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Association between diabetes and dental implant complications: a systematic review and meta-analysis

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ABSTRACT

Objectives: The aim of this study was to explore the possible association between diabetes mellitus and dental implant complications.

Material and methods: A systematic literature review was conducted to answer the following PICO (Participants, Intervention, Comparison, and Outcome) question: Is there association between diabetes mellitus and dental implant complications? Two independent searchers performed a literature search of the PubMed/MEDLINE, Web of Science, Cochrane Library and EMBASE databases for studies published until February 2020, focussing on studies including continuous outcomes, marginal bone loss (primary outcome), probing depth, and bleeding upon probing (secondary outcomes).

Results and conclusions: A final total of 10 published studies were included in this systematic review. There were statistically significant differences between the groups with regard to marginal bone loss ($p < .00001$), probing depth ($p < .00001$) and bleeding around dental implants ($p < .00001$), and subjects without diabetes had lower complication rates. Additionally, in the subgroup analysis performed with loading time and HbA1c levels, a more evident association was found in immediate loading for probing depth. Moreover, the analysis results of bleeding around dental implants suggested that as HbA1c level increases, the bleeding of the tissues surrounding the implant will also increase. With regard to dental implant complications, there were statistically significant differences favouring patients without diabetes mellitus.

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Dental implants; diabetes mellitus; meta-analysis

Introduction

Diabetes mellitus comprises a group of metabolic disorders that are characterized by hyperglycaemia, which is caused by defective insulin secretion, dysfunction or both. According to the latest statistics from the International Diabetes Federation, the number of people aged 20 to 79 years with diabetes mellitus had risen to 424.9 million in 2017, roughly three times the prevalence in 2000. The number of patients with diabetes worldwide is expected to rise to 629 million by 2045[1]. Diabetes mellitus is closely related to oral health, especially periodontal health [2], and has long been known to be a risk factor for implant failure due to susceptibility to infection, impaired healing and other complications [3]. Although diabetes mellitus has always been considered a relative contraindication to treatment with dental implants [4], dental implant restoration has been increasingly favoured by the majority of patients with tooth loss due to its advantages of reduced damage to adjacent teeth and reduced impact on alveolar bone compared to fixed bridge treatment and removable restoration, respectively [5]. A recent study surveyed a 40-year trend of tooth loss among people over the age of 25 years with and without diabetes mellitus in the United States and found that patients with diabetes lost almost twice as many teeth as patients without diabetes [6]. This observation corresponds to an increasing need for dental implant restoration among patients with diabetes.

Long-term hyperglycaemia may injure the vascular endothelium, leading to pathological changes of large vessels or microvessels, which promotes the differentiation of osteoclasts and inhibits the proliferation and differentiation of osteoblasts [7]. Hyperglycaemia also leads to excessive immune response to pathogens. Inflammatory mediators closely related to diabetes, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8) and tumour necrosis factor-α (TNF-α), can all be detected in the gingiva, serum and saliva. The presence of these factors aggravates the inflammation of oral tissues and reduces collagen synthesis, thereby effecting the formation of bone matrix and effecting the healing of both hard and soft tissues [8].

Although implants have a relatively high success rate during routine procedures, dentists need to identify patients at higher risk of complications, such as peri-implantitis and peri-implant mucositis. However, for many years, the definition of peri-implant diseases has been controversial. Although these diseases were initially classified as periodontal diseases, the specificity of peri-implant bone remodelling,

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the loss of periodontal ligaments, and other factors complicate the diagnosis of peri-implant diseases [9,10]. Recently, marginal bone loss (MBL), probing depth (PD) and bleeding on probing (BOP) have been used to identify peri-implant diseases. MBL is considered to be an important factor in evaluating the quality of survival bone, as bone loss may lead to the formation of pockets [11]. PD and BOP are indispensable parameters of peri-implant inflammation. Changes in the three indicators listed above may ultimately lead to adverse implant outcomes [12]. Considering the high prevalence of diabetes mellitus and the increasing number of people who expect to use dental implants to restore missing teeth, the aim of this meta-analysis was to conduct a review of the literature to explore a possible association between diabetes mellitus and dental implant complications. The null hypotheses were as follows: 1) There is no difference between individuals with and without diabetes mellitus in terms of peri-implant marginal bone loss. 2) There are no differences between these groups regarding indicators of probing depth and bleeding on probing.

Methods

Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13] and was registered with PROSPERO, the international prospective register of systematic reviews (PROSPERO: CRD42019143213).

Eligibility criteria

The PICO that we used to guide article selection was as follows. Population: individuals with dental implants; intervention: patients with diabetes mellitus; comparison: healthy patients without any sign of diabetes mellitus; and outcomes: complications containing MBL (primary outcome), PD and BOP (secondary outcomes). The focussed question to be addressed was: Is there association between diabetes mellitus and dental implant complications?

The following inclusion criteria were adopted: 1) studies of both diabetes (study) patients and healthy (control) participants; 2) randomized controlled trials (RCTs) and retrospective or prospective cohort studies; 3) available MBL, PD and BOP values; 4) study duration $\geq$6 months; 5) sample size of each group $\geq$10 participants; and 6) no language restrictions. The exclusion criteria were: 1) reviews or case reports and 2) animal studies.

Search strategy

Both electronic and manual searches were performed of electronic the PubMed/MEDLINE, Web of Science, Cochrane Library, EMBASE databases, system for information on Grey literature in Europe (http://www.opengrey.eu) and the ClinicalTrials.gov database (www.clinicaltrials.gov). The databases were searched for relevant literature published until February 2020. In addition, manual search was performed in the following journals for studies published between June 2016 and February 2020: Journal of Periodontology, Journal of Dental Research, Journal of Periodontal Research, Clinical Oral Implants Research, and Clinical Implant Dentistry and Related Research. References related to the included articles were also screened to determine whether they met the inclusion criteria. We used combinations of medical subject heading (MeSH) terms and free text words for all searches. To avoid missing any relevant literature, we combined population (Dental Implants[MeSH] OR dental implants[All Fields] OR (surgical[All Fields] AND dental[All Fields] AND prosthesis[All Fields]) with intervention (Diabetes Mellitus[MeSH] OR Diabetes Insipidus [MeSH] OR Diabetes Complications[MeSH] OR Diabetes Mellitus[MeSH] OR Type 2, Diabetes Mellitus, Type 1). The search strategy framework is shown in Table 1.

Data collection and extraction

According to the inclusion and extraction criteria, two reviewers independently screened the titles and abstracts and read the full text of papers for which final inclusion was difficult to decide. We extracted the following data: first author name, title, study design, country, sex ratio, average age, HbA1c, MBL, PD, and BOP. If the experiment had multiple follow-ups, we selected the data from the last follow-up. If the important data were not available in the paper, we contacted the corresponding author by email to request the missing data; if no response was received after a reminder, the study was excluded from the review.

Risk of bias and quality assessment

The retrospective and prospective cohort studies that we included in our review were assessed by the Newcastle-Ottawa scale (NOS)[14], in which a maximum of one star was scored for the selection and outcome categories, and two stars were scored for compatibility. A study can earn up to nine stars. If the score is equal to or more than 7, the research quality is considered high. If the score is between 4 and 6, the study is considered to be moderate quality.

Statistical analysis

Review Manager 5.3 software was used for the analysis of the data and to construct the forest plots. The three outcomes extracted in this review were all continuous variables, for which the mean and standard deviation (SD) were used to calculate the mean difference (MD) in millimetres with a 95% CI. When only standard error of mean (SEM) was mentioned, the SD could be obtained by indirect calculation. The heterogeneity of the results was tested by the Q method, and the I^2 statistic was used to express the percentage of variation attributable to heterogeneity. When there was no statistically significant heterogeneity ($p > .1$, $I^2 < 50\%$) between studies, we conducted the analysis using a fixed effects model. However,

Table 1. Search strategy.

Database	Search strategy
PUBMED	((((("Diabetes Mellitus"[Mesh] OR "Diabetes Insipidus"[Mesh]) OR "Diabetes Complications"[Mesh]) OR "Diabetes Mellitus, Type 2"[Mesh]) OR "Diabetes Mellitus, Type 1"[Mesh]) AND (((((((((("Dental Implants"[Mesh] OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("implants"[All Fields] AND "dental"[All Fields]) OR "implants, dental"[All Fields])) OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("dental"[All Fields] AND "prosthesis"[All Fields] AND "surgical"[All Fields]))) OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("surgical"[All Fields] AND "dental"[All Fields] AND "prosthesis"[All Fields]) OR "surgical dental prosthesis"[All Fields])) OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("dental"[All Fields] AND "implant"[All Fields]) OR "dental implant"[All Fields])) OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("implant"[All Fields] AND "dental"[All Fields]) OR "implant, dental"[All Fields])) OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("dental"[All Fields] AND "prostheses"[All Fields] AND "surgical"[All Fields]))) OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("surgical"[All Fields] AND "dental"[All Fields] AND "prostheses"[All Fields]))) OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("prostheses"[All Fields] AND "surgical"[All Fields] AND "dental"[All Fields]))) OR ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields] OR ("prosthesis"[All Fields] AND "surgical"[All Fields] AND "dental"[All Fields]))) AND "humans"[MeSH Terms]
Web of Science	#1 diabetes #2 dental implant #1 and #2
Cochrane Library	#1 ("diabetes insipidus"):ti,ab,kw OR ("diabetes mellitus"):ti,ab,kw OR ("diabetes mellitus type 1"):ti,ab,kw OR ("diabetes mellitus type 2"):ti,ab,kw OR (diabetes complications):ti,ab,kw #2 (dental implant):ti,ab,kw #3 - #1 AND #2
Embase	#1 'tooth implantation' OR 'tooth implant' OR 'dental abutment' OR 'single tooth implant' OR 'dental anchor' OR (dental AND implant AND complication) #2 'diabetes mellitus' OR 'non insulin dependent diabetes mellitus' OR 'diabetic complication' #3-#1 AND #2

if the heterogeneity was statistically significant ($p < .1$, $I^2 > 50\%$), a random effects model was adopted [15,16].

Subgroup analysis was used to explore whether some factors (HbA1c, loading time, follow-up time) were the source of heterogeneity. Publication bias was identified by Egger's regression test using STATA 14 statistical software and funnel plots [17].

Results

Literature search

The process for searching and selecting articles is shown in Figure 1. According to the set search strategy, a total of 1153 articles were initially retrieved: 215 articles from PubMed/MEDLINE, 558 from Web of Science, 31 from Cochrane Library, and 349 from EMBASE. After eliminating 461 duplicates, 692 articles remained. Following the screening of titles and abstracts, 525 studies were determined to be irrelevant to our subject, 48 described animal experiments, 42 were reviews, and 7 were case reports. Among the 70 remaining articles, 50 were excluded after full-text analysis. Of the remaining 20 studies [18–37], 10 were excluded for the following reasons [22,23,30–37]. 1) The implants in one study had been functioning for approximately 6.5 years at the time of the study, but disease duration in the diabetes and prediabetes groups was 2 or 3 years; in other words, some patients did not have diabetes at the time of implantation, which may make the final results unreliable [23]. 2) The mean values of MBL, DB and BOP provided in some of the papers did not meet the data extraction standards of this meta-analysis, and relevant data were not obtained after contacting the corresponding authors [30,31,33,35]. 3) After comparison, it was determined that two studies by Al Amri MD [24,32], Al Zahrani S [21,34] and Cabrera-Domínguez [19,22] may have been from the same team, and there may have been data overlap between the papers. The articles by Al Amri [32] and Cabrera-Domínguez [22] had minimal content and a short observation time and were excluded. We also excluded the study by Al Zahrani S because the control group was well-controlled patients with diabetes rather than healthy individuals [34]. 4) Finally, selected patients had pairs of adjacent implants, which may influence MBL, PD and BOP [36,37].

Characteristics of included studies

The characteristics of the included studies in this review are shown in Table 2. Eight were prospective cohort studies [18,21,24–29], and two were retrospective cohort studies [19,20]. Of the 625 participants in all of the studies, 360 had diabetes, and 265 were healthy. The number of participants ranged from 24 to 119, with an average age ranging from 43.1 to 65 years. Three studies were grouped according to HbA1c levels [24,25,27]. Two of the studies [24,25] divided the diabetes group into groups with HbA1c levels of 6.1–8.0% (well-controlled) and 8.1–10.0% (moderately controlled), while the other [27] added a group with HbA1c levels of $\geq$10.0% (poorly controlled). Two of the studies [24,25] recruited participants with immediately loaded implants, while the patients in six studies [18,19,21,26,27,29] received implants with delayed loading; the remaining two studies did not describe loading [20,28].

Quality assessment

The quality analysis results of the studies are shown in Table 3. The mean NOS score of the 10 studies was 6.3 ± 1.3.

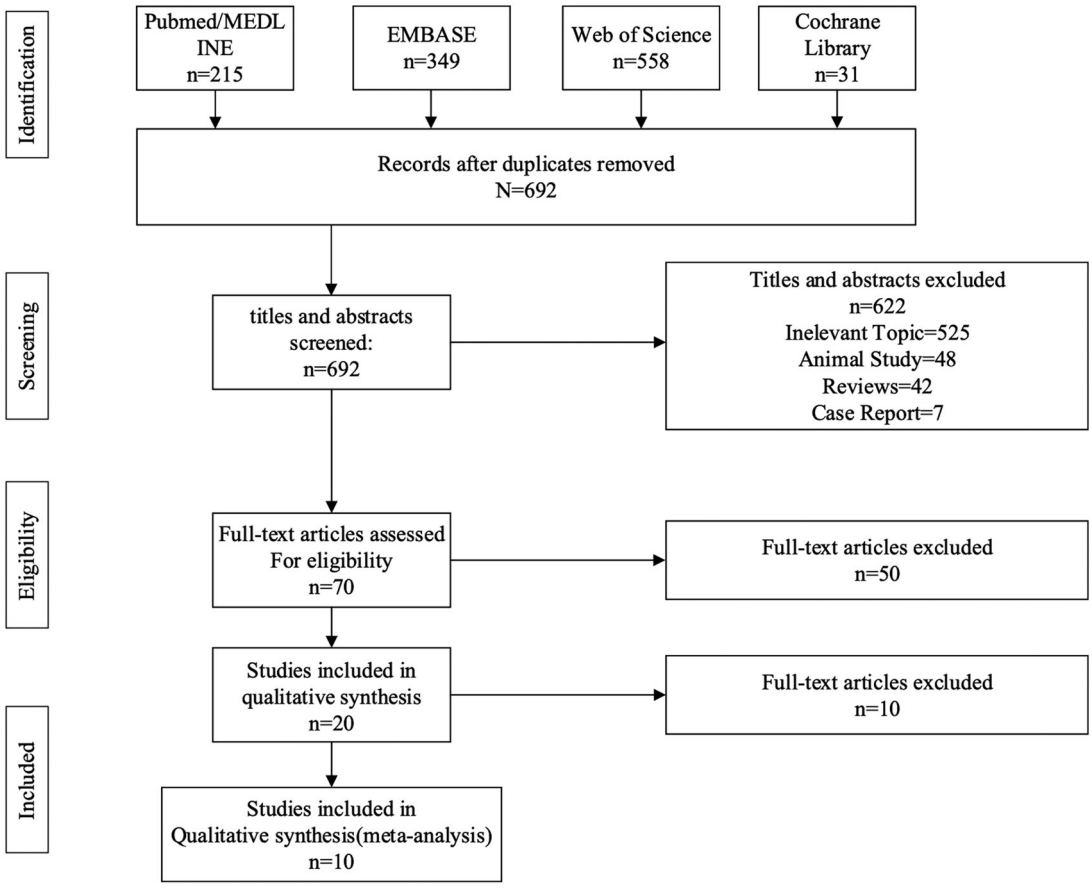

Figure 1. PRISMA flow diagram of the study selection process.

Results of the meta-analysis

This review evaluated three outcome indicators: MBL, PD, and BOP. Among these studies, nine compared MBL [18,19,21,24–29], seven compared PD [18,19,24,25,27–29], and seven compared BOP [18,20,24,25,27–29] between participants with and without diabetes.

Marginal bone loss

In this study, a fixed effects model was used to evaluate MBL in patients with diabetes because of low heterogeneity between studies ($p = .47$, $I^2 = 0\%$). Implant marginal bone loss was higher among patients with diabetes compared to healthy patients, and the difference was statistically significant. The MD of MBL in comparison between diabetes and patients without diabetes was 0.15 (95% CI = 0.10, 0.20; $p < .00001$) (Figure 2).

Probing depth

The pooled effect size from all evaluated studies showed significant differences in PD between participants with and without diabetes mellitus (MD: 0.30; 95% CI 0.08, 0.51; $p = .007$). However, heterogeneity was high between studies ($p < .00001$, $I^2 = 78\%$). To determine the possible sources of heterogeneity, we performed a subgroup analysis based on loading time (delayed loading, immediate loading and other) and HbA1c levels (6.1–8.0%, 8.1–10.0%, ≥10.0%) (Figure 3).

Bleeding on probing

We also compared BOP around the implants in patients with and without diabetes, and found that BOP in the control group was better than that in the diabetes mellitus group; this difference was statistically significant (MD: 22.62; 95% CI 16.82, 28.43; $p < .00001$). As the heterogeneity among studies was high, we conducted a similar subgroup analysis of the included studies for BOP as for PD; that is, we examined loading time (delayed loading, immediate loading and other) and HbA1c levels (6.1–8.0%, 8.1–10.0%, ≥10.0%) (Figure 4).

Publication bias

Egger's regression test was used to analyse whether there was publication bias in each of the studies for the three different outcome indicators. The results showed that there was no significant publication bias in the studies of MBL ($p = .146$) or BOP ($p = .558$); however, there was possible publication bias in the studies of PD ($p = .002$).

Discussion

This review was designed to evaluate the dental implant complications of MBL, PD and BOP between participants with and without diabetes mellitus. We found that there were significant differences in MBL between patients with and without diabetes. Three studies [21,24,25] showed that

Table 2. Characteristics of included studies.

Author (Year)	Study design	Country	Follow up	Study group (HbA1c)	Subjects M/F	Mean age	Implant placed
Abdulaziz (2019)	RA	Saudi Arabia	3y	DM (≧6.5%)	119	52.7	65
				PreDM (5.7–6.4%)	76/43	46.1	78
				NoDM (4–5%)		43.4	52
Cabrera-Domínguez (2019)	PA	Spain	2y	DM (>6.0%)	28	56.75	NR
				NoDM (≦6.0%)	12/16		
Al-Sowygh (2018)	RA	Saudi Arabia	NA	DM (≧6.5%)	79	43.1	NR
				NoDM (self-report)	79/0	44.2	
Al Zahrani (2018)	PA	Saudi Arabia	7y	DM (>6.0%)	70	54.6	59
				NoDM (≦6.0%)	46/24	46.8	59
Al Amri (2016)	PA	Saudi Arabia	2y	DM (8.1–10%)	91	50.5	NR
				DM (6.1–8%)	91/0	50.1	
				NoDM (<6%)		48.5	
Aguilar (2016)	PA	Spain	2y	DM (8.1–10%)	85	61	22
				DM (6.1–8%)	44/41	57	30
				NoDM (≦6%)		59	33
Erdogan (2015)	PA	Turkey	1y	DM (6–7.5%)	24	52.6	22
				NoDM (self-report)	12/12	49.5	21
Gómez-Moreno (2015)	PA	Spain	3y	DM (≧10%)	67	64	11
				DM (8.1–10%)	33/34	62	11
				DM (6.1–8%)		59	24
				NoDM (≦6%)		60	21
Tatarakis (2014)	PA	America	1y	DM (self-report)	32	65	27
				NoDM (self-report)	16/16	64	41
Bignozzi (2013)	PA	Roma	2y	DM (self-report)	30	55.13	15
				NoDM (self-report)	15/15	56.05	36

Author (Year)	HbA1c (baseline)	MBL (mm) Mean (SD)	Probing Depth (mm) Mean (SD)	Bleeding on Probing (%) Mean (SD)
Abdulaziz (2019)	7.9%	0.69 (1.37)	2.39 (1.45)	53 (56.4)
	6.4%	0.59 (1.41)	2.23 (1.85)	42 (70.7)
	4.6%	0.51 (1.3)	2.18 (1.3)	21 (43.4)
Cabrera-Domínguez (2019)	6.64%	0.68 (0.67)	2.13 (0.68)	NR
	5.19%	0.75 (0.49)	2.07 (0.78)	
Al-Sowygh (2018)	10.2%	NR	NR	62.3 (7.9)
	4.4%			24.7 (9.5)
Al Zahrani (2018)	8.2%	1.1 (0.81)	NR	NR
	4.7%	0.58 (0.70)		
Al Amri (2016)	8.7%	0.59 (0.2)	2.3 (0.62)	62 (5.0)
	6.8%	0.58 (0.15)	2.3 (0.15)	62 (7.0)
	4.5%	0.46 (0.16)	1.6 (0.05)	40 (6.0)
Aguilar (2016)	NR	1.92 (1.78)	3.68 (2.25)	74 (23.45)
		0.98 (1.48)	2.79 (1.31)	51 (27.39)
		0.72 (1.55)	2.67 (0.80)	44 (40.21)
Erdogan (2015)	6.7%	1.13 (0.34)	NR	NR
	NR	0.93 (0.31)		
Gómez-Moreno (2015)	NR	0.70 (0.63)	2.40 (0.83)	72 (19.9)
		0.64 (0.56)	2.34 (0.66)	62 (19.9)
		0.57 (0.78)	2.30 (1.13)	56 (34.3)
		0.53 (0.78)	2.26 (0.87)	45 (27.5)
Tatarakis (2014)	7.1%	0.19 (0.45)	2.35 (0.67)	67 (22.45)
	5.7%	−0.08 (0.25)	2.20 (0.89)	56 (25.46)
Bignozzi (2013)	9.05%	1.07 (0.12)	2.81 (0.31)	31 (14.0)
	5.95%	0.88 (0.25)	2.68 (0.3)	15 (23.0)

RA: retrospective analysis; PA: prospective analysis;NA: not applicable; y: year; m: month; NR: not reported.

bone loss values of the diabetes group were significantly higher than that of the control group; five other studies [18,19,26,27,29] reported higher marginal bone loss in diabetes patients, than that in patients without diabetes, but the difference was not statistically significant. In regard to PD, probing depth of patients without diabetes was significantly lower than that of patients with diabetes. Six studies [18,19,24,25,27,29] reported higher PD among patients with diabetes than those without, but the difference was not statistically significant. Due to high heterogeneity between studies, we conducted a subgroup analysis and found that loading time – but not HbA1c levels – may be the source of heterogeneity. With delayed loading, there was no statistically significant difference in PD between patients with and without diabetes ($p = .15$); however, the PD of diabetes patients with immediate loading implants was significantly higher. In terms of BOP, the review results showed worse BOP in patients with diabetes mellitus versus those without. In four studies [18,20,25,27], the BOP of participants with diabetes was significantly higher than that of the participants without diabetes; in the remaining two studies [24,29], the differences in BOP between the two groups were not statistically significant. To determine the source of this high heterogeneity, we performed a subgroup analysis, which indicated that both loading time and HbA1c could be sources of heterogeneity. As HbA1c levels increase, BOP of the

surrounding tissues of the implant will also increase. This result could occur because increased HbA1c levels inhibit oxygen-carrying capacity and reduce the resistance of tissues [38]. In terms of loading time, subgroup analysis results suggested that the heterogeneity could have been caused by a third 'other' group. In fact, neither Al-Sowygh [20] nor Tatarakis [28] distinguished between various dental implant loading times; their papers were therefore categorized into a separate group, considering that the study participants could include patients with both immediate and delayed loading. However, the hypothesis that loading time may be the source of high heterogeneity should be considered with caution.

In a meta-analysis, Moraschini et al. [39] compared the implant success rate and marginal bone loss of diabetes patients with that of healthy patients and found no statistically significant difference between the two groups in terms of implant success rate; however, the marginal bone loss of the diabetes group was significantly higher than that of the healthy group. In another meta-analysis, Alberto et al. [40] found a significantly higher risk of peri-implantitis in diabetes patients than in healthy participants, but the risk of peri-implant mucositis was not significantly different between the two groups. However, there are no globally accepted definitions of peri-implant disease [41], rendering the homogeneity of the included studies potentially low, and direct comparison should be conducted with caution. The successful implant criteria proposed by Albrektsson et al. [42] in 1986 have been widely recognized, mainly including: no mobility of the implant, no evidence of radiolucency around the implant, bone loss in the vertical direction is less than 0.2 mm per year following the implant's first year of service, For non-persistent or irreversible complications after implantation, the above conditions were satisfied for more than 85% in 5 years and 80% in 10 years.The clinical assessment level proposed by the International Congress of Oral Implantologists Consensus Conference in 2007[43] was widely recognized and defined implant success as: No pain or tenderness upon function, 0 mobility, <2 mm radiographic bone loss from initial surgery, No exudates history. peri-implantitis refers to the pathological state of the peri-implant tissues caused by plaque, characterized by the appearance of mucosal inflammation around the implant and the gradual absorption of the supporting bone tissues. It is a major reason of implant failure, accompanied with bleeding, increased probing depth, and marginal bone loss [44,45].

Whether immediate loading affects the survival rate and long-term consequences of dental implants has remained controversial. Al Amri et al. [24] and Aguilar et al. [25] reported that immediate loading and delayed loading had no significant effect on the severity of peri-implant complications in patients with well-controlled diabetes mellitus. In contrast, Michaeli et al. [4,42] supported the hypothesis that the implant for diabetes patients should not be immediately loaded, as it may lead to impaired healing of the bone around the implant; however, this may be because HbA1c were not well controlled in that study. Thus, regarding immediate implantation and implant loading for patients with diabetes mellitus, it is suggested that doctors carefully consider indications and ensure that HbA1c is well-controlled.

HbA1c is the main manifestation of stable glycosylated haemoglobin, which is essentially an irreversible product of the red blood cell cycle. HbA1c reflects changes in the blood glucose level over the preceding 2–3 months and can be modified into advanced glycosylation products (AGEs); these can inhibit the development of osteoblasts and promote the inflammatory response of periodontal tissues [43–48]. HbA1c

Table 3. Quality assessment of 10 studies included in the qualitative evaluation according to the New Castle Ottawa Scale (NOS)

Author (Year)	Study design	Selection (Max 4)	Comparability (Max 2)	Outcome (Max 3)
Abdulaziz (2019)	RC	★★	★★	★★
Cabrera-Dominguez (2019)	PC	★★★	★★	★★★
Al-Sowygh [20]	RC	★★	★	★
Al Zahrani [21]	PC	★★★	★★	★★★
Al Amri [24]	PC	★★	★	★★
Aguilar-Salvatierra [25]	PC	★	★★	★★★
Erdogan [26]	PC	★★★	★	★★
Gomez-Moreno (2015)	PC	★★★	★	★★
Tatarakis [28]	PC	★★★	★	★★
Bignozzi [29]	PC	★★★★	★	★★★

A maximum of one star for each item within the selection categories: representativeness of the exposed cohort, selection of external control, ascertainment of exposure, outcome of interest not present at start.
A maximum of one star for each item within the outcome categories: assessment of outcome, follow-up was long enough for outcome to occur, adequacy of follow-up of cohorts.
A study can be awarded maximum two stars in the comparability.

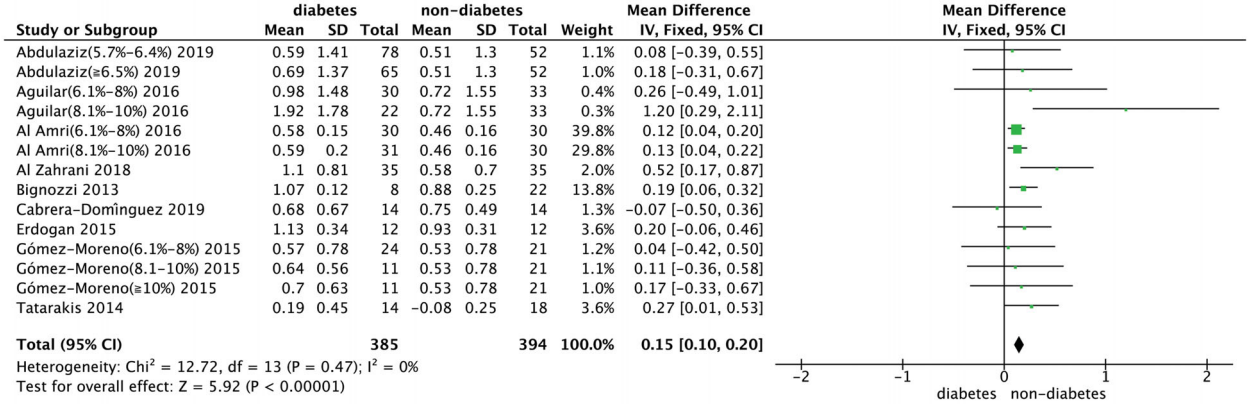

Figure 2. Forest plot of the random effects model meta-analysis of studies reporting MBL.

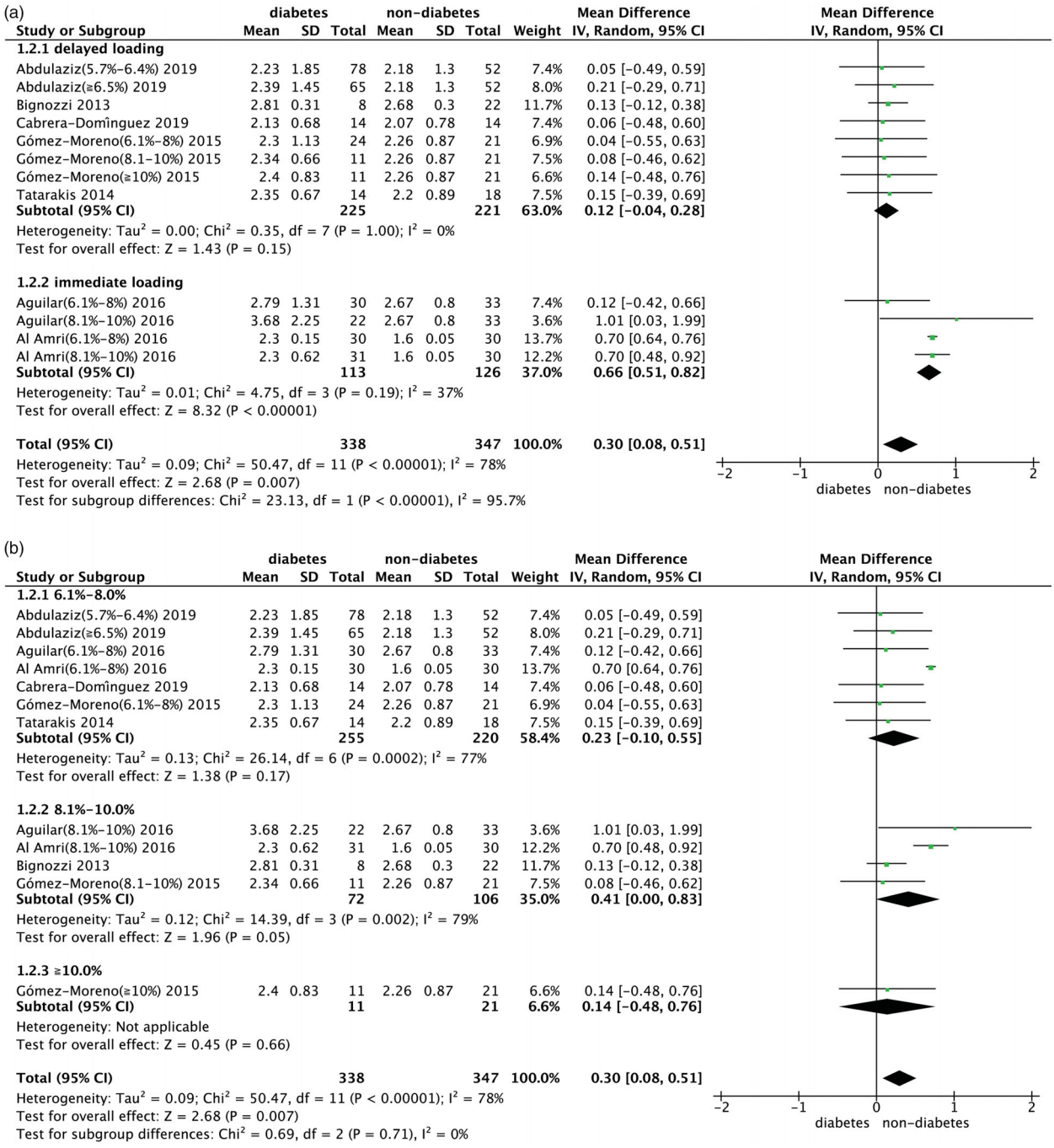

Figure 3. Forest plot of the random effects model meta-analysis of the effect of diabetes mellitus on the probing depth of dental implants, and subgroup analysis based on loading time (a) and HbA1c levels (b).

is considered the diagnostic standard for diabetes mellitus, and controlling HbA1c levels is the main method for controlling and monitoring diabetes [4,46,49,50]. Three studies [24,25,27] were grouped according to different control levels of HbA1c and analysed for variables related to tissue response around implants, which was found to be related to HbA1c levels and time.

Our findings seem to suggest that MBL, PD and BOP around dental implants are higher in individuals with diabetes mellitus. However, some issues should be considered.

First, the control level of diabetes was evaluated by measuring HbA1c. However, most of the ten papers included in this review only provided initial data of HbA1c. Although three articles [22,25,27] mentioned this indicator for monitoring diabetes, these papers did not provide the relevant data or analysis. One article [24] described a reduction in patients' HbA1c levels by means of periodontal maintenance and that peri-implant inflammation indicators were then improved. Another study [28] mentioned that HbA1c levels in patients with diabetes were maintained at initial levels and that they remained stable throughout the follow-up period. Second, the search strategy we adopted did not retrieve relevant RCTs, and mainly retrieved cohort studies. Compared with RCTs, nonrandomized controlled methods are more likely to

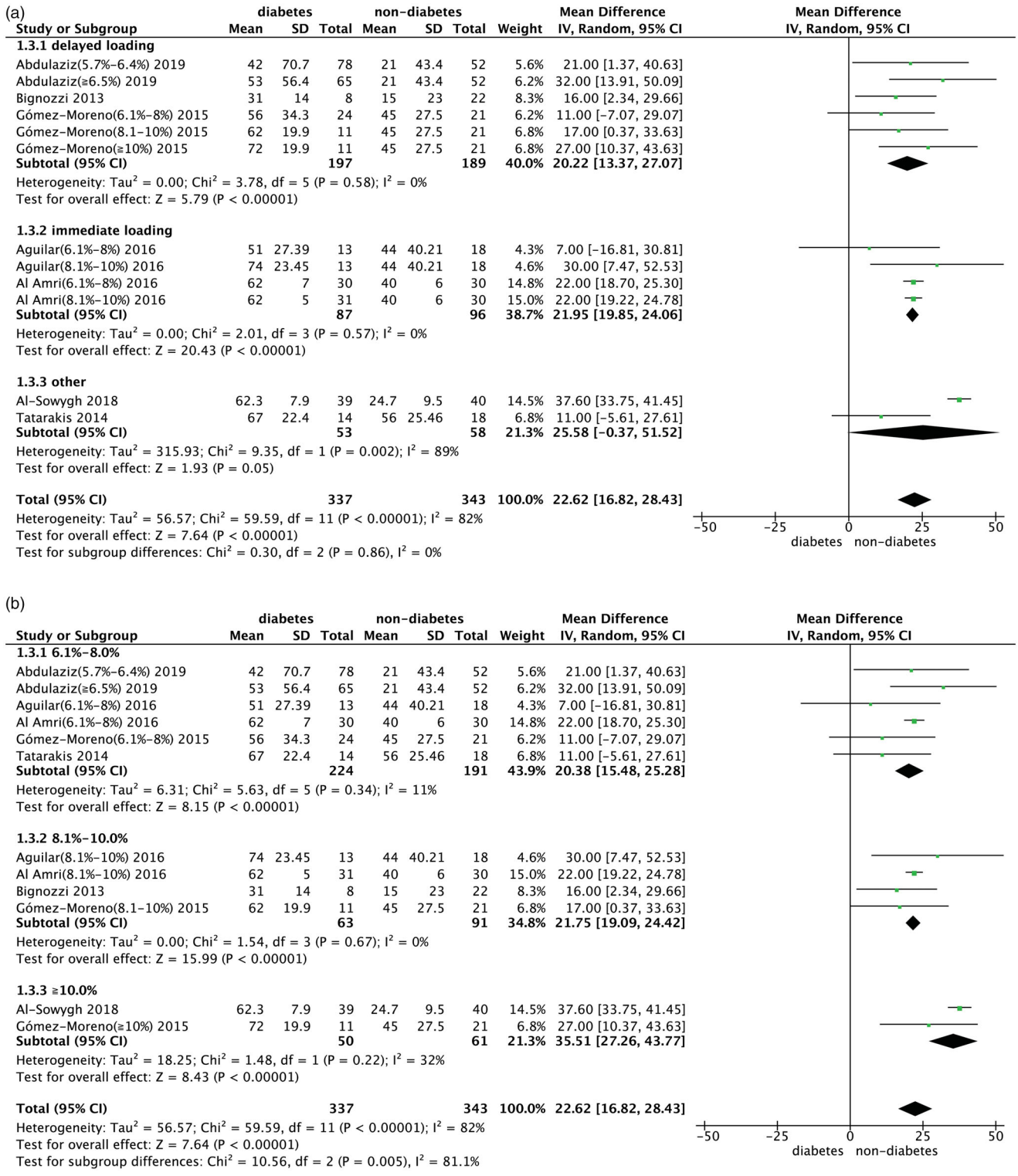

Figure 4. Forest plot of the random effects model meta-analysis for the comparison between diabetic group and control group regarding bleeding on probing. 'forest plot' of subgroup based on loading time (a) and HbA1c levels (b).

generate potential bias. Finally, although the results were statistically significant, the small number of studies and participants results in lower statistical power.

In conclusion, despite the limitations of this review, implants are feasible for patients with diabetes. There is evidence, however, that these patients are more likely to have clinical complications than patients without diabetes. For primary outcome (marginal bone loss), there was a statistically significant difference favouring non-diabetic subjects. Additionally, for secondary outcomes, the comparison of different HbA1c levels showed no evidence of a higher PD for all of the groups. However, the differences of BOP around implants were significant of all the three HbA1c levels, favouring systemically healthy individuals. This evidence

suggests that dental implant eligibility criteria for patients with diabetes should be more strict, that local and systemic factors should be controlled for after surgery, and that long-term follow-up and evaluations should performed.

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