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SYSTEMATIC REVIEW

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Association between diabetes mellitus/hyperglycaemia and peri-implant diseases: Systematic review and meta-analysis

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Abstract

Aim: This systematic review investigates whether hyperglycaemia/diabetes mellitus is associated with peri-implant diseases (peri-implant mucositis and peri-implantitis).

Materials and Methods: Electronic and manual literature searching was conducted. An a priori case definition for peri-implantitis was used as an inclusion criterion to minimize risk of bias. The Newcastle-Ottawa Scale was used for quality assessment; random effect models were applied; and results were reported according to the PRISMA Statement.

Results: Twelve studies were eligible for qualitative and seven of them for quantitative analyses. Meta-analyses detected the risk of peri-implantitis was about 50% higher in diabetes than in non-diabetes (RR = 1.46; 95% CI: 1.21–1.77 and OR = 1.89; 95% CI: 1.31–2.46; $z = 5.98$; $p < .001$). Importantly, among non-smokers, those with hyperglycaemia had 3.39-fold higher risk for peri-implantitis compared with normoglycaemia (95% CI: 1.06–10.81). Conversely, the association between diabetes and peri-implant mucositis was not statistically significant (RR = 0.92; 95% CI: 0.72–1.16 and OR = 1.06; 95% CI: 0.84–1.27; $z = 1.06$, $p = .29$).

Conclusions: Within its limits that demand great caution when interpreting its findings, this systematic review suggests that diabetes mellitus/hyperglycaemia is associated with greater risk of peri-implantitis, independently of smoking, but not with peri-implant mucositis.

KEYWORDS

dental implants, diabetes complications, epidemiology, gestational diabetes, glycosylated, haemoglobin A, humans, review, systematic

1 | INTRODUCTION

Peri-implant diseases—that reportedly affect around half the individuals with dental implants (Derks & Tomasi, 2015)—constitute one of the major challenges in contemporary implant dentistry and hence require primary prevention and early diagnosis (Sanz, Chapple, & Working Group 4 of the VIII European Workshop on Periodontology 2012; Tonetti, Chapple, Jepsen, & Sanz, 2015; Tonetti, Eickholz et al., 2015). One of the main obstacles to early diagnosis is the lack of standard case definitions for peri-implant diseases (Sanz & Chapple, 2012). Moreover, local and systemic factors have been shown to substantially and negatively impact the peri-implant tissues, leading to increased susceptibility, which—in the presence of biofilm on the fixture surface—may trigger an inflammatory response that ultimately will lead to tissue breakdown in especially susceptible persons (Renvert & Polyzois, 2015). Therefore, identification of risk indicators based on patients' risk profiles is essential to prognosticate disease occurrence and provide individually tailored preventive intervention (Jepsen et al., 2015; Tonetti, Eickholz et al., 2015; Tonetti, Chapple, Jepsen, & Sanz, 2015).

With the realization that the individual host inflammatory response is the main promoter of several chronic diseases and conditions,

including diabetes (Shi & Hu 2014) and chronic periodontitis (Bartold & Van Dyke, 2013; Borgnakke, 2016a), hyperglycaemia could be a potentially important factor in the development of biologic complications of dental implants, especially at greater severity as seen in poorly controlled diabetes. Hyperglycaemia (dysglycaemia) will refer to elevated blood glucose levels regardless of any classification and categorization, such as pre-diabetes, gestational diabetes, type 1 diabetes, type 2 diabetes, and maturity-onset diabetes of the young (MODY) or surgically provoked diabetes (American Diabetes Association 2017).

The prevalence of diabetes is increasing in many countries in the world and it is currently estimated that 415 million adults (8.4%) worldwide have diabetes with a 642 million projected for the year 2040 (International Diabetes Federation 2015). A full one-third of adults are expected to have diabetes in 2050 in the United States (Centers for Disease Control and Prevention (CDC, 2014, 2015) and by 2040, it is predicted that there will be 71.1 million adults living with diabetes in Europe (International Diabetes Federation 2015). Traditionally, diabetes has been regarded a risk factor for periodontitis, but only rather recently has it become evident that it is not merely the diagnosis of diabetes that is important, but rather the level of elevated blood glucose levels (hyperglycaemia) that is pivotal (Borgnakke, 2016a, 2016b; Genco & Borgnakke, 2013). The underlying mechanism/connection between these two chronic diseases could briefly be described by 1) the perpetual chronic inflammatory responses stimulated by bacterial biofilm in a vicious cycle in which the two conditions mutually and adversely affect each other (Bartold & Van Dyke, 2013; Borgnakke, 2016b; Loos, 2005), and 2) the elevated blood glucose levels that produce advanced glycation end products (AGEs) that activate expression of receptor for AGEs (RAGEs) and contribute to impaired repair of the periodontal tissues that are broken down by the exaggerated and sustained inflammation caused by the bacterial biofilm (dental plaque) (Lalla & Papapanou, 2011). Such hyperglycaemia-induced matrix glycation is shown to modulate cell behaviour leading to a level of inflammation similar to that seen upon inoculation by the periodontal bacterium *Porphyromonas gingivalis* and its toxins, lipopolysaccharides (LPS) (Chang, Chien, Chong, Kuo, & Hsiao, 2013; Chang, Chien, Yeo et al., 2013). The presence of diabetes is also shown to facilitate attachment loss due to the greater inflammatory response and persistent bone resorption activity (Chang, Chien, Chong et al., 2013; Chang, Chien, Yeo et al., 2013). Moreover, hyperglycaemia affects all aspects of wound healing. It is also noteworthy that gingivitis is more prevalent in people with diabetes, regardless of the abundance of plaque accumulation, which suggests that hyperglycaemia is associated with hyperinflammatory responses in the gingival tissue (Hasturk & Kantarci, 2015).

Similar to periodontitis, peri-implantitis is a plaque-initiated and host-mediated destructive process that is influenced by modifiable and non-modifiable local, systemic, and environmental factors (Berglundh, Gotfredsen, Zitzmann, Lang, & Lindhe, 2007; Lang & Berglundh, 2011; Sanz & Chapple, 2010) and presents with matrix degradation and break down of bone (Carcuac & Berglundh, 2014; Wang et al., 2016).

It is concluded by systematic reviews that implant osseointegration can occur in people with diabetes with optimal glycaemic control, but that poorly controlled diabetes adversely impacts such osseointegration (Javed & Romanos, 2009); that osseointegration takes longer in diabetes, although there is no difference in implant stability after 1 year compared to non-diabetes (Naujokat, Kunzendorf, & Wiltfang, 2016); that no statistically significant difference in implant failure rates in patients with and without diabetes is identified, despite people with diabetes experience more marginal bone loss (Chrcanovic, Albrektsson, & Wennerberg, 2014), whereas implant survival was found to be lower in diabetes as per another systematic review (Naujokat et al., 2016); and that type 2 diabetes under poor glycaemic control increased clinical periodontal probing depth and radiographic marginal bone level (based on only one study identified on diabetes in a systematic review of medially compromised patients with implants) (Turri, Rossetti, Canullo, Grusovin, & Dahlin, 2016). Nonetheless, little is still known about the associations between diabetes/hyperglycaemia and peri-implant diseases and even less about any directionality of such potential association.

Clinical Relevance

Scientific rationale for the study: Although recent evidence suggests that implant failure rates are not greatly elevated in diabetes, it is unknown whether hyperglycaemia is associated with peri-implant diseases. Hence, this systematic review was conducted.

Principal findings: Based on 12 eligible studies, meta-analyses calculated that hyperglycaemia is associated with the risk of peri-implantitis, but not with peri-implant mucositis.

Practical implications: Because there currently is no effective treatment for peri-implantitis, it is important to consider the elevated risk for peri-implantitis in patients with diabetes, both during treatment planning together with the patient and throughout the maintenance during the lifespan of the implant.

To remedy a gap in the existing body of literature, the objective of this systematic review was to investigate the associations between hyperglycaemia and peri-implant diseases (peri-implant mucositis and peri-implantitis) applying strict inclusion criteria, especially using a priori determined case definitions, and synthesizing the evidence qualitatively and also quantitatively, provided sufficiently similar studies were identified to allow meta-analyses.

2 | REVIEW OF CURRENT LITERATURE

2.1 | Objective

Our aim was to identify and assess the existing scientific evidence from epidemiologic, non-experimental, observational studies of associations between hyperglycaemia/diabetes mellitus and peri-implant disease through conducting a systematic review and performing meta-analyses, if possible.

The focused questions to be addressed were:

1. Are hyperglycaemia (diabetes) and peri-implant diseases (peri-implant mucositis or peri-implantitis) associated?
   1a. If yes to 1): What is the strength of the evidence for associations between hyperglycaemia and peri-implant diseases compared to other potential risk factors?
2. In participants with implants and no peri-implant diseases, do those with hyperglycaemia develop more (incident) peri-implant diseases than normoglycaemic patients over time?
3. If yes to 1) or 2): Is the prevalence of peri-implant diseases (peri-implant mucositis or peri-implantitis) in participants associated with degree of hyperglycaemia?

2.2 | Data extracted/measures

In brief, our PECO (P = population, E = exposure, C = comparison, O = outcome measures)(Stone, 2002) measures were:

Population: participants with osseointegrated dental implants
Exposure: hyperglycaemia (diabetes mellitus, pre-diabetes)
Comparison: normoglycaemic (with normal glucose levels) participants
Outcome: implant-related biologic complications (i.e. peri-implant mucositis or peri-implantitis)

2.2.1 | Population

The *population* of interest consisted of people with missing teeth replaced by restored dental implants placed in completely or partially edentulous, mandibular or maxillary dental/alveolar arches.

2.2.2 | Exposure

We chose the term "hyperglycemia" (also known as "dysglycemia") for the *exposure* to capture any level of elevated blood glucose levels, regardless of severity and underlying cause or diagnosis because 1) we realize it is the severity of the hyperglycaemia (dysglycaemia) that is important, as opposed to an unqualified diagnosis of "diabetes," regardless of glycaemic control; and 2) even slightly elevated glucose concentrations that do not qualify for being diagnosed as overt diabetes still could exert adverse effects. Hyperglycaemia includes pre-diabetes and type 1 and type 2 diabetes as well as gestational diabetes and diabetes due to other causes [e.g. maturity-onset diabetes of the young [MODY] (American Diabetes Association 2017)]. Hyperglycaemia is measured as levels of glycated haemoglobin A1c (A1c) ≥5.7% or fasting plasma glucose (FPG) ≥ 100 mg/dl. More specifically, pre-diabetes is diagnosed for A1c 5.7%–6.4% or FPG 100–125 mg/dl; and manifest diabetes is diagnosed when A1c ≥ 6.5% or FPG ≥ 126 mg/dl. These categories correspond to hyperglycaemia A1c ≥ 39 mmol/mol; pre-diabetes A1c 39–47 mmol/mol or FPG of 5.6–6.9 mmol/L; and manifest diabetes A1c ≥ 48 mmol/mol or FPG of 7.0 mmol/L. A1c is a measure of the degree of enzymatic, irreversible glycosylation (binding of glucose) to haemoglobin, the oxygen carrying protein in red blood cells.

2.2.3 | Comparison

We included only studies that reported results for a *comparison (*or *control)* group consisting of persons with implants but without hyperglycaemia ("normoglycemic").

2.2.4 | Outcome

The *outcomes* were the presence or development (incidence) of the implant related biologic complications peri-implant mucositis or peri-implantitis, reported at implant or patient levels. In order to standardize the case definition of peri-implantitis to eliminate bias arising from using too different case definitions, we included only studies that applied the diagnosis of *peri-implant mucositis* as an inflammatory condition manifested by swelling (*tumour*) and redness (*rubor*) but no pathological bone loss. *Peri-implantitis* needed to be defined as clinical inflammation in combination with radiographic marginal bone loss >2 mm. Hence, we used the definitions proposed by the 8th European Workshop in Periodontology in 2011 and reported on behalf of its Workgroup 4 (Sanz, Chapple, & Working Group 4 of the VIII European Workshop on Periodontology 2012), hereafter referred to as the European peri-implant disease case definitions.

3 | METHODS

3.1 | Protocols

3.1.1 | Study registration

The review protocol was registered and allocated the identification number CRD42016039090 in the PROSPERO International Prospective Register of Systematic Reviews hosted by the National Institute for Health Research, University of York, Centre for Reviews and Dissemination (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016039090).

3.1.2 | Reporting format

For describing and summarizing the results of our review, we used the 27-item Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group 2009). Moreover, the Assessment of Multiple Systematic Reviews guidelines (AMSTAR) was followed (Shea et al. 2009) to fulfil the standards of reporting systematic reviews.

3.1.3 | Quality assessment

Assessment of the quality of non-randomized, non-interventional studies is essential for proper evaluation of the evidence provided by

each study. We followed the Newcastle-Ottawa System (NOS) protocol (Wells et al., 2011), however because the NOS was designed to assess cohort and case–control studies, but not cross-sectional studies, adaptation was necessary. A modification of the Newcastle-Ottawa Scale (NOS) previously published elsewhere (Borgnakke, Ylöstalo, Taylor, & Genco, 2013) was adapted for our purpose and used to evaluate the methodological quality of the included studies. Two authors (AM, WSB) independently evaluated all the included reports (Stang, 2010) and subsequently obtained mutual agreement regarding discrepancies. The three dimensions evaluated were (1) selection of study groups, (2) comparability of the study groups, and (3) outcome. Each study received a maximum of 13 points for cohort studies, 10 points for case–control studies, and seven for cross-sectional studies (Table S1). The Cohen kappa coefficient was used to assess inter-rater agreement.

3.2 | Information sources and data extraction

Electronic and manual literature searches were conducted independently by two authors (AM, WSB) in several databases, including MEDLINE (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials (Cochrane Library), Cochrane Oral Health Group Trials Register (Cochrane Library), Web of Science (Thomson Reuters), and SciVerse (Elsevier) databases for reports published up to May 2016 without language restrictions. Additionally, the "grey literature" at the New York Academy of Medicine Grey Literature Report (http://greylit.org) and the register of clinical studies hosted by the US National Institutes of Health (www.clinicaltrials.gov) were searched to further identify potential candidates for inclusion. As well, the authors conducted manual searches of periodontics- and implantology-related journal issues published in the most recent 3 years (i.e. June 2013 through May 2016), including *Journal of Dental Research*, *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Oral and Maxillofacial Implants*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *and The International Journal of Periodontics & Restorative Dentistry*. Bibliographies of identified candidates were also searched. Reports in languages other than English and Spanish were translated by native speakers of the pertinent foreign languages for inclusion/exclusion determination. The authors independently extracted predetermined data from the included reports.

3.3 | Electronic literature searching

For the PubMed library, combinations of controlled terms (MeSH and EMTREE) and keywords were used whenever possible, and other terms not indexed as MeSH and filters were also applied. The key terms used were: ((((((((((((((((("dental implants"[MeSH Terms] OR "dental implantation, endosseous"[MeSH Terms]) OR "dental implantation, endosseous, endodontic"[MeSH Terms]) OR "dental implants, single-tooth"[MeSH Terms]) OR "dental implantation, endosseous"[MeSH Terms]) OR "dental implantation, endosseous"[MeSH Terms]) OR "dental implantation, endosseous"[MeSH Terms]) AND "diabetes complications"[MeSH Terms]) OR "diabetes complications"[MeSH Terms]) OR "diabetes mellitus, type 2"[MeSH Terms]) OR "diabetes insipidus"[MeSH Terms]) OR "hemoglobin c"[MeSH Terms]) OR diabetes[Title/Abstract]) OR diabetic[Title/Abstract]) AND peri-implantitis[Title/Abstract]) OR periimplantitis[Title/Abstract]) OR (peri-implant[All Fields] AND complication[Title/Abstract])) OR (periimplant[All Fields] AND complication[Title/Abstract])) OR biologic complication[Title/Abstract] AND "humans"[MeSH Terms]. On the other side, for the EMBASE Library the key terms used were: 'diabetes'/exp OR 'diabetes' OR 'diabetes mellitus'/exp OR 'diabetes mellitus' AND ('dental implants'/exp OR 'dental implants') OR 'endosseous implants' AND ('peri-implantitis'/exp OR 'peri-implantitis') OR 'peri implantitis'/exp OR 'peri implantitis' OR 'periimplantitis'/exp OR 'periimplantitis' AND 'periimplantitis'/de AND 'human'/de AND 'article'/it. For searching the remaining electronic databases, combinations of 'diabetes' OR 'diabetes mellitus' AND 'dental implant' AND 'peri-implantitis' OR 'periimplantitis' terms limited to titles/abstracts were used.

3.4 | Eligibility criteria

In order to be potentially eligible for inclusion, study populations needed to consist of humans whose peri-implantitis or peri-implant mucositis was clinically diagnosed. Cases should be defined by hyperglycaemia and a normoglycaemic comparison group should be included in the study. The results needed to include at least one parameter related to hyperglycaemia (exposure) and report presence of peri-implant mucositis or peri-implantitis as defined by the European peri-implant disease case definitions (Sanz, Chapple, & Working Group 4 of the VIII European Workshop on Periodontology 2012) (outcomes).

Studies were eligible for inclusion in this systematic review if they met the following criteria:

- original, prospective or retrospective non-interventional (other than implant placement) cohort, case–control, or cross-sectional studies exploring the presence or progression of peri-implant diseases in humans with known glycaemic status (HbA1c or FPG; diabetes status)
- normoglycaemic (non-diabetes) comparison (control) group
- overall enrolment of ≥10 subjects
- duration ≥6 months
- ≥1 parameter reported laboratory or self-reported measure of hyperglycaemia, including taking prescribed anti-diabetic medication
- ≥1 parameter reported of clinical or radiographic assessment of peri-implant diseases
- implants should have a rough surface and be screw-shaped. This criterion would exclude studies that only reported on smooth surface implants due to their limited use in modern implant dentistry and possible different disease progression.
- any language

Studies in which the prevalence of peri-implant diseases by glycaemic level could not be clearly determined were included in the qualitative

assessment, but excluded from the quantitative analyses (meta-analyses). Corresponding authors were contacted for clarifying information about studies lacking clearly described peri-implantitis case definitions.

3.5 | Statistical analysis

The Metan package included in STATA was used to explore the influence of the presence/absence of diabetes and prevalence rates of peri-implant mucositis and peri-implantitis using odds ratios (ORs) in cross-sectional studies and risk ratios (relative risks) (RRs) in case–control and cohort studies. We used DerSimonian and Laird random effects model, with the heterogeneity estimate obtained from the inverse-variance fixed-effect model to estimate the effects of hyperglycaemia/diabetes. The random model was selected because it is more general than fixed effects models and we assumed a priori heterogeneity between studies. The I^2 statistic test was applied and calculated to quantify this heterogeneity. When data were extracted from sufficiently similar studies, they were pooled for meta-analyses.

4 | RESULTS

4.1 | Study selection

A total of 382 records were identified through the electronic search after removal of duplicates and supplemented with 19 citations from the manual search and through screening bibliographies of relevant included/excluded articles for a total of 401 citations as illustrated in Figure 1.

Upon exclusion of reports deemed ineligible based on their 401 titles and abstracts, 74 studies remained for full-text evaluation. Finally, 62 studies were excluded for not meeting the inclusion criteria (Table S2), leaving 12 studies eligible for inclusion in the qualitative analyses (Aguilar-Salvatierra et al., 2016; Al Amri & Abduljabbar, 2017; Al Amri, Abduljabbar, Al-Kheraif, Romanos, & Javed, 2017; Al Amri et al., 2016; de Araujo Nobre, Malo, & Antune, 2014; Dalago, Schuldt Filho, Rodrigues, Renvert, & Bianchini, 2017; Daubert, Weinstein, Bordin, Leroux, & Flemming, 2015; Erdogan et al., 2015; Ferreira, Silva, Cortelli, Costa, & Costa, 2006; Konstantinidis, Kotsakis, Gerdes, & Walter, 2015; Marrone, Lasserre, Bercy, & Brecx, 2013; Renvert, Aghazadeh, Hallström, & Persson, 2014) (Figure 1; Table 1).

Of the 12 studies included in the qualitative evaluation, five were prospective cohort studies, one retrospective cohort study, and six cross-sectional studies. These 12 studies comprised a total of 1,955 participants of whom 12 had pre-diabetes and 468 had manifest diabetes, whereas 1,487 did not have diabetes. The participants had a total of 2,892 implants that were assessed.

Upon further scrutiny, three prospective cohort studies were excluded from the quantitative synthesis as they were highly heterogeneous compared to the rest of the reported data as the authors reported only on successful implants and the three reports

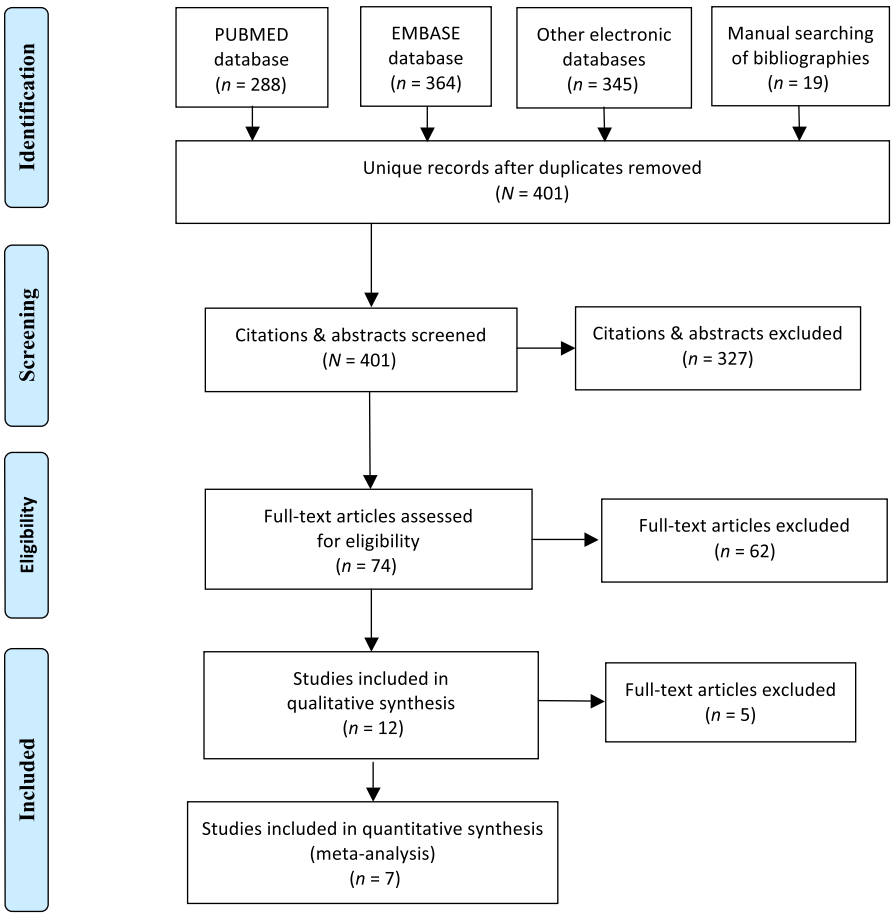

FIGURE 1 Identification and selection of eligible studies (PRISMA) (Moher et al., 2009)

also seem to represent possible data overlap (Al Amri & Abduljabbar, 2017; Al Amri et al., 2016, 2017). Consequently, of the 12 studies included in qualitative analysis, nine could be synthesized based on their OR or RR for having mucositis and/or peri-implantitis (Aguilar-Salvatierra et al., 2016; de Araujo Nobre et al., 2014; Dalago et al., 2017; Daubert et al., 2015; Erdogan et al., 2015; Ferreira et al., 2006; Konstantinidis et al., 2015; Marrone et al., 2013; Renvert et al., 2014).

Seven of these studies, namely two prospective cohort studies (Aguilar-Salvatierra et al., 2016; Erdogan et al., 2015), one retrospective cohort study (Renvert et al., 2014), and four cross-sectional studies (de Araujo Nobre et al., 2014; Dalago et al., 2017; Ferreira et al., 2006; Marrone et al., 2013), presented prevalence data that could be synthesized by meta-analyses to assess the association between hyperglycaemia/diabetes mellitus and peri-implantitis.

4.2 | Associations between hyperglycaemia/diabetes mellitus and peri-implant diseases

Heterogeneity tests from pooled data revealed statistical significance in the comparison between diabetes (DM) *versus* non-DM in the prevalence of peri-implant diseases (Chi-squared = 44.07, $p < .001$).

To explore time at risk for the implant as a potentially important factor, we used generalized estimated equation (GEE) to estimate the association between peri-implantitis prevalence and time at risk prior to conducting the main analysis. However, there was no evidence favouring such an association in the pool of data summarized (estimated coefficient = .28, $z = 1.10$, $p < .28$, 95% confidence interval (CI): −0.22 to 0.77). Therefore, time at risk was not included as a factor in the main analysis.

1. Are hyperglycaemia (diabetes) and peri-implant diseases (peri-implant mucositis or peri-implantitis) associated?

Figure 2 displays the ORs in the pooled cross-sectional studies and the RRs in the pooled case–control and cohort studies for having peri-implant mucositis and peri-implantitis, respectively.

4.2.1 | Peri-implant mucositis

Neither the OR nor the RR for having peri-implant mucositis were statistically different between the two groups (hyperglycaemic *versus* normoglycaemic) (OR = 1.06; 95% CI: 0.84–1.27 and RR = 0.92; 95% CI: 0.72–1.16, $z = 1.06$, $p = .29$).

4.2.2 | Peri-implantitis

On the contrary, both the OR and RR for peri-implantitis were statistically significantly higher in hyperglycaemia than in normoglycaemia. Upon pooling the data from the seven studies, Figure 2 illustrates the statistically significant differences between the hyperglycaemic *versus* normoglycaemic groups (RR = 1.46; 95% CI: 1.21–1.77 and OR = 1.89; 95% CI: 1.31–2.46; $z = 5.98$; $p < .001$). Interpreting the lower and upper 95% CIs limits for the OR and RR taken together, the risk of peri-implantitis in hyperglycaemia is between 1.21- and 2.46-fold statistically significantly higher than in normoglycaemia.

Figure 3 displays the RRs in each of the seven studies as well as their pooled RR of 1.46 for having peri-implantitis in hyperglycaemia compared to normoglycaemia that were included in Figure 2. That is, participants with elevated blood glucose have almost 50% (46%) higher risk of peri-implantitis compared to people with normal glucose blood levels (Figures 2 and 3).

4.3 | Importance of hyperglycaemia in peri-implantitis compared to other risk factors

1a. If yes to 1): What is the strength of the evidence for associations between hyperglycaemia and peri-implant diseases compared to other potential risk factors?

No study reported the prevalence of peri-implant diseases in hyperglycaemia *versus* otherwise healthy without the presence of other confounders (e.g. smoking, [recent] history of periodontitis, or poor plaque control). Likewise, haphazard data were found regarding the rate of peri-implantitis in hyperglycaemia compared to rates among smokers or participants with a history of periodontitis in otherwise healthy subjects. Interestingly, when comparing the prevalence and OR of peri-implantitis in smokers *versus* diabetes mellitus/hyperglycaemia, no statistical significant differences were found ($p = .16$, 95% CI = −3.32 to 6.35; and $p = .424$, 95% CI = −18.30 to 29.32) (not shown). These findings suggest that smoking poses no more risk of having peri-implantitis than diabetes mellitus/hyperglycaemia.

Three reports excluded smokers (Aguilar-Salvatierra et al., 2016; Erdogan et al., 2015; Ferreira et al., 2006). When pooled and meta-analysed, the data retrieved from these three studies, a higher statistically significant risk of peri-implantitis was calculated for individuals with hyperglycaemia (RR = 3.39, 95% CI: 1.06, 10.81), $z = 2.06$, $p < .04$) (Figure 4).

The RRs for the three studies were of similar magnitude and each was not statistically significant individually. However, when pooled, these three studies showed that participants with hyperglycaemia had a 3.39-fold higher risk of peri-implantitis than their normoglycaemic counterparts (95% CI: 1.06–10.81). These three studies comprised 247 participants with hyperglycaemia and 74 with healthy blood glucose levels who together had a total of 706 implants.

2. In participants with implants and no peri-implant diseases, do those with hyperglycaemia develop more (incident) peri-implant diseases than normoglycaemic patients over time?

There was insufficient evidence to conduct subset meta-analyses using pooled data solely extracted from longitudinal studies to answer the question whether patients with hyperglycaemia develop more (incident) peri-implant diseases than normoglycaemic patients.

TABLE 1 Characteristics of the 12 studies included in the qualitative syntheses

#	Author (Year) Country	Study design	Duration (mos)	Study Group	# Subjects M/F (n)	Age Mean (*SD*)/ [Range] (years)	# Impl (n)	Peri-implantitis case def	Metabolic control			Peri-implant dz by DM (subject-level: presence/ absence/control)	
									Classification		BL	Mucositis	
									HbA1c (%)	FPG) (mg/dl)	A1c (%)/ FPG (mg/dl)	OR (95% CI)	Prev (%)
1	Aguilar-Salvatierra et al. (2016) Spain	PC	24	NoDM	33 (18/15)	59 (2.3)	33	PD>5 mm; MBL>2 mm	≤6.0	NR	NR	NR	NR
				DM	30 (13/17)	57 (3.8)	30		6.1–8.0	NR			
				DM	22 (13/9)	61 (1.9)	22		8.1–10.0	NR			
2	Al Amri and Abduljabbar (2017) Saudi Arabia	PC	24*	NoDM	22 (22/0)	41.8 (NR)	22	BOP, pathologic MBL	NoDM (Self rep)	NR	NR	NR	NR
				DM	23 (23/0)	42.4 (NR)	45		T2DM (Self rep)	NR			
3	Al Amri et al. (2017) Saudi Arabia	PC*	24	NoDM	30	48.5 [45–52]	30	BOP, >2 mm MBL	<6.0	NR	4.5	0	0
				DM	30	50.1 (46–55)	30		6.1–8.0	NR	6.80	0	0
				DM	31	50.5 (45–59)	31		8.1–10.0	NR	8.7	NR	0
4	Al Amri et al. (2017) Saudi Arabia	PC*	12	NoDM	12 (12/0)	43.4 (NR)	12	BOP, >2 mm MBL	4–5.5%	NR	4.40%	NR	NR
				PreDM	12 (12/0)	44.5 (NR)	12		5.7–6.4%	NR	6.10%	NR	NR
5	Dalago et al. (2017) Brazil	CS	60	NoDM	167*	59.3 (NR)	830	PD>5 mm or (BOP & MBL ≥2 mm)	<6.5	<126	NR	NR	NR
				DM	16*		86		≥6.5	≥126			
6	Daubert et al. (2015) USA	CS	132	NoDM	88*	67.6 (10.6)	225	PD>4 mm & BOP & MBL>2 mm	NoDM (self-rep)	NR	NR	NR	NR
				DM	8*				DM** (self-report)	NR			
7	de Araujo Nobre et al. (2014) Portugal	CS	96	NoDM	569*	55.8 (10.2)	NR	PD≥5 mm & BOP & MBL≥2 mm	NR	NR	NR	NR	NR
				DM	67*		NR		NR	NR			
8	Erdogan et al. (2015) Turkey	PC	12	NoDM	12 (7/5)	49.5 (9.3)	21	≥2 mm MBL	NR	NR	NR	NR	NR
				DM	12 (5/7)	52.6 (7.3)	22		6.0–7.5*	NR	6.7 (0.3)/ 126 (22.8)		
9	Ferreira et al. (2006) Brazil	CS	33 (6–60)	NoDM	29 (NR)	NR*	578	PD>5 mm & BOP/ sup&BL & MBL>2 mm	<6.5**	<126**	NR	1	65.6
				DM	183 (NR)				≥6.5**	≥126**		1.2 (1.0–1.8)	58.6
10	Konstantinidis et al. (2015) Germany	CS	66 (12–198)	NoDM	170*	63 (21–91)	597 (316 ≥ 5 years)	PD>5 mm & BOP & MBL>2 mm	NR	NR	NR	1	64.4
				DM	16*				MedHx	NR	All <7.0%	1.0 (0.8–1.3)	
11	Marrone et al. (2013) Belgium	CS	102	NoDM	96*	62 (13.4)	266	>5 mm PD, BOP, 2 mm MBL	<6.5	<126	NR	NR	NR
				DM	7*				≥6.5	≥126			
12	Renvert et al. (2014) Sweden	RC	≥60*	NoDM	259 (NR)**	59.7 (NR)	NR	PD≥4 mm & BOP & MBL>2 mm[(a)]	NR	NR	NR	NR	NR
				DM	11 (NR)**		NR		NR	NR		NR	NR

@, at; A1c, HbA1c, glycated haemoglobin; BL, baseline; btw, between; CI, confidence interval; comorbid, comorbidity, comorbidities; CS, cross-sectional; CVD, cardiovascular disease; diff, difference; def, definition; DM, diabetes mellitus; dz, disease; excl, excluded; FM, full-mouth; FPG, fasting plasma glucose; FU, follow-up; Hx perio dz, history of periodontal disease; impl, implant(s);MBL, marginal bone loss; mos, months or monthly; NR, not reported; OR, odds ratio; PC, prospective cohort; PD, probing depth; PI, peri-implant/peri-implantitis; Prev, prevalence; Pts, Patients; RC, retrospective cohort; stat, statistical/ statistically; subj, subject; Self rep, Self-reported; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; tx, treatment; w/, with.

[a]Peri-implant diseases case definition suggested by the VIII European Workshop in Periodontology (Sanz & Chapple, 2012).

Peri-implantitis		Peri-implantitis confounders						Overall peri-implantitis prevalence (%)		
		Smoking		Hx perio dz		Poor plaque control				
OR (95% CI)	Prev (%)	OR (95% CI)	Prev (%)	OR (95% CI)	Prev (%)	OR (95% CI)	Prev (%)	Subj.-level	Impl level	Comments
NR	0 3.4* 12.7*	Smokers excl	Smokers excl	NR	NR	Pts w/poor plaque control excl	Pts w/poor plaque control excl	16.1*	16.1*	* Failure @24 months due to peri-implant dz - 1-piece impl; immediate placement - Maxilla incisors-1st premolar - Impl feasible for A1c <8.0%; - A1c increased with time - # drop-out unknown: results only for those w/all visits & no DM complications
NR	0 0	Smokers excl	Smokers excl	NR	NR	NR	NR	0	0	* Possible data overlap with Al Amri et al. (2017, 2016) - Platform-switched impl; mandible only - Young age (~40 years); T2DM short duration (~14 months); BL A1c = 6.9%(T2DM, all<8%)/ 4.4% (noDM), no diff@124 months (all~5%)
0 0 0	0 0 0	Smokers excl	Smokers excl	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	*States to be "case–control" study - <30% had plaque; <5% had PPD ≥ 4 mm - HbA1c not statistically diff btw study arms @ 6 months (4.4/5.8%) & 12 months (4.2/5.5%)
0 0	0 0	Smokers excl	Smokers excl	0 0	0 0	0 0	0 0	0 0	0 0	* States to be "case–control" study - A1c not stat. diff btw study arms at 6 months (4.4/5.8%) & 12 months (4.2/5.5%) - <30% had plaque; <5% had—PPD ≥ 4 mm
NR	17.4 6.2	NR	19	2.2 (1.2–4.1)	18.2	NR	NR	16.4	7.3	*N = 183 (69 M/114 F) - PI risks: Hx perio dz, cemented prostheses, wear facets, FM rehabilitation, not smoking
1 3.0 (1.2–7.7)**	NR	1.5 (0.5–4.0)**	NR	2.1–3.0**(†)	NR	NR	NR	26	16	*48 M/48 F; **Risk ratio (RR) †Periodontal condition: mild/severe - DM type NR; No exclusion criteria - Impl placed by periodontics residents - PI risks: DM & young age at BL, perio dz @FU, greater impl diameter
NR	8.8 13.9	2.0 (1.5–2.7)**	NR	25.1 (17.8–35.3)**	NR	NR	NR	NR	NR	* N@BL = 1,350 (270 cases w/comorbid + 1,080 controls): 38.3% M/62.7% F ** Peri-impl pathology w/bone loss - PI risks: Hx perio dz, smoking, not comorbid
NR	0 8.3**	Smokers excl	Smokers excl	NR	NR	NR	NR	4.2**	2.3**	* Inclusion criterion **1 impl, all other impl and mean MBL <2 mm - Impl tx feasible in ctrl DM (A1c<7.5%)
1 1.9 (1.0–2.2)***	6.6 24.1	Smokers excl	Smokers excl	3.1 (1.1–3.5)	26.7	3.8 (2.1–6.8)	8.1	8.9	7.4	*33.0% ≤45 years ** As per chart at time of impl surgery in the past *** "Uncontrolled" (undefined) DM - Similar data used for Costa et al. (2012)
NR	NR	NR	NR	1.1 (0.8–1.1)	20.4	NR	NR	12.9 (13.3 ≥ 5 years)	6.2 (6.2 ≥ 5 years)	* 74 M/112 F ** N = 22 smokers (11.8%, 14 former smokers (7.5%), 150 (80.6%) non-smokers - PI risks: Hx perio dz, maxilla (but not DM)
1 0.9 (0.1–5.3)	36.5 42.9	NR 1 (0.3–3.1)	30	0.8 (0.3–2.3)	39.3	0.72 (0.3–1.6)	47.1	37	23	* 38 M 65 F; 60% developed PI long term -PI risks: age, Hx perio dz, tooth loss, rough impl surface
1 6.1 (0.8–48.1)	62.5 90.9	2.5 (1.4–4.2)	70.0***	4.5 (2.1–9.7)	69.2	NR	NR	63.7	NR	-3 centers * Overall: 11.8 years (PI); 7.0 years (mucositis/health) ** Overall: 109 M/161 F [118/172 = 68.8%, F(PI); 43/98 = 43.9% F (mucositis/health)] *** Current or past smoking; - PI risks: CVD,, Hx perio dz;

3. Is the prevalence of peri-implant diseases (peri-implant mucositis or peri-implantitis) in participants associated with degree of hyperglycaemia?

Currently, there is a gap of knowledge to answer this question.

4.4 | Quality assessment using the Newcastle-Ottawa Scale (NOS)

All 12 studies were assessed by the modified and adapted Newcastle–Ottawa Scale (NOS). The mean NOS score was 3.6 (±1.6) for mucositis and 5.0 (±1.9) for peri-implantitis. Interestingly, for both mucositis and peri-implantitis, the domain "Selection" was the highest ranked, while "Outcome" was the lowest (Table S3).

5 | DISCUSSION AND CONCLUSION

Since this is the first systematic review and meta-analysis of its kind, to the best of our knowledge, there is no prior review to which our findings can be directly compared. However, some comparable information regarding these topics is provided by other reports (Chrcanovic et al., 2014; Javed & Romanos, 2009). The role of hyperglycaemia in the pathogenesis of periodontal diseases has been described by several authors (Borgnakke, 2016b; Chang, Chien, Chong et al., 2013; Chang, Chien, Yeo et al., 2013; Genco & Borgnakke, 2013; Hasturk & Kantarci, 2015; Lalla & Papapanou, 2011; Cianciola et al., 1982).

Similar mechanisms are activated in peri-implant tissues and thus increase the susceptibility for peri-implantitis (Salvi et al., 2010). Nonetheless, little is known about the links between hyperglycaemia and its clinical implication of biologic complications related to dental implants. Two systematic reviews have demonstrated the feasibility of providing implant therapy to patients with diabetes (Chrcanovic et al., 2014; Javed & Romanos, 2009). Based on seven controlled clinical trials, Chrcanovic and colleagues reported in their meta-analysis a statistically significant difference between participants with and without diabetes, favouring the latter with regard to peri-implant marginal bone loss (Chrcanovic et al., 2014).

One of the main challenges in conducting a systematic review like the current is the lack of globally accepted and applied case definitions for peri-implantitis (Sanz, Chapple, & Working Group 4 of the VIII European Workshop on Periodontology 2012), which leads to low homogeneity detected among the studies. Consequently, three studies from the same research group were ultimately excluded from the quantitative analysis due to high heterogeneity ($p < .01$) (Al Amri & Abduljabbar, 2017; Al Amri et al., 2016, 2017). Interestingly, these three studies reported exceedingly low peri-implantitis rates in both patients with (0%) and without diabetes (0%). In contrast, Ferreira et al. showed that individuals with uncontrolled diabetes measured at the last glycaemic checkup presented a peri-implantitis rate of 26.6%, compared to only 6% in healthy controls. Not surprisingly, most of the peri-implantitis cases were further associated with poor oral hygiene and periodontitis (Ferreira et al., 2006). These findings are in accord

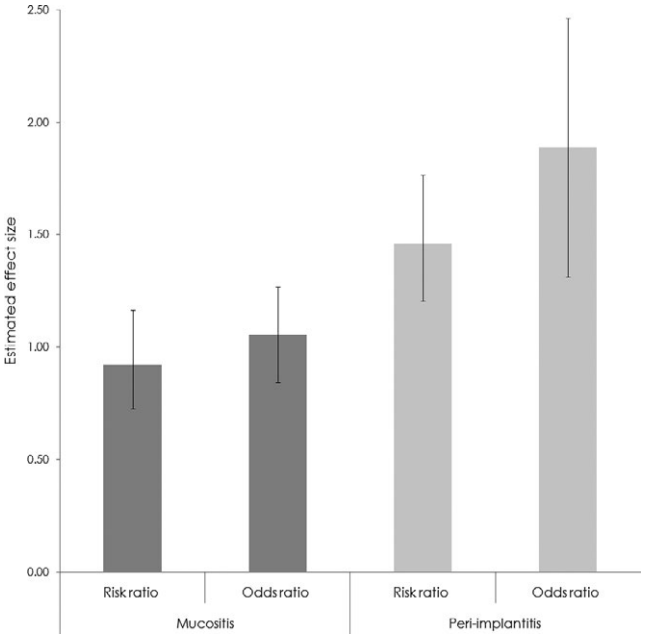

FIGURE 2 Risk of peri-mucositis and peri-implantitis, respectively, in hyperglycaemia/diabetes mellitus compared to normoglycaemia. OR = odds ratio; RR = relative risk ratio

with ours. In further agreement, recent findings from a study involving 96 patients with 225 implants demonstrated in a cross-sectional study 11 years post-implant placement a threefold risk (RR = 3.0; 95% CI: 1.2–7.7) for having peri-implantitis in subjects who had diabetes at the time of implant placement compared to diabetes-free participants (Daubert et al., 2015). Additionally, our results based on this limited evidence seem to suggest that the higher the glycaemic level (i.e. poor glycaemic control such as HbA1c >8%) at baseline, the greater is the prevalence of peri-implant mucositis and peri-implantitis. Similarly, Aguilar-Salvatierra and colleagues reported such findings in an investigation in which bias was reduced by excluding smokers and individuals with poor plaque control. The researchers showed a dose–response relationship between HbA1c level at baseline and peri-implantitis rate 2 years after implant placement (Aguilar-Salvatierra et al., 2016).

The three studies among non-smokers exclusively (Figure 4) report consistent results as they all find participants with hyperglycaemia to have about three times greater risk of peri-implantitis compared to normal glucose levels, despite their different numbers of participants. As far as we know, this is the first attempt to synthesize the evidence for risk for having peri-implantitis in non-smokers specifically. Its finding is important as it demonstrates that the risk for peri-implantitis indeed is elevated in hyperglycaemia without any potential synergistic effect of smoking.

In conclusion, when discussing treatment options with patients with hyperglycaemia/diabetes and planning therapy that could include restoration with dental implants, it seems reasonable to recommend taking into careful consideration the heightened risk of development of peri-implantitis with increasing glycated haemoglobin level. The patient should be made aware that a strict home oral hygiene regimen complemented with professional maintenance visits is likely to be required for long-term implant retention and success (Monje et al.,

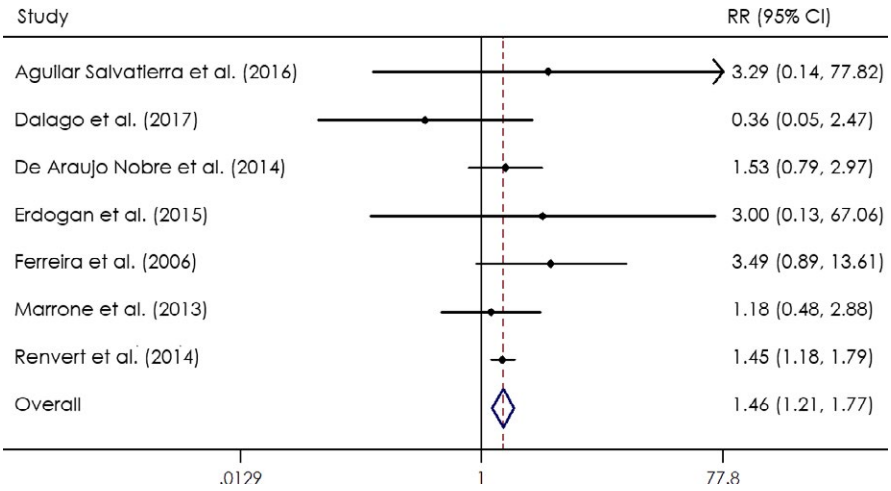

FIGURE 3 Risk of having peri-implantitis in hyperglycaemia/diabetes mellitus compared to normoglycaemia (seven studies). OR = odds ratio; RR = relative risk ratio

2016). Given the suggested dose–response relationship between blood glucose level and implant complications, patients with (pre-)diabetes should not only be advised regarding the importance of attaining and maintaining good glycaemic control both for general health, but also for the sake of preventing implant failure. Furthermore, due to the high rate of undiagnosed (pre-)diabetes that leaves the patient unaware of his or her hyperglycaemia, it would also be prudent to be prepared to offer the patient chairside assessment that could be done by collecting blood samples and sending them to a laboratory on a weekly basis for measurement of the HbA1c from a dry blood spot (Teeuw, Kosho, Poland, Gerdes, & Loos, 2017).

5.1 | Do our findings make biologic sense? Mechanisms underlying the findings

Hyperglycaemia that results from impairment of insulin secretion, action, or both, has been demonstrated to have a negative impact on periodontal tissue stability (Borgnakke et al., 2013; Chapple, Genco & Working group 2 of joint EFP/AAP Workshop 2013; Genco & Borgnakke, 2013; Lalla & Papapanou, 2011). The mechanism/connection could be briefly explained understanding the chronic inflammatory condition stimulated by dental plaque biofilm, but mediated by the host as in periodontitis (Bartold & Van Dyke, 2013; Loos, 2005). Similarly, peri-implantitis, which is also regarded a plaque-initiated, destructive entity susceptible to modifiable and non-modifiable systemic and local factors (Berglundh, Zitzmann, & Donati, 2011; Lang & Berglundh, 2011; Lang, Bosshardt, & Lulic, 2011), presents with matrix degradation and bone turnover (Carcuac & Berglundh, 2014; Wang et al., 2016). Similarly, peri-implantitis should be sensitive to every known major factor that induces tissue inflammation [e.g., smoking, poor plaque control, or hyperglycaemia (Chang, Chien, Chong et al., 2013; Chang, Chien, Yeo et al., 2013) and thereby is regarded a risk factor for periodontitis (Borgnakke, 2016a, 2016b; Genco & Borgnakke, 2013).

As aforementioned, the present systematic review is the first to explore associations between hyperglycaemia/diabetes mellitus and peri-implant diseases. Of special importance is the inclusion of studies that include participants with poor glycaemic control (>7.0% HbA1c). In previous reports, it has been demonstrated that diabetes per se (regardless of the degree of glycaemic control) does not represent a stringent contraindication for implant therapy. Another especially important finding is that the elevated risks for peri-implantitis exists in non-smokers exclusively, as any potentially confounding, synergistic effect of smoking is excluded, separating out the hyperglycaemia independently of smoking.

Nonetheless, our findings seem to suggest that elevated glycaemic levels are associated with greater prevalence of peri-implantitis, which should be taken into account both during treatment planning and during the necessary maintenance throughout the lifetime of the implants in order to prevent development peri-implantitis. Within the limits of this review, it suggests that hyperglycaemia could be as

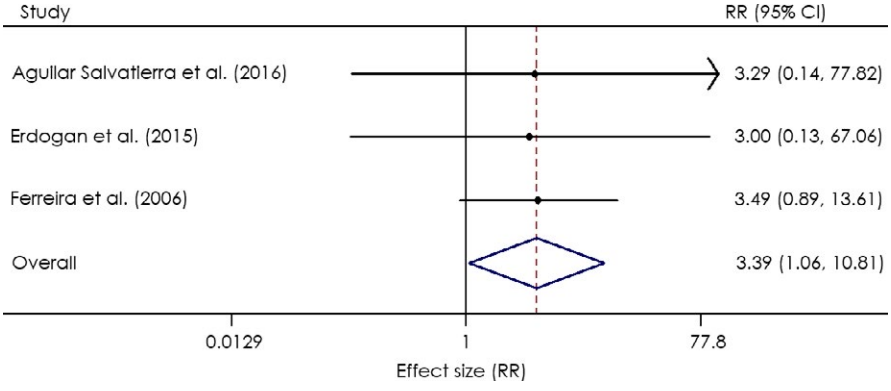

FIGURE 4 Risk of having peri-implantitis in hyperglycaemia/diabetes mellitus compared to normoglycaemia among non-smokers only (three studies). RR = relative risk ratio

strongly associated with peri-implantitis as smoking, the most important risk factor for peri-implantitis.

6 | LIMITATIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Caution must be exerted when interpreting these results, although the authors attempted to minimize the risk of bias through applying stringent inclusion criteria.

Only three included studies included in the quantitative assessment excluded smokers and therefore, in the remaining three studies, smoking may have confounded the impact of hyperglycaemia.

Even though smoking was reported in five studies (de Araujo Nobre et al., 2014; Dalago et al., 2017; Daubert et al., 2015; Marrone et al., 2013; Renvert et al., 2014), none of them reported the impact of smoking on the prevalence of peri-implant diseases in participants with diabetes mellitus. Therefore, although the confounder smoking was not found to be significantly influential when compared to diabetes mellitus/hyperglycaemia ($p = .16$, 95% CI = −3.32, 6.35), it could not be accurately assessed whether smoking has a synergistic detrimental effect with hyperglycaemia. Furthermore, while 11% of the studies exclusively included subjects exhibiting adequate plaque control, the remaining 89% did not report any oral hygiene parameters and hence probably included subjects with poor plaque control, which confounder might have affected our results.

The lack of globally accepted, standard definitions of peri-implant diseases prevents the direct comparison and potential synthesis of study results. Therefore, we selected one case definition that is increasingly becoming the norm as an inclusion criterion to greatly decrease the bias inherent in using different case definitions. In the current review, all studies in which the exact case definitions used could not be ascertained even after contacting the corresponding authors—or which did not adhere to the definition proposed by the VIII European Workshop in Periodontology (Sanz, Chapple, & Working Group 4 of the VIII European Workshop on Periodontology 2012)—were excluded.

Another issue to keep in consideration to adequately interpret our findings is the weight of certain studies. For instance, one study represents 68% of the weight in investigating the overall prevalence (Renvert et al., 2014). Last, but not least, a major challenge detected at pooling the data for statistical analysis was the lack of homogeneity in reporting the glycaemic control level at baseline along with the subtype of hyperglycaemia (pre-diabetes, manifest type 1 or type 2 diabetes). As a matter of fact, more than half (55%) the reports evaluated did either not define the hyperglycaemic condition by means of glycaemic level or accepted patient self-report as the source for the diagnosis of diabetes. Self-reported diabetes grossly underestimates the actual presence of hyperglycaemia due to the mentioned unawareness among more than one-quarter of people with manifest diabetes and up to 90% of pre-diabetes cases (CDC, 2014, 2015). Naturally, it is not possible to estimate the actual HbA1c levels in those individuals, and participants may have been misclassified as not having diabetes in the presence of (pre-) diabetes. Nonetheless, such misclassification would strengthen our results as we still report significant findings, even with some hyperglycaemia cases potentially being included in the normoglycaemic group.

Importantly, the goal of a systematic review is not only to qualitatively synthesize the scientific evidence, but also to map or scope out the existing pertinent literature (Grant & Booth, 2009). This is undertaken in order to characterize the quantity and quality of available information and based on this new knowledge to provide recommendations for future investigations as bias-free as possible. Accordingly, investigators are encouraged to examine the effect of hyperglycaemia as an independent risk factor for the development, progression, and severity of peri-implant diseases compared to completely healthy, normoglycaemic subjects to validate or refute our findings. Researchers should include study participants with different levels of blood glucose concentrations throughout the entire spectrum from normoglycaemic health via pre-diabetes through well-controlled to uncontrolled manifest diabetes.

In order to examine the effect in the opposite direction in this probable, two-way relationship, research is also needed to explore the effect of placement of dental implants and of peri-implant diseases on the blood glucose levels. Hence, it is necessary to assess the glycaemic control both prior to and upon implant placement, followed by periodic monitoring during a longitudinal study to detect any changes in blood glucose levels in conjunction with both implant placement and development of peri-implant mucositis or peri-implantitis. Finally, evidence is missing in the literature for any effect on blood glycaemic level of peri-implantitis treatment.

7 | CONCLUSION

Within the limitations of this systematic review, the following conclusions can cautiously be drawn:

1. The current evidence suggests the risk of *peri-implantitis* is greater in people with hyperglycaemia (pre-diabetes, diabetes mellitus) compared to those with normal blood glucose levels.
2. Hyperglyacemia in non-smokers is associated with a more than threefold higher risk of *peri-implantitis*, which demonstrates that smoking is not needed to enhance the effect of hyperglycaemia.
3. Hyperglycaemia is not significantly differently associated with *peri-implantitis* compared to smoking.
4. The association between hyperglycaemia and *peri-implant mucositis* did not reach statistical significance
5. None of the included studies explored the relative importance of hyperglycaemia compared to other potential risk factors for *peri-implant diseases*.
6. Scant evidence proposes that baseline poorer glycaemic control is associated with greater incidence (development) of new *peri-implant diseases*, possibly in a dose–response relationship.
7. The potentially higher risk for *peri-implant diseases* in hyperglycaemia should be taken into account when considering implant therapy in patients with diabetes mellitus, especially the elevated risk for *peri-implantitis*

Future studies should be of longitudinal design; apply globally accepted, standard case definitions for peri-implant diseases; and monitor blood glucose levels prior to and throughout the study to provide more homogeneous, quantitative data that would allow proper comparisons between studies.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest with this study.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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