreatment: 500 mg of amoxicillin 3 times per day, 2 d Posttreatment: 500 mg of amoxicillin 3 times per day, 1 wk; 0.2% CHX twice per day, 2 wk; oral hygiene maintenance program
Al-Shibani and Colleagues,[24] 2019	Straumann (3.3 or 4.1 × 10)	Maxilla and mandible (NM)	NM	Sufficient oral hygiene	Submerged	Delayed	NM	Pretreatment: NM Posttreatment: 600 mg of ibuprofen; 500 mg of amoxicillin, 3 times per day, 1 wk; 0.2% CHX, twice per day, 2 wk

conducted using Review Manager, Version 5.3 for Mac (The Cochrane Collaboration). $P < .05$ was considered to be statistically significant.

RESULTS

Literature search

A total of 149 studies were identified through the electronic search. After removing duplicates and excluding articles that did not fulfill our inclusion criteria, only 9 studies[6-8,20-25] were included in our study. The article selection process is shown in Figure 1.

Study characteristics

The main characteristics of the 9 included studies[6-8,20-25] are summarized in Table 1. Among the included studies, 7 were cohort studies[6-8,20-23] and 2 were controlled clinical trials.[24,25] The length of follow-up ranged from 12 through 36 months. A total of 415 patients with T2DM and 301 ND patients were enrolled, with 500 and 363 implants, respectively. According to glycemic level (HbA_{1c}) at study enrollment, 4 studies[20,23-25] enrolled patients with WC-T2DM only, and 5 studies[6-8,21,22] enrolled patients with WC-T2DM and PC-T2DM. The glycemic levels in 6 studies[7,20,21,23-25] were measured within the observation period. Researchers from only 2 studies[7,22] reported implant failure during follow-up periods. Information on BOP and PD could be found in 6 studies,[6,20-22,24,25] and researchers from 7 studies[6,20-25] provided information on PIBL.

Additional characteristics of the included studies are shown in Table 2. In 5 of the included studies,[6,8,21-23] implants were placed in partially edentulous jaws, and in 1 study[7] they were inserted in fully edentulous jaws. In 8 studies,[6-8,20-22,24,25] periodontal conditions and oral hygiene status were well maintained before or after implant operations. According to the loading protocol, implants received delayed loading in 5 studies,[6-8,24,25] and in 2 studies[21,22] implants were exposed to immediate loading.

Quality assessment

All 9 included studies received no fewer than 5 stars and were considered high quality (Table 3). Therefore, all of them were included in the meta-analysis.

Implant failure

Figure 2 shows that there was no statistically significant difference in failure rates between patients with T2DM and ND patients (risk ratio, 1.39; 95% confidence interval [CI], 0.58 to 3.30; $P = .46$).

Table 3. Quality assessment of included studies using modified Newcastle-Ottawa Scale.*

STUDY	SELECTION				COMPARABILITY OF COHORTS ON THE BASIS OF THE DESIGN OR ANALYSIS	OUTCOME			TOTAL SCORE 9/9
	Representative of Exposed Cohort	Selection of The Nonexposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Present at Start		Assessment of Outcome	Follow-up Long Enough For Outcomes to Occur†	Adequacy of Follow-up of Cohorts	
Oates and Colleagues,[7] 2014	★	★	★	★	★	NM‡	NM	NM	5/9
Gómez-Moreno and Colleagues,[6] 2015	★	★	★	★	★★	NM	NM	★	7/9
Aguilar-Salvatierra and Colleagues,[22] 2016	★	★	★	★	★	★	NM	★	7/9
Al-Amri and Colleagues,[21] 2016	★	★	★	★	★★	★	NM	★	8/9
Ghiraldini and Colleagues,[8] 2016	★	★	★	★	★★	★	NM	★	8/9
Al-Amri and Colleagues,[23] 2017§	★	★	★	★	★★	NM	NM	★	7/9
Al-Amri and Colleagues,[25] 2017§	★	★	★	★	★	★	NM	★	7/9
Alsahhaf and Colleagues,[20] 2019	★	★	★	★	★	★	NM	★	7/9
Al-Shibani and Colleagues,[24] 2019	★	★	★	★	★	NM	NM	★	6/9

* We allotted the score of 0 through 9 (allocated as stars) for each study. For the selection and outcome categories, 1 star was given for each item. For the comparison category, 2 stars were given. Studies that scored 5 stars or more were considered to be of high quality. † Five years of follow-up was considered "long enough for outcomes to occur." ‡ NM: Not mentioned. § There are 2 different 2017 clinical trials by Al-Amri and colleagues.

Researchers reported occurrences of implant failure in only 2 studies.[7,22] Estimates could not be obtained in the other 7 studies because they had 100% implant survival rates.

BOP

We found a significant difference in BOP between patients with T2DM and ND patients, favoring ND patients (mean difference [MD], 0.32; 95% CI, 0.19 to 0.45; $P < .00001$; Figure 3A). The random-effects model was chosen because of high heterogeneity ($I^2 = 98\%$). No significant subgroup effect of glycemic status was found between patients with WC-T2DM and those with PC-T2DM ($P = .32$; Figure 3B).

PD

No significant difference in PD was observed between patients with T2DM and ND patients (MD, 0.2; 95% CI, −0.04 to 0.44; $P = .1$; $I^2 = 97\%$; Figure 4A). No significant subgroup effect of glycemic status was found between patients with WC-T2DM and PC-T2DM ($P = .16$; Figure 4B).

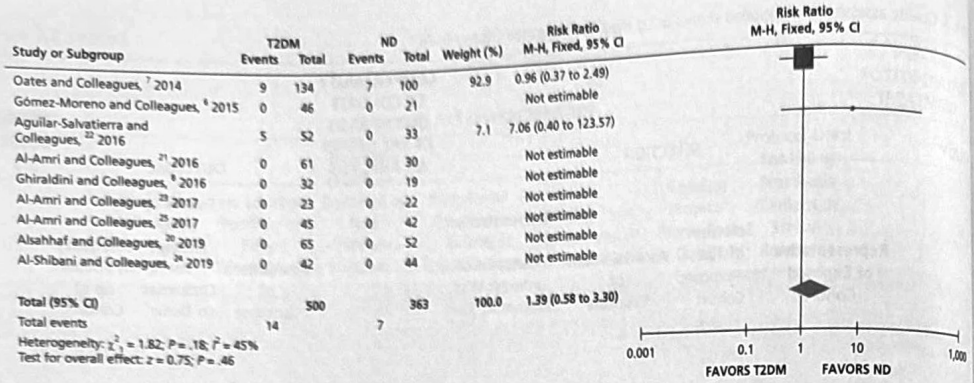


Figure 2. Forest plot of the comparison of the rates of implant failure between patients with type 2 diabetes mellitus (T2DM) and nondiabetic (ND) patients. CI: Confidence interval. M-H: Mantel–Haenszel.

PIBL

We found a statistically significant difference in PIBL between patients with T2DM and ND patients, favoring ND patients (MD, 0.12; 95% CI, 0.02 to 0.22; $P = .02$; $I^2 = 94\%$; Figure 5A). No significant subgroup effect was observed ($P = .12$; Figure 5B).

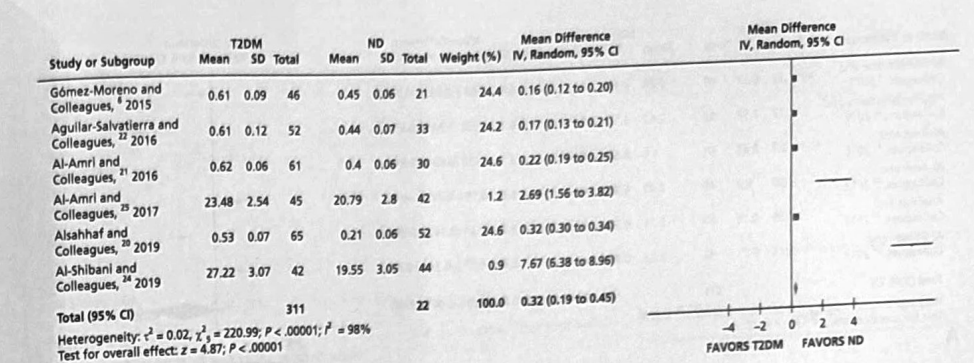
Publication bias

In Figure 6A, 2 studies in which researchers reported implant failure were located in a symmetrical and inverted funnel. However, the number of studies was too small to detect publication bias. Figures 6B through 6D show asymmetrical plots. The publication bias was significant in BOP ($P < .0001$), but not significant in PD ($P = .7559$) and PIBL ($P = .231$).

DISCUSSION

In our systematic review and meta-analysis, we aimed to evaluate the rates of dental implant failure as well as peri-implant parameters (BOP, PD, PIBL) among diabetic and nondiabetic patients. After careful screening, 9 studies were considered to match our inclusion criteria, and only 2 of them reported implant failures. Researchers from 1 study[22] reported a 9.6% failure rate in the diabetic group compared with 0% in the ND group. In another study, researchers observed similar rates of implant failure in both diabetic (6.7%) and ND (7%) patients.[7] According to the results of the 2 studies, no significant difference in the rate of implant failure between diabetic and healthy patients was found ($P = .46$), indicating that diabetic patients were able to obtain a similarly satisfying survival rate of implants as healthy patients. However, the impact of patient loss to follow-up on the statistical results needs to be taken into consideration. In the study from Oates and colleagues,[7] the patients who dropped out of follow-up were considered to have failed implants. Without this consideration, the rates of implant failure in the diabetic and ND groups were actually both approximately 1%, which indicated that the survival rate of implants was conservatively estimated. In the study from Ghiraldini and colleagues,[8] patients who dropped out of the observation period were not included in the process of data analyses. However, the other included studies did not provide information about loss to follow-up.

Peri-implant mucositis is the inflammation in mucosa around an implant with no sign of supporting bone loss.[26] BOP and PD are considered 2 essential peri-implant parameters in evaluating the condition of peri-implant soft tissue. In the meta-analysis from Lagunov and colleagues,[13] diabetic patients had higher BOP than healthy patients. In accordance with their study, we found a statistically significant difference in BOP ($P < .00001$) between the diabetic and ND groups, favoring ND patients. This finding indicates that patients with T2DM were associated with a higher risk of experiencing peri-implant mucosa inflammation than healthy patients. However, no significant subgroup difference was found between WC-T2DM and PC-T2DM, indicating that diabetic patients with higher glycemic levels were not prone to peri-implant mucositis. A smaller



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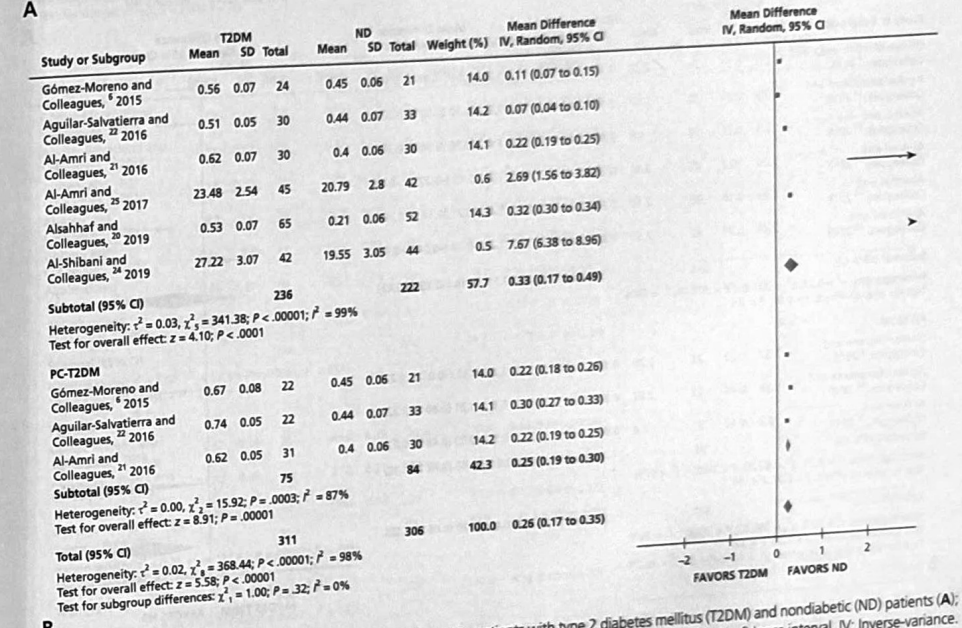

B

Figure 3. Forest plot of the comparison of bleeding on probing between patients with type 2 diabetes mellitus (T2DM) and nondiabetic (ND) patients (**A**); forest plot for subgroup. analysis of bleeding on probing based on glycemic levels of patients with T2DM (**B**). CI: Confidence interval. IV: Inverse-variance. PC: Poorly controlled. SD: Standard deviation. WC: Well-controlled.

number of trials and participants contributed data to PC-T2DM, meaning that the analysis might not be able to detect subgroup differences. We failed to find any difference in PD between diabetic and ND patients, indicating that diabetic patients might have similar PD to healthy patients. However, this result should be interpreted with caution. Researchers in a 10-year prospective study found that the PD of healthy peri-implant mucosa is often greater than 4 millimeters.[27] The PD values in our included studies were all less than 4 mm (range 1.6-3.17 mm), which were too small to be considered pathologic.

Peri-implantitis results in not only soft-tissue infection but also progressive bone loss. PIBL is considered the reference standard for diagnosing peri-implantitis. Several authors of systematic reviews have confirmed the association between hyperglycemia and the pathogenesis of peri-implantitis.[11,14,28] In accordance with these studies, we found that diabetic patients showed significantly higher PIBL than healthy patients ($P = .02$), indicating that diabetic patients have higher risks of developing peri-implantitis. No significant difference was found in subgroup analysis, which might be due to the small sample size of the PC-T2DM group.

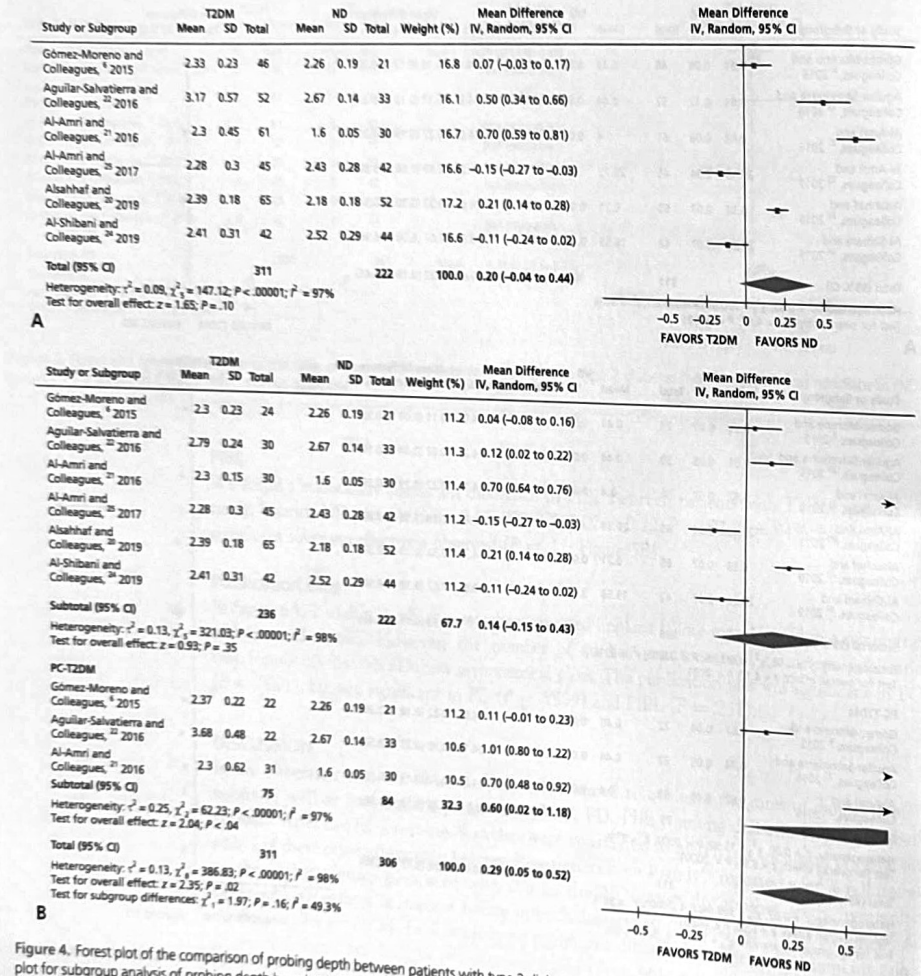

Figure 4. Forest plot of the comparison of probing depth between patients with type 2 diabetes mellitus (T2DM) and nondiabetic (ND) patients (**A**); forest plot for subgroup analysis of probing depth based on glycemic levels of patients with T2DM (**B**). CI: Confidence interval. IV: Inverse-variance. SD: Standard deviation.

Researchers have found that nonsurgical mechanical debridement can not only release a load of adhered bacteria in the peri-implant area, but could also reduce hyperglycemia in diabetic patients and thereby balance the impact of hyperglycemia on peri-implant tissue.[29,30] Researchers in a clinical cohort study evaluated the effect of oral hygiene maintenance on peri-implant BOP, PD, and PIBL.[21] At the 6-month follow-up, the parameters were significantly higher in patients with poorly controlled glycemic levels (HbA_{1c}, 8.7%) than in patients with well-controlled glycemic levels. At the 24-month follow-up, the differences were no longer significant. A significant decrease in diabetic patients' glycemic levels was observed between the 6-month and 24-month follow-ups, indicating that good maintenance of oral hygiene could reduce hyperglycemia and the peri-implant parameters in diabetic patients with varying glycemic levels. In most of our included studies, the oral hygiene of the patients was well maintained. Reductions in HbA_{1c} values throughout the observation period were reported in 5 of the included studies.[20,21,23-25] This could explain the nonsignificant subgroup differences in peri-implant parameters between the WC-T2DM and PC-T2DM groups.

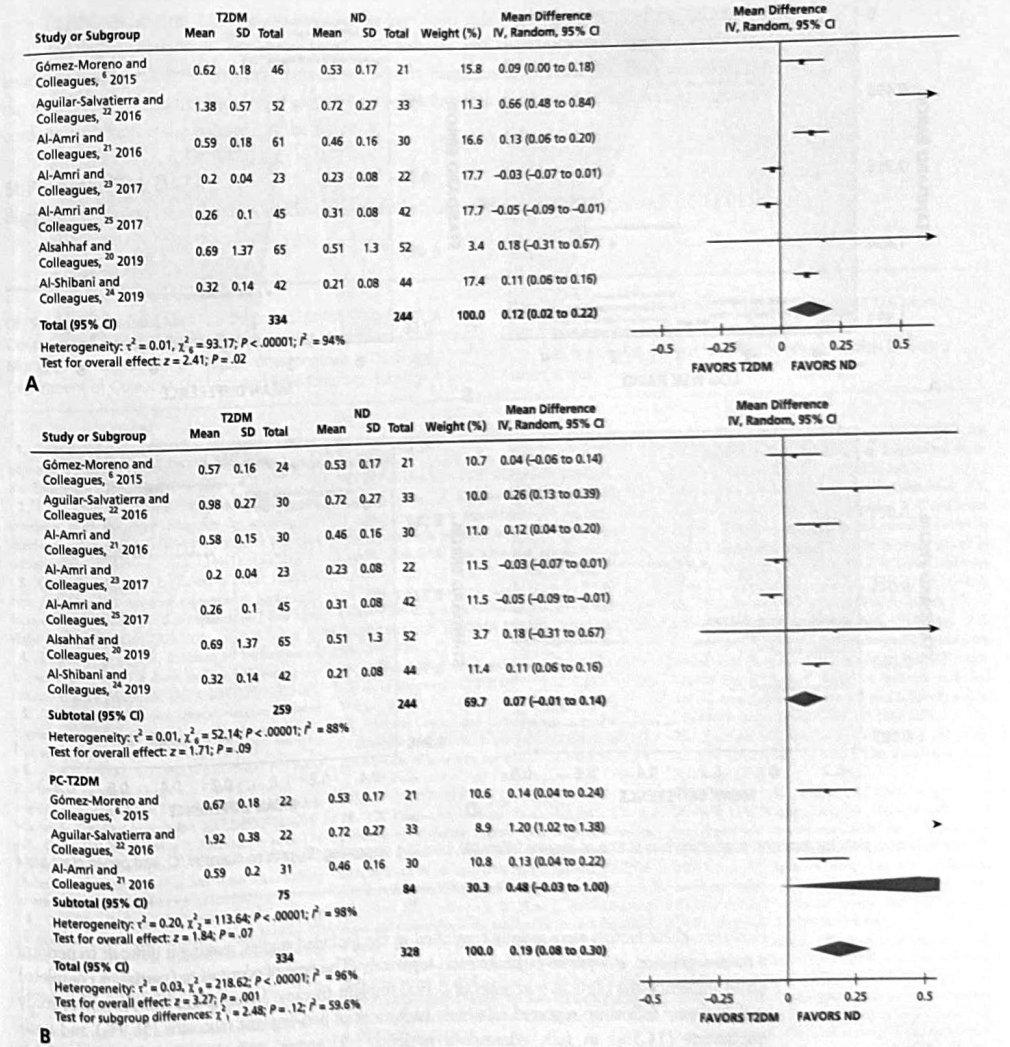

Figure 5. Forest plot of the comparison of peri-implant bone loss between patients with type 2 diabetes mellitus (T2DM) and nondiabetic (ND) patients (**A**); forest plot for subgroup analysis of peri-implant bone loss based on glycemic levels of patients with T2DM (**B**). CI: Confidence interval. IV: Inverse-variance. SD: Standard deviation.

Previous systematic reviews and meta-analyses in which researchers focused on explaining the association between hyperglycemia and peri-implant inflammation had several inherent flaws, including uncontrolled confounding factors (such as smoking,[11,13,14,28,31] bone augmentation or regeneration,[13,14] periodontitis,[11] cardiovascular diseases,[14] and type 1 diabetes mellitus[11]), no ND control group,[31] short follow-up of less than 6 months,[11,31] and inclusion of cross-sectional studies.[14,28] In comparison with these studies, important patient-related confounding factors were strictly controlled in our study. Moreover, cross-sectional studies were excluded because the design was not suitable for investigating causal relationships. However, our study also had limitations.

First, significant publication bias could lower the evidence power of our study. Second, the subgroup analyses failed to explain the high heterogeneity, which might be a result of uncontrolled implant therapy–related confounding factors (such as type of edentulism and loading protocol).

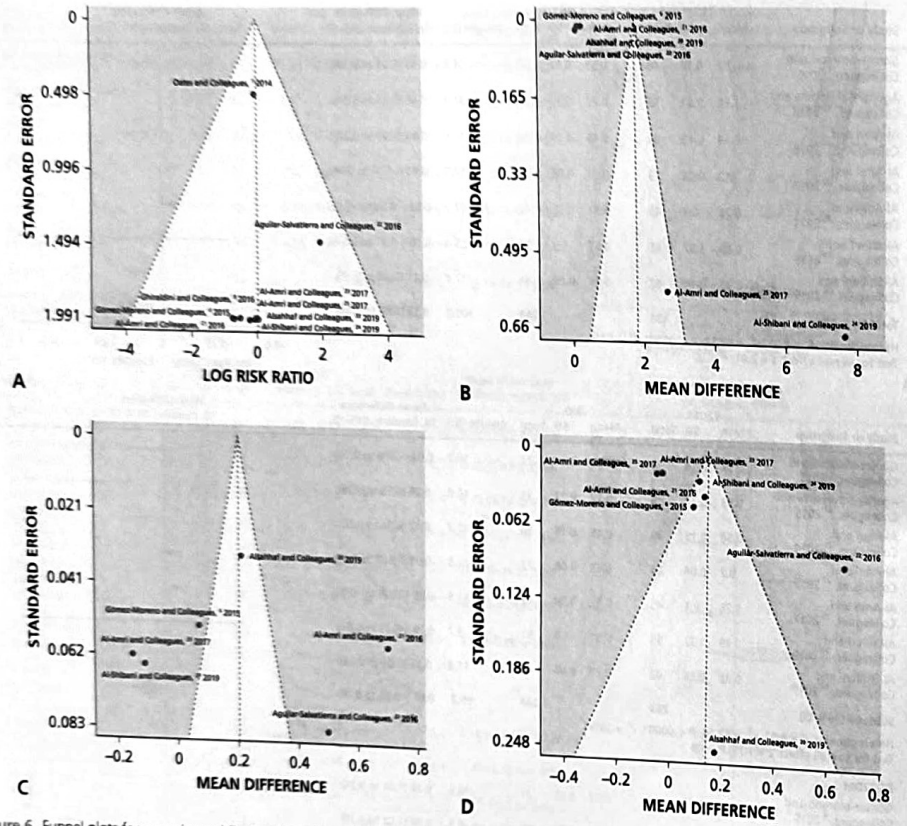

Figure 6. Funnel plots for assessing publication bias of rate of implant failure (**A**), bleeding on probing (**B**), probing diameter (**C**), and peri-implant bone loss (**D**).

However, these factors were usually combined in the included studies, making it difficult to perform a meta-regression analysis to estimate each separately. The type of edentulism (partial or complete) could influence the clinical outcomes of dental implant therapy. Investigators from a cohort study with a 9-year follow-up reported relatively high rates of peri-implant mucositis (56.9%) and peri-implantitis (14.3%) in fully edentulous patients.[32] However, only 1 included study,[7] which enrolled completely edentulous patients, reported implant failure. The loading protocol is another important confounding variable. However, participants with immediately loaded implants were recruited in 2 studies only,[21,22] and in 1 study[22] researchers reported implant failure in both diabetic and ND groups. Another limitation of our meta-analysis was that most of the included studies had small sample sizes, with the largest having 126 participants. Furthermore, the included studies had relatively short-term follow-up periods, ranging from 12 through 36 months, which could underestimate the impact of hyperglycemia on the clinical performance of dental implants. Extended follow-up could provide information on long-term complications; for instance, the rate of implant failure can increase over time. Therefore, to obtain a more definite conclusion, clinical trials with larger sample sizes, long-term follow-up periods, and well-controlled confounding factors are required.

CONCLUSIONS

Patients with T2DM seem to be able to achieve a rate of implant survival similar to that of healthy patients. Regarding peri-implant parameters, no significant difference was found in PD between patients with T2DM and ND patients; however, BOP and PIBL are remarkably higher in patients with T2DM, indicating that hyperglycemia is an important risk factor for peri-implant inflammation. Among patients with T2DM, an association between peri-implant parameters and glycemic level was not found, providing oral hygiene was strictly maintained. Considering the limitations of our study, clinical studies with larger sample sizes, long-term follow-up periods, and well-controlled confounding factors are required in the future. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2020.11.015.

Dr. Shang is a Dr. med. dent. candidate and dentist, Department of Operative Dentistry and Periodontology, Ludwig-Maximillians-University of Munich, Munich, Germany. Address correspondence to Dr. Shang, Department of Operative Dentistry and Periodontology, Ludwig-Maximillians-University of Munich, Goethestr. 70, D-80336 Munich, Germany, e-mail ren.shang@campus.lmu.de.

Dr. Gao is a dentist, Nanhai Hospital, Southern Medical University, Foshan, China.

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