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Diabetes mellitus como fator de risco para peri-implantite: revisão sistemática e meta-análise

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RESUMO

Diabetes Mellitus (DM) é uma doença altamente prevalente em todo o mundo. Alguns estudos indicaram que indivíduos com DM são mais propensos a sofrer falha do implante do que indivíduos sem DM. No entanto, não há consenso na literatura se o DM atualmente pode ser considerado um fator de risco para peri-implantite. Portanto, o objetivo deste estudo foi realizar uma revisão sistemática e meta-análise da literatura para verificar se os implantes instalados em indivíduos com DM têm maior probabilidade de desenvolver peri-implantite do que em indivíduos não-DM. Foi realizada uma pesquisa nos bancos de *dados Pubmed, Cochrane, Lilacs* e *Web of Science*. A busca resultou em 207 artigos, dos quais 4 estudos observacionais foram selecionados. Dados relacionados ao número de implantes, número de participantes e prevalência de indivíduos com DM e não-DM com peri-implantite foram extraídos e tabulados. Quatro estudos eram qualificados para meta-análise (software R). A análise quantitativa dos dados revelou que os pacientes com DM apresentaram 1,222 mais chances de desenvolver peri-implantite do que os não-DM, sem, no entanto, mostrar significância estatística (IC 95%: 0,769-1,979; p> 0,05). Todos os estudos da metanálise usaram os mesmos critérios de definição da peri-implantite e todos os pacientes participaram da terapia de suporte peri-implantar. Foram identificadas deficiências, como composição da amostra e falta de definições de casos aceitas para DM e peri-implantite. A análise da qualidade mostrou que os trabalhos selecionados apresentaram baixo risco de viés. As evidências geradas por essa revisão sistemática e metanálise demonstraram que pacientes com DM reabilitados por implante submetidos a SPIT não apresentam chances significativamente maiores de desenvolver peri-implantite quando comparados a indivíduos não-DM. Estudos futuros com desenhos metodológicos mais rigorosos são necessários para verificar se essa diferença realmente existe.

Palavras-chave: Indicador de risco; Diabetes Mellitus; Peri-implantite.

ABSTRACT

Diabetes Mellitus (DM) is a highly prevalent disease worldwide. Some studies have indicated that DM individuals are more likely to suffer from implant failure than non-DM individuals. However, there is no consensus in the literature whether DM can currently be considered a risk factor for peri-implantitis. Therefore, the objective of this study was to conduct a systematic review and meta-analysis of the literature to ascertain whether implants installed in DM individuals are more likely to develop peri-implantitis than in non-DM individuals. A search on Pubmed, Cochrane, Lilacs and Web of Science databases was conducted. The search yielded 207 articles, from which 4 observational studies were selected. Data related to the number of implants, number of participants, and prevalence of DM and non-DM individuals with peri-implantitis were extracted and tabulated. Four studies qualified for meta-analysis (R software). Quantitative data analysis revealed that DM patients were 1.223 more likely to develop peri-implantitis than non-DM patients, without, however, showing statistical significance (95% CI: 0.769-1.979; $p>0.05$). All the studies in the meta-analysis used the same peri-implantitis definition criteria and all patients participated in supportive peri-implant therapy. Shortcomings such as sample composition, and lack of accepted case definitions for both DM and peri-implantitis were identified. Quality analysis showed that selected papers presented low risk of bias. The evidence generated by this systematic review and meta-analysis demonstrated that implant-rehabilitated DM patients undergoing **SPIT** do not have significantly higher chances of developing peri-implantitis when compared to non-DM subjects. Future studies with stricter methodological designs are required to ascertain if such a difference actually exists.

Keywords: Risk Indicator; *Diabetes mellitus*; Peri-implantitis

LISTA DE ABREVIATURAS E SIGLAS

PI	Peri-implantite
DM	*Diabetes mellitus*
DMT2	*Diabetes mellitus* tipo 2
DMT1	*Diabetes mellitus* tipo 1
AGEs	Produtos finais de glicação avançada
RAGEs	Receptores para produtos finais de glicação avançada
PROSPERO	International Prospective Register of Systematic Reviews
PRISMA	Diretrizes Sobre Comunicação Transparente de Revisões Sistemáticas e Meta-análise
MeSh	Medical Subject Headings
PEO	P = população, E = exposição, O = medidas de resultado
OR	Odds ratio
IC	Intervalo de confiança
PS	Profundidade de sondagem
PO	Perda óssea
SS	Sangramento à sondagem
SUP	Supuração
SPIT	Terapia peri-implantar de suporte
NOS	Escala Newcastle-Ottawa
C*	Diabético controlado
U*:	Diabético não-controlado
N:	Número
NR:	Dados não relatados pelo autor.

SUMÁRIO

CAPITULO 1 - REVISÃO DE LITERATURA

1.1. Implantes dentários: Taxa de sobrevivência e taxa de sucesso

A terapia reabilitadora com implantes dentários é documentada com elevadas taxas de sobrevivência que variam de 90,2 a 98,8% dependendo o local de instalação do implante e do tempo de acompanhamento (BUSER et al., 1999; LEKHOLM, et al., 1999; JEMT, JOHANSSON, 2006; KAROUSSIS et al., 2003; BUSER et al., 2012). Desta maneira, implantes podem permanecer em boca por um longo período de tempo e suportar variados tipos de próteses dentárias, promovendo melhoras na estética e função mastigatória dos pacientes (RENVERT et al., 2018).

Por outro lado, as taxas de sucesso variam de acordo com o critério adotado (ADELL ,1983; QUIRYNEN et al., 1992; KAROUSSIS et al., 2003; BUSER et al., 2012). Segundo um estudo de coorte prospectivo de 10 anos, que analisou as taxas de sucesso de implantes dentários em pacientes com e sem histórico de periodontite crônica, a taxa de sucesso foi de 52,4% em indivíduos com histórico de periodontite e 79,1% em indivíduos sem histórico de periodontite (KAROUSSIS et al.,2003). Nesse estudo, sucesso foi considerado como ausência de mobilidade do implante, ausência de queixas (dor e sensação de corpo estranho), profundidade de sondagem (PS) menor que 5 mm, ausência de radiolucidez contínua ao redor do implante e perda óssea anual vertical menor que 0,2 mm. No entanto, quando o critério de sucesso foi considerado apenas como PS ≤ 6mm e sangramento, esta taxa chegou a 81% e 96,7% para o grupo com e sem histórico de periodontite, respectivamente (KAROUSSIS et al., 2003).

Desta maneira, deve-se notar que, os critérios de sucesso são mais abrangentes, indo além da mera permanência na boca (ESPOSITO, GRUSOVIN e WORTHINGTON, 2012) como seria o caso do conceito de sobrevivência. O sucesso em longo prazo não é o mesmo, ou é tão alto quanto a sua sobrevivência, pois os implantes e suas restaurações podem estar sujeitos a complicações mecânicas e biológicas.

1.2. Doenças peri-implantares e fatores de risco

As complicações biológicas tardias associadas aos implantes dentários são condições inflamatórias nos tecidos circundantes. De acordo com Renvert et al. (2018), estas condições, denominadas mucosite e peri-implantite, devem ser bem definidas e diferenciadas para que o clínico possa atribuir um diagnóstico e selecione uma modalidade de tratamento adequada nos casos em que a doença está presente.

Enquanto na mucosite é observada a presença de sangramento em linha ou gota após a sondagem e ausência de perda óssea além da remodelação inicial (RENVERT et al., 2018), na peri-implantite, observa-se além de uma inflamação no tecido mole peri-implantar e a presença de perda óssea progressiva (ALBREKTSSON, ISIDOR, 1994; LINDHE, MEYLE, 2008; LANG, BERGLUNDH, 2011; SANZ, CHAPPLE, 2012; SCHWARZ, et al., 2018).

As condições histopatológicas e clínicas que levam à conversão da mucosite peri-implantar para peri-implantite não são completamente compreendidas (MOMBELLI et al., 2011). A peri-implantite caracteriza-se por um processo inflamatório modulado pelo hospedeiro que pode ser mais ou menos susceptível (LAINE et al., 2006), sendo o biofilme um fator de risco para a doença (FERREIRA et al., 2006; SCHWARZ et al., 2018) uma vez que a remoção do mesmo resulta em melhora do quadro (HEITZ-MAYFIELD e MOMBELLI, 2014). Portanto, interferir na formação de biofilme durante todas as fases do tratamento, desde a colocação do implante até a manutenção (DALAGO et al., 2019) é considerada uma medida universal de prevenção (MOMBELLI, 2011).

Devido a sua alta prevalência (MARRONE et al., 2013; DERKS et al., 2015; MATARAZZO et al., 2018) e ausência de um tratamento previsível, (HEITZ-MAYFIELD, MOMBELLI, 2014), o reconhecimento dos fatores de risco para a doença é essencial para o prognóstico do implante e para fornecer intervenção preventiva individualizada contra a peri-implantite (JEPSEN et al., 2015; TONETTI et al., 2015; CANULLO et al., 2016; DALAGO et al., 2017).

Fortes evidências indicam que existe um risco aumentado de desenvolvimento de peri-implantite em pacientes com histórico de periodontite (KAROUSSIS et al., 2003) , fracas habilidades de controle de placa (FERREIRA et al., 2006) e nenhum cuidado de manutenção regular após a terapia com

implantes (COSTA et al., 2012). Outros fatores os quais o indivíduo pode estar sujeito têm sido questionados como aumento da possibilidade do aparecimento da peri-implantite (SCHWARZ et al., 2018). Fatores genéticos, presença de mucosa queratinizada, fatores iatrogênicos, partículas de titânio, excesso de cimento, condições sistêmicas e uso de mediamentos, fumo e diabetes necessitam de mais estudos para serem considerados riscos para a peri-implantite (SCHWARZ et al., 2018) .

1.3. Diabetes e implantes dentários

As estatísticas globais de *diabetes mellitus* demonstraram que 135 milhões de pessoas apresentavam a doença em 1995, 240 milhões em 2005 (FERREIRA, PITITTO, 2019) e que no ano de 2013 cerca de 382 milhões foram diagnosticados com esta doença em todo o mundo, sendo o diabetes tipo 2 o mais representativo, com 90% dos casos (SHI, HU, 2014). Isso equivale a 8,3% da população adulta com taxas iguais em mulheres e homens (TAO, SHI, ZHAO, 2015). Em 2012 e 2013, o diabetes resultou em mortalidade de 1,5 a 5,1 milhões de pessoas por ano, tornando-se a 8ª causa de morte no mundo (SHI, HU, 2014). Prevê-se que no ano de 2035, cerca de 592 milhões de pessoas morrerão de diabetes (TAO, SHI, ZHAO, 2015). Essas tendências destacam a urgência de uma melhor compreensão do diabetes, bem como de melhorar o atendimento de pacientes com diabetes (FERREIRA, PITITTO, 2019).

As complicações da doença estão relacionadas principalmente ao tempo de exposição à hiperglicemia; Entre as principais são encontradas doenças cardiovasculares, macroangiopatia, retinopatia, nefropatia e neuropatias as quais podem ser muito debilitantes ao indivíduo e onerosas ao sistema de saúde pública (FERREIRA, PITITTO, 2019).

Cada vez mais perguntas sobre a reação do indivíduo diabético após a instalação de implantes em comparação aos não-diabéticos têm surgido e têm sido reforçadas por estudos que mostram diferenças entre grupos de indivíduos diabéticos e não-diabéticos. Alguns estudos apontam que indivíduos diabéticos apresentam quase três vezes mais chances de desenvolver falha do implante quando comparados aos indivíduos saudáveis, sendo o diabetes um fator de

influência para o insucesso de implantes (MOY, MEDINA, SHETTY, 2005; ZUPNIK et al., 2011).

Siqueira et al. (2003) e de Morais et al. (2009) realizaram estudos em animais hiperglicêmicos e detectaram uma piora na osseointegração comparados a animais normoglicêmicos (SIQUEIRA et al., 2003; de MORAIS et al., 2009;). Javed e Romanos (2009), em uma revisão sistemática, observaram que o diabetes mal controlado afeta negativamente a osseointegração fazendo com que esta leve mais tempo para acontecer, entretanto, sob controle glicêmico sérico ideal, a osseointegração pode ocorrer de maneira semelhante a indivíduos sem diabetes (JAVED, ROMANOS, 2009). De acordo com Naujokat, Kunzendorf e Wiltfang, 2016, quando o diabetes está sob controle, os procedimentos de implante são seguros e previsíveis, com uma taxa de complicações semelhante à de pacientes saudáveis.

Dowell, Oates e Robinson, 2007, não encontraram nenhuma evidência de menor sucesso para implantes em pacientes não diabéticos ou diabéticos bem controlados, em comparação aos diabéticos descontrolados. Sendo assim, para Michaeli, Weinberg e Nahlieli, 2009, o diabetes é uma contra-indicação relativa para a instalação dos implantes. Os resultados ainda são controversos e as verdadeiras diferenças nos efeitos metabólicos entre o diabetes tipo 1 e tipo 2 ainda permanecem obscuras (DREYER et al., 2018).

Cabe ao cirurgião instruir os pacientes sobre os cuidados e realizar a verificação dos níveis glicêmicos de seu paciente periodicamente, além das precauções necessárias ao longo de todo o tratamento odontológico (TAYLOR, 2001; TAWIL, OD, YOUNAN, 2007).

1.4. Diabetes e peri-implantite

Estudos mostram que indivíduos diabéticos apresentam mais perda óssea marginal (TAWIL, OD; YOUNAN, 2007; CHRCANOVIC, ALBREKTSSON, WENNERBERG, 2014; GÓMEZ-MORENO et al., 2015; TURRI et al., 2016; AL-SOWYGH et al., 2018, AL ZAHRANI et al., 2018) e maior profundidade de sondagem ao redor de implantes (TURRI et al., 2016, AGUILAR-SALVATIERRA et al., 2018). No entanto, o aumento da prevalência da peri-implantite entre indivíduos diabéticos ainda é controversa.

Ferreira et al. (2006) realizaram um estudo transversal com 212 pacientes e detectaram que o diabetes apresentou relação significativa no aumento do risco de desenvolvimento de peri-implantite em implantes instalados em pacientes diabéticos, quando comparados à indivíduos não-diabéticos (FERREIRA et al., 2006). Outros estudos, porém, não encontraram relação significativa entre diabetes e peri-implantite (DVORAK et al., 2011; MARRONE et al., 2013; RENVERT et al., 2014; ROKN et al., 2017) . Daubert et al. (2015) observaram entre mulheres com osteoporose, que pacientes diabéticas apresentaram uma maior chance de desenvolver peri-implantite e maior perda de implantes quando comparadas às pacientes não-diabéticas, porém, sem diferença estatisticamente significante entre os grupos (DAUBERT et al., 2015). Dalago et al. (2016) encontraram relação significativa entre diabetes e peri-implantite na análise univariada, mas ao realizar uma análise multivariada não foi encontrada a mesma relação.

No esforço desta investigação, Turri et al. (2016) com o objetivo de verificar se a diversidade de condições médicas sistêmicas e tabagismo atuam como agentes biológicos associados à peri-implantite, relataram que tabagismo e diabetes são fatores biológicos associados à peri-implantite. Dreyer et al. (2018), publicaram uma revisão sistemática seguida de meta-análise com o objetivo de avaliar a prevalência, incidência e fatores de risco de peri-implantite. De acordo com as evidências geradas por esta revisão, indivíduos diabéticos apresentariam 2 vezes mais chances de desenvolvimento da peri-implantite que os não-diabéticos. No entanto, os autores concluem que ainda não está claro se todos os tipos de diabetes aumentam o risco de peri-implantite na mesma extensão (DREYER et al., 2018).

Uma outra recente revisão sistemática e meta-análise realizada por Monje et al. (2017) buscou avaliar estudos observacionais de associações entre hiperglicemia/*diabetes mellitus* e peri-implantite. Os autores foram bastante criteriosos em sua seleção e encontraram em seus resultados uma forte associação entre diabetes e o aumento do risco para a peri-implantite. No entanto, a amostra incluiu estudos com diferentes critérios diagnóstico de peri-implantite, baseados em médias de parâmetros clínicos, não necessariamente o parâmetro clínico em si. Além disso, os autores avaliaram estudos com duração maior ou igual a 6 meses (MONJE et al., 2017). Os próprios autores destas recentes revisões publicadas sugerem ainda novas revisões, com dados mais homogêneos durante a seleção dos estudos incluídos (MONJE et al. 2017; DREYER et al., 2018).

1.5. Justificativa

Até o momento, as evidências não são claras sobre a possibilidade do diabetes ser considerado realmente um indicador de risco para a peri-implantite (SCHWARZ et al., 2018). Sendo necessários mais estudos para que isto possa ser comprovado. Neste sentido, algumas revisões sistemáticas tentaram gerar evidências mais concretas, mas é observada uma diversidade de metodologias entre os estudos analisados e a falta de padronização diagnóstica tanto sobre o diagnóstico de diabetes quanto sobre o de peri-implantite. Apesar de idealmente a identificação de um fator de risco ser através da avaliação de estudos longitudinais (DREYER et al., 2018), submeter um paciente à exposição de um risco acaba se tornando difícil até mesmo do ponto de vista ético (STROUP, BERLIN, MORTON, 2008). Por isto, apesar dos desafios, revisões sistemáticas e meta-análises baseadas em estudos observacionais, continuam sendo um dos poucos métodos para avaliar a eficácia dos estudos e seus resultados em relação a um determinado risco.

Considerando que as revisões sistemáticas com meta-análise apresentadas até o presente momento possuem critérios pouco definidos na seleção de estudos apoiados em um único diagnóstico de peri-implantante e diabetes, além da união de metodologias estatísticas baseadas em diferentes medidas resumidas. O presente estudo apresenta um diferencial de seleção de estudos que possuam uma mesma metodologia estatística usando frequência absoluta e prevalência dos dados para a análise do risco através da formação de uma “odds pura”, evitando viés estatístico devido as derivações. Foi realizada a seleção de estudos que possuam um critério diagnóstico semelhante e que façam a avaliação de peri-implantite através de parâmetros clínicos específicos, após 1 ano em função dos implantes, permitindo uma análise mais padronizada do nível ósseo ou perda óssea. Além disso, durante a seleção dos estudos, a meta-análise foi baseada em artigos que apresentassem pacientes em manutenção, reduzindo o risco de viés por conta da presença deste fator de risco para peri-implantite. Desta maneira, buscamos preencher uma lacuna da pergunta clínica central, onde é questionado o potencial da doença *Diabetes*

Mellitus gerar maiores chances de desenvolvimento de peri-implantite em pacientes que a possuem, comparados à indivíduos não-diabéticos.

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CAPITULO 2 - DIABETES MELLITUS AS A RISK FACTOR FOR PERI-IMPLANTITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

MANUSCRIPT FORMATTED ACCORDING TO GUIDELINES BY **BRAZILIAN ORAL RESEARCH**

Implantodontology

Diabetes mellitus as a risk factor for peri-implantitis: a systematic review and meta-analysis

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ABSTRACT

Diabetes Mellitus (DM) is a highly prevalent disease worldwide. Some studies have indicated that diabetic individuals (DI) are more likely to suffer from implant failure than non-diabetic individuals. However, there is no consensus in the literature whether DM can currently be considered a risk factor for peri-implantitis. Therefore, the objective of this study was to conduct a systematic review and meta-analysis of the literature to ascertain whether implants installed in DI are more likely to develop peri-implantitis than in non-DI. A search on Pubmed, Cochrane, Lilacs and Web of Science databases was conducted. The search yielded 207 articles, from which 4 observational studies were selected. Data related to the number of implants, number of participants, and prevalence of DI and non-DI with peri-implantitis were extracted and tabulated. Among the studies selected for qualitative analysis, all evaluated grouped patients under support peri-implant therapy (TPIS). Four studies qualified for meta-analysis (R software). Quantitative data analysis revealed that DI were 1.223 more likely to develop peri-implantitis than non-DI, without, however, showing statistical significance (95% CI: 0.769-1.979; $p>0.05$). All the studies in the meta-analysis used the same peri-implantitis definition criteria and all patients participated in supportive peri-implant therapy. Shortcomings such as sample composition, and lack of accepted case definitions for both DM and peri-implantitis were identified. Quality analysis showed that selected papers presented low risk of bias. The evidence generated by this systematic review and meta-analysis demonstrated that implant-rehabilitated DM patients undergoing **SPIT** do not have significantly higher chances of developing peri-implantitis when compared to non-DM subjects. Future studies with stricter methodological designs are required to ascertain if such a difference actually exists.

Keywords: Risk Indicator; *Diabetes mellitus*; Peri-implantitis.

INTRODUCTION

While dental implant rehabilitation is documented in the literature as presenting high survival rates,[1] the reported success rates, on the other hand, vary greatly depending on the criteria used.[1-5] The difference between long-term implant survival rates and success rates is due to the fact implants and their restorations may be subject to mechanical and/or biological complications over time. Peri-implantitis is a late biological complication characterized by mucosal inflammation and progressive bone tissue loss,[6] which can result in implant rehabilitation failure. Due this increase incidence [7-9] and the absence of a predictable treatment,[10] peri-implantitis prevention is still the only feasible alternative. Thus, a more comprehensive understanding of the risk factors involved in the onset and development of the disease is essential for implant prognosis and the establishment of individualized preventive measures.[11,12]

Diabetes Mellitus (DM) is considered one of the major worldwide epidemics of the 21st century.[13] Although some studies have shown that DM individuals have more marginal bone loss[14-18] and greater probing depth around implants[15] than non-DM individuals, the increased prevalence of peri-implantitis among DM individuals is still controversial. In a cross-sectional study with 212 patients conducted by Ferreira et al. (2006),[19] the authors found that non-DM individuals were significantly associated with an increased risk of developing peri-implantitis when compared to non-DM individuals. Other studies, however, failed to find a clear association between DM and peri-implantitis.[7,8,20-24] Daubert et al. (2015)[25] observed among women with osteoporosis that DM patients had a higher chance of developing peri-implantitis and losing implants when compared to non-DM patients, but no statistically significant differences were observed between groups. Dalago et al. (2017)[26] found a significant relationship between DM and peri-implantitis in the univariate analysis, which, however, was not observed in the multivariate analysis.

Previous systematic reviews have attempted to generate more concrete evidence on the association between DM and peri-implantitis, but the diversity methodologies used in the studies and the lack of standardized generally accepted case definitions for both DM and peri-implantitis have imposed some important limitations on the analysis of the main findings. In an attempt to verify if different systemic medical conditions and smoking acted as biological agents associated with peri-implantitis, Turri et al. (2016)[15] found an association between smoking and DM and peri-implantitis. Nonetheless, the authors concluded that the body of evidence is

still controversial, calling for more studies. In a recent systematic review that specifically aimed at verifying if hyperglycemia/DM was associated with peri-implant diseases, Monje et al. (2017)[27] reported that DM individuals presented between 1.21- and 2.46-fold greater chance of developing peri-implantitis than non-DM individuals. An even more recently systematic review, Dreyer et al. (2018)[28] observed that DM patients were two times more likely to present peri-implantitis when compared to non-DM patients. However, the authors reported that it was unclear whether all types of DM presented the same the risk due to the lack of data not only on the type of DM but also on the appropriate tests for DM diagnosis.

Importantly, the aforementioned studies point out to the need of further studies based on longitudinal and prospective designs, that make use of globally accepted case definitions for peri-implant diseases, blood glucose level monitoring before and during the experimental time, as well as a clear description of DM type.[27,28] These would provide more homogeneous quantitative data and allow more appropriate comparisons between studies.[27] However, although the identification of a risk factor should ideally be based on longitudinal studies,[28] in many circumstances to expose the patient to a known risk may be unacceptable from an ethical point of view.[29] Therefore, systematic reviews and meta-analyzes based on observational studies remain one of the possible methods in the search of evidence that can assist in the understanding of a particular risk.[29] Nonetheless, more reliable evidence may emerge from a more adequate research question and refined search strategy.

Therefore, the aim of this study was to conduct a systematic review of the literature and meta-analysis based on observational studies in an attempt to identify whether implants installed in DM individuals have a higher chance of developing peri-implantitis when compared to non-DM individuals.

METHODOLOGY

Protocol and Registration

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [(30)], and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol number CRD42019147095.

Literature search

The research question that guided this systematic review was: “Do DM patients rehabilitated with dental implants have a higher risk of developing peri-implantitis than non-DM patients?”

To answer this question, a search was performed in the following electronic databases: Pubmed Medline, Lilacs, Cochrane, and Web of Science. Additionally, the reference lists of selected articles were also searched for the identification of possible further studies.

Search strategy

Studies published without restrictions concerning time and language were initially considered based on MeSH terms following the PEO strategy (P = population; E = exposure; O = outcome measures), which in the case of the present study were as follow:

P: Patients rehabilitated with dental implants;

E: DM, DM type I; DM type II, controlled DM; uncontrolled DM;

O: Peri-implantitis prevalence; absolute frequency; odds ratio (OR).

The keywords and search strategies performed in the Pubmed, Lilacs, Cochrane and Web of Science databases are presented in Table 1.

Eligibility criteria

The inclusion criteria were as follows: case control, cohort or cross-sectional observational studies; human studies; patients rehabilitated with dental implants at least 1 year in function; clear case definitions for peri-implantitis and DM diagnostic; studies showing peri-implantitis frequency in DM and non-DM individuals in absolute terms. The exclusion criteria were: studies from which the absolute frequency and prevalence of peri-implantitis could not be extracted.

Study Selection

All titles and abstracts of the articles retrieved were independently assessed by two reviewers (LOC and HBAP), who were trained and standardized to apply the inclusion and exclusion criteria (Kappa = 0.92). Each reviewer read all studies independently. Disagreements were resolved through discussion and whenever a consensus could not be reached, a final decision was taken with the assistance of a third reviewer (FM).

Quality assessment

Methodological quality was independently assessed by two reviewers (LOC and HBAP), following the Newcastle-Ottawa Scale (NOS) criteria.[31] Because NOS was designed to be used in the analysis of cohort and case-control studies, a previous adaptation of the NOS criteria was applied to the analysis of cross-sectional studies.[32] Three aspects were evaluated: i) sample selection; ii) comparability of study groups; and iii) results. Each study was then classified according to scores that ranged from 0 to 9 (cohort and case control) or 6 (cross-sectional). Disagreements were again resolved with the assistance of a third reviewer (FM).

Data extraction

The following data was extracted from each selected study[8,19,20,21,25,33] into a spreadsheet: authors, year of publication, number of implants, number of participants, study design, DM definition, peri-implantitis definition, DM type, DM control, prevalence of DM individuals with peri-implantitis, prevalence of non-DM individuals with peri-implantitis, supportive peri-implant therapy (SPIT). To allow comparisons, selected articles were grouped according to study design.

Data analysis

The quantitative meta-analysis was performed using patient-based data retrieved from studies presenting the absolute frequency of individuals with and without peri-implantitis, exposed or not to DM, using the Software R. Tarone test was used to verify the homogeneity of the odds ratio in the different studies. A fixed effect model was used when there was no statistically significant heterogeneity ($p>0.05$). The summary of measures was described as OR, 95% CI and p values. The primary outcome was peri-implantitis (presence or absence). Subgroup analysis was conducted by study design. Additionally, meta-analyses were performed on the DM patients reported in the studies. Reporting bias was assessed qualitatively using Egger test and the funnel plot.

RESULTS

Selected Studies

Figure 1 illustrates the study selection process. The initial search in the electronic

databases yielded 207 articles. After the removal of duplicates (47 articles); title and abstract evaluations (156 articles), 24 articles were considered potentially eligible. Full texts were retrieved and analyzed by applying the eligibility criteria. After the analysis of the references of these articles, no new articles were included.

After full text analysis of the 27 articles selected, 20 were excluded for not presenting the specific objective of studying peri-implantitis, or the data did not allow comparisons (Table 2). Four articles presented the necessary criteria for the systematic review.[8,19,26,33] Among them, four qualified for the meta-analysis, containing the prevalence of DM and non-DM individuals with peri-implantitis.[8,19,26,33]

Summary of Results

Among the 4 studies selected for the systematic review, one was retrospective cohort[33] while three were cross-sectional studies.[8,19,26] Additionally, all the studies presented the same diagnostic parameters for case definition of peri-implantitis [(34)], i.e., probing depth ≥ 5 mm, bone loss ≥ 2 mm, in association with bleeding on probing and/or suppuration.

Regarding DM definition, most studies simply used questionnaires for the self-reporting of the condition, while two studies went beyond that. Al-Askar et al. (2018)[33] communicated with patients' physicians and requested further exams such as glycated hemoglobin. Ferreira et al. (2006)[19], in addition to the patient's self-report on the use of oral hypoglycemic or DM drugs, requested fasting blood glucose tests. One study classified individuals only as having DM,[8] without detailing DM type (type I or type II), or whether these patients had controlled or uncontrolled DM. Two studies only reported DM type II individuals,[19,33] while one study reported DM type I and II individuals.[26] Only two of the studies stated that in their sample they evaluated uncontrolled DM individuals.[19,33]

All the studies evaluated individuals enrolled in SPIT.[8,19,26,33] The study with the largest number of DM individuals in its sample, as well as the highest prevalence of DM and non-DM individuals with peri-implantitis was Al-Askar et al. (2018).[33] Although the study by Ferreira et al. (2006)[19] presented the lowest prevalence of non-DM individuals with peri-implantitis, it also presented the lowest overall prevalence of peri-implantitis among all the studies. The study by Marrone et al. (2013)[8] presented the highest prevalence of individuals with peri-implantitis among all other studies.

The study with the highest overall prevalence of implant-level peri-implantitis was by Marrone et al. (2013),[8] with 23%. Only Dalago et al. (2017)[26] presented data on peri-implantitis at implant-level among DM and non-DM patients, with similar prevalence values.

Meta-analysis

In the four studies selected for the meta-analysis,[8,19,26,33] 669 individuals were evaluated, 132 classified as DM and 537 as non-DM individuals, with 2348 implants installed.

The results showed statistical heterogeneity between the odds ratio (p=0.029). The odds ratio for each study, as well as the overall odds ratio, are presented in Figure 2. Only the study by Ferreira (2006)[19] presented a significant association between DM and peri-implantitis. However, when all studies were considered, the results showed that DM patients presented a higher chance of having peri-implantitis than non-DM patients, without, however, reaching statistical significance (OR =1.223; 95% CI: 0.769-1.979; p=0.443).

Risk of bias

Both cohort (Table 3) and cross-sectional studies (Table 4) showed low risk of bias according to the NOS criteria. Egger's test showed a possible statistically significant reporting bias in the study by Ferreira et al. (2006)[19] ($p<0.05$). This was confirmed by the funnel plot created with patient-level data, which visually suggests some reporting bias (Figure 3).

DISCUSSION

This study evaluated whether implant-rehabilitated DM individuals are more likely to develop peri-implantitis compared to non-DM individuals. Although our findings indicated that DM patients are more likely to develop peri-implantitis than non-DM patients, this association was weak, without reaching statistical significance (OR: 1.223; $p>0.05$). Thus, the results of the present meta-analysis are insufficient to categorically say that DM individuals with dental implants have a higher risk of developing peri-implantitis when compared to non-DM individuals.

An interesting finding in the present study was the fact that all studies included in the meta-analysis involved patients undergoing supportive peri-implant

therapy (SPIT), and followed the same case definition for peri-implantitis. The reason for that probably involve not only the search strategy but also the selection criteria for the meta-analysis.[34] All studies in the quantitative analysis defined peri-implantitis based on the presence of bone loss ≥ 2 mm, probing depth ≥ 5 mm, in addition to bleeding on probing and/or suppuration were included. Moreover, only articles in which both DM and non-DM patients were part of the sample and DM diagnosis, and with specific data on the prevalence of peri-implantitis were considered. The present meta-analysis was also only based on data collected directly from the included studies with implants with a minimum of one year in function. The reason for that was that, due to the nature of progressive bone loss around implants.[6] During the first year after implant placement, there is a period of healing and bone remodeling, after which the annual rate of vertical bone loss should not exceed 0.2 mm.[35] It is generally accepted that after loading and healing, small bone crest loss between 0.5 and 2 mm tend to occur.

As a result, the weak association between DM and peri-implantitis at patient level found in the present study contrasts with other previously published systematic reviews.[27,28] Based on the results of the present study it may be inferred that when DM patients are enrolled in SPIT, the chances of developing peri-implantitis decrease, reinforcing the perception that SPIT is not only beneficial but also advisable. In general, the absence of regular SPIT has been considered a risk factor for the development of peri-implantitis,[36] and clinicians should develop individualized care programs to meet specific needs of their patients.[37] Risk-based SPIT can be useful to detect early signs of inflammation, preventing the progression of the disease from treatable mucositis to peri-implantitis. In case of DM patients, ensuring that they follow adequate glycemic control can improve implant osseointegration and long-term survival.[38]

The fact that the present meta-analysis was conducted with studies involving subjects undergoing SPIT and followed the same case definition for peri-implantitis probably reduced the risk of reporting bias, because of the similar conditions of DM and non-DM patients. In fact, when analyzed according to the NOS criteria, the studies selected presented low risk of bias. Nonetheless, it is important to remember that most of the selected studies had a cross-sectional design. Because the NOS criteria was originally established for cohort and case-control studies, a modified NOS was employed.[32] Moreover, Egger' test showed that one of the studies

selected for the meta-analysis[19] showed a statistically significant reporting bias.

Thus, due to the observational nature of the included studies, caution should be exercised while interpreting the results. Despite the attempt to select studies with as similar design as possible, a significant heterogeneity was observed among the analyzed odds ratio. Another important characteristic of the selected studies was the lack of acceptable DM diagnostic criteria based on clinical data in association with adequate laboratory tests.[39] Thus, studies that defined DM based on glycated hemoglobin[33] or fasting glucose tests,[19] could possibly be considered as presenting more reliable evidence than those that simply asked patients to self-report DM.[8, 26] Future peri-implantitis studies involving DM patients, should collect a complete set of clinical data (patient medical history, laboratory tests, and medications used), use a clear definition for controlled and uncontrolled DM, and DM type (type I or type II).[39] Moreover, peri-implantitis diagnosis should also follow accepted definition criteria,[40] based on clinical and radiographic examinations in order to decrease methodological heterogeneities as much as possible. Additionally, risk factors such as poor plaque control, and history of periodontal disease should also be considered to obtain results with higher power of evidence. Ideally, future clinical prospective studies involving DM and non-DM individuals should be conducted. Because of the difficulty in grouping together a significant number of DM patients, multicenter studies are warranted.

CONCLUSIONS

The evidence generated by this systematic review and meta-analysis demonstrated that implant-rehabilitated DM patients undergoing **SPIT** do not have significantly higher chances of developing peri-implantitis when compared to non-DM subjects. Future studies with stricter methodological designs are required to ascertain if such a difference actually exists.

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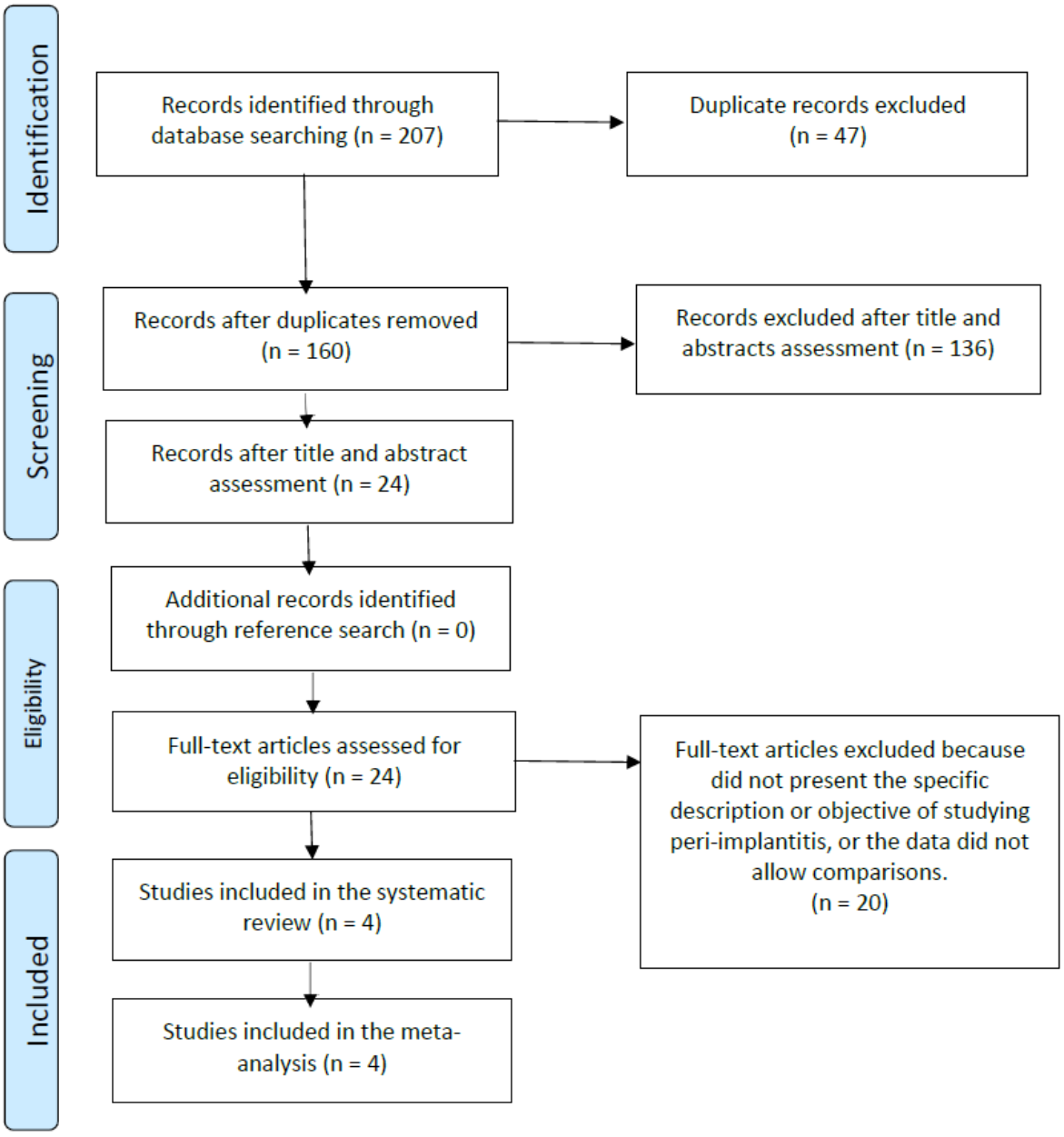
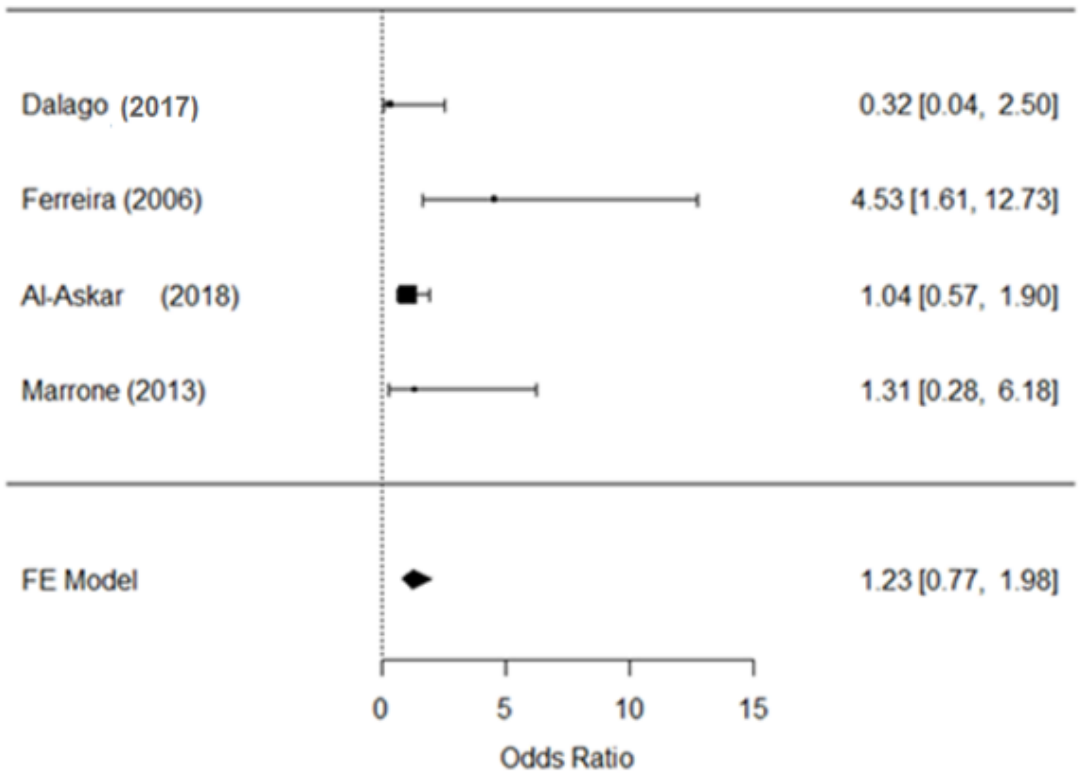
Figure 1. Flowchart of the studies identified and select according to PRISMA recommendations



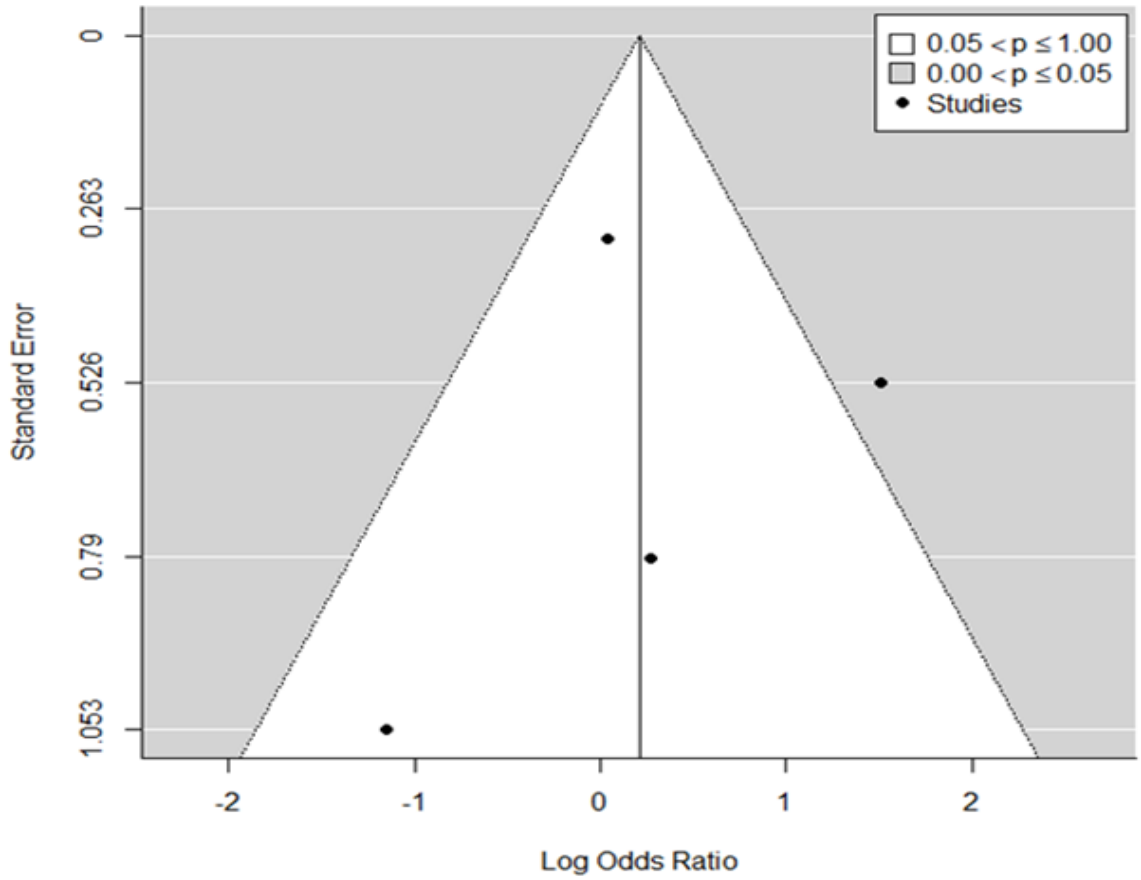
Systematic review study selection flowchart according to PRISMA recommendations

Figure 2. Forest graph using the fixed effect model: Patient risk of peri-implantitis among diabetic patients compared to non-diabetic patients (four studies)



Forest graph using the fixed effect model: Patient risk of peri-implantitis among DM patients compared to non-DM patients (four studies)

Figure 3. Funnel plot using fixed effect model of the four studies included in the meta-analysis.



Funnel meta-analysis graph using fixed effect model for the four studies included in the meta-analysis

Table 1. Keywords and search strategies performed in the Pubmed, Lilacs, Cochrane and Web of Science databases.

Database	Search Strategy
PUBMED	((((dental implant) AND peri-implantitis) OR peri-implantitis) AND "diabetes mellitus") NOT review
LILACS	(tw:(implantes dentários)) AND (tw:(diabetes mellitus)) AND (tw:(peri-implantite)) OR (tw:(periimplantite)) AND NOT (tw:(review))
Cochrane	“dental implant” in Keyword AND "peri-implantitis" OR "periimplantitis" in Title Abstract Keyword AND "diabetes mellitus" in Title Abstract Keyword NOT review in Title Abstract Keyword - (Word variations have been searched)
Web of Science	("dental implants") AND TÓPICO: ("peri-implantitis "OR" periimplantitis") AND TÓPICO: ("diabetes mellitus "OR" diabetes mellitus type 1 "OR" diabetes mellitus type 2") NOT TÓPICO: (review)

Table 2. Reasons for the exclusion of articles after reading the whole paper

Author/year	Does not show comparative PI prevalence	Implants less than 1 year in function	Different PI diagnosis criteria	Shows mean peri-implant parameters, not PI	DM patients only	Explanation
Krennmeir et al. (2018)	X	-	Does not mention PD, only BoP	-	-	Shows MBL comparative data, not DM and PI comparative data
Dvorak et al. (2011)	X	-	-	-	-	Does not shows comparative data prevalence between DM and non-DM for PI.
Daubert et al. (2015)	X	-	-	-	-	Does not shows comparative data prevalence between DM and non-DM for PI.
Renvert et al. (2014)	X	-				Does not shows comparative data prevalence between DM and non-DM for PI.
Al-Sowyg et al. (2017)	X	-	-	X	-	Shows mean peri-implant parameters.
Aguilar-Salvatierra et al. (2016)	X	X	-	X	X	Shows MBL comparative data, not DM and PI comparative data.
Alouf et al. (2009)	X	NI	NI	X		
Alrabiah et al (2018)	X	-	-	X	-	Shows mean peri-implant parameters.
Gomez-Moreno et al. (2014)	X	-	-	X	X	Shows mean peri-implant parameters.
Lee et al. (2009)	X					
Araújo Nobre et al. (2014)	X	-	-	-	-	Does not shows comparative data between DM and non-DM for PI.
Maximo et al. (2008)	X	X	-	-	-	Does not shows comparative data prevalence between DM and non-DM for PI.
Rokn et al. (2016)	X					
Tawil et al. (2008)	X	-	-	-	X	Does not shows comparative data between DM and non-DM for PI.
Erdogan et al. (2015)	X	X	-	-	X	Shows MBL comparative data.
Venza et al. (2010)	X	-	-	-	X	Biomarker assessment data, not DM and PI comparative data.
Eskow et al. (2016)	-	-	-	-	X	Survival analysis.
Curcurella- Flores et al. (2016)	X	X	-	X	-	Shows MBL comparative data, not DM and PI comparative data.
Al Zahrani (2018)	X	NI	-	X	-	Shows MBL comparative data, not DM and PI comparative data.
Moy et al. (2005)	X	-	-	-	-	Evaluation of implant failures.

Legend: PI: peri-implantitis; DM: diabetes mellitus; MBL: marginal bone loss; BoP: bleeding on probing; NI: not informed.

Table 3: Characteristics of the 7 studies included in the qualitative analysis

Author/year	Design	PI Definition	DM Definition	SPIT	Total Individuals (N)	DM individuals (N)	DM prevalence with PI (%)	Non-DM prevalence with PI (%)	Total prevalence with PI (%)	Total implants (N)	PI prevalence in implants in DM and non-DM individuals	Total PI prevalence at implant level
Al-Askar et al. 2018 [31] Arábia Saudita	Cohort	PD ≥ 5 mm MBL ≥ 2 mm BoP or SUP	Glycated hemoglobin DMT2 U*	Yes	171	80	43.75%	42.8%	NR	171	NR	NR
Dalago et al. 2017 [26] Brazil	Cross-sectional	PD ≥ 5 mm MBL ≥ 2 mm BoP or SUP	Patient Records DMT1/T2	Yes	183	16	6.25%	17.4%	16.4%	916	DM: 8.1% Non-DM: 7.2%	16%
Ferreira et al. 2006 [19] Brazil	Cross-sectional	PD ≥ 5 mm MBL ≥ 2 mm BoP or SUP	Fasting blood glucose ≥126 mg/dl or use of anti-diabetic medication in the last 2 weeks DMT2 U*	Yes	212	29	24.13%	6.65%	8.9%	578	NR	7.44%
Marrone et al. 2013 [8] Bélgica	Cross-sectional	PD ≥ 5 mm MBL ≥ 2 mm BoP or SUP	Questionnaire DM	Yes	103	7	42.9%	36.5%	37%	266	NR	23%

Legend: PI: peri-implantitis, PS: pocket depth; BL: radiographic bone loss; BoP: bleeding on probing; SUP: suppuration; DM: diabetes mellitus; C*: controlled diabetes; U*uncontrolled diabetes;; DMT1: diabetes mellitus type I; DMT2: diabetes mellitus type II; SPIT: supportive peri-implant therapy; N: number; NR: data not reported by authors.

Table 4. Newcastle-Ottawa Scale-based risk of bias assessment for cohort studies included in the meta-analysis

Author/year	Sample selection (4 stars max)	Comparability (2 stars max)	Results (3 stars max)	Total (9 stars max)
Al-Askar et al., 2018[31]	3 / 4	1/2	3/3	7/9

Modified Newcastle-Ottawa Scale.[31]

Table 5. Newcastle-Ottawa Scale-based risk of bias analysis of cross-sectional studies included in the meta-analysis

Author/year	Sample selection (2 stars max)	Comparability (2 stars max)	Results (2 stars max)	Total (6 stars max)
Ferreira et al., 2006[19]	2/2	2/2	1/2	5/6
Dalago et al., 2016[26]	2/2	2/2	1/2	5/6
Marrone et al., 2013[8]	2/2	2/2	1/2	5/6

Modified Newcastle-Ottawa Scale [31] adapted by Ferreira et al. (2018)[32]