Ana Karolina Almeida de Lima

Cárie em pacientes com Diabetes Mellitus: uma revisão sistemática e metanálise

Brasília
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Trabalho de Conclusão de Curso apresentado ao Departamento de Odontologia da Faculdade de Ciências da Saúde da Universidade de Brasília, como requisito parcial para a conclusão do curso de Graduação em Odontologia.

Orientador: Prof. Nailê Damé-Teixeira

Coorientadores: Prof. Cristine Miron Stefani e Prof. Adriano de Almeida de Lima

Brasília
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À Deus, minha mãe e meu pai.

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Á Deus, por essa vida cheia de bênçãos e aprendizados, cheia de amor e carinho. Por essa oportunidade de formar em odontologia pela Universidade de Brasília, e não só isso, por ter colocado no meu caminho os obstáculos certos para que eu me tornasse a mulher que sou hoje. Pelos amigos e anjos que me emprestou ao longo dessa jornada, sou imensamente grata, pois tenho certeza que sem eles eu não chegaria onde estou, e não seria metade de quem sou. Obrigada Deus por me dar tudo na dose certa, e por estar sempre a frente abençoando toda essa trajetória.

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“Era a lição definitiva que tirava daquilo tudo: uma lasca de felicidade pode apagar todos os infortúnios do passado. A vida é maravilhosa porque se renova.”.

Otávio Bravo

RESUMO

DE LIMA, Ana Karolina Almeida. Cárie em pacientes com Diabetes Mellitus: uma revisão sistemática e metanálise. 2019. Trabalho de Conclusão de Curso (Graduação em Odontologia) – Departamento de Odontologia da Faculdade de Ciências da Saúde da Universidade de Brasília.

Essa revisão sistemática e meta-análise objetivou avaliar a relação entre doença cárie e Diabetes Mellitus (DM). A pesquisa foi realizada nas bases de dados PubMed, LILACS, Web of science, Scopus, Cochrane e Livivo, além de uma busca na literatura cinzenta no Google Scholar Web Search, ProQuest e Open Grey. Também houve pesquisa manual das bibliografias dos estudos incluídos. A inclusão dos artigos, extração de dados e risco de viés foi realizada por 2 revisores a partir da leitura do título e resumo e leitura completa. No caso de conflitos, um terceiro revisor foi consultado. Cinco meta-análises diferentes foram conduzidas: duas baseadas nos relatos de cárie reportados nos estudos em pacientes com Diabetes Mellitus e pacientes sem Diabetes Mellitus (prevalência e CPOD); duas baseadas nos relatos de cárie reportados nos estudos em pacientes de diferentes níveis de controle glicêmico (prevalência e CPOD); e a quinta baseada na prevalência de cárie radicular em pacientes diabéticos e não-diabéticos. Dos 3.300 títulos encontrados pelas pesquisas, 27 atenderam aos critérios de inclusão e foram incluídos. O resultado da meta-análise mostrou que não há diferença estatisticamente significativa na prevalência de cárie dentária entre o grupo diabético e não-diabético (OR=1.79; 95% CI 0.74-4.34; p=0.20; I^2=93%); Foi observado maior CPOD para o grupo diabético em comparação com o não-diabético MD=1.71; 95% CI 1.08-2.33; p<0.00001; I^2=55%); Indivíduos com DM tipo 2 apresentaram maior prevalência de cárie radicular quando comparados com o grupo não-diabético

(OR=3.17; 95% CI 1.19-8.49; p=0.02; I^2 = 70%); Pacientes descompensados apresentaram maior prevalência (OR=6.75; 95% CI 3.65-12.50; p<0.00001; I^2=34%) e maior CPOD (MD=2.61; 95% CI 1.14-4.08; p=0.0005; I^2=75%) quando comparados com indivíduos compensados. Em conclusão, pacientes com diabetes estão mais propensos a ter maior CPOD que não-diabéticos, mas eles são capazes de ter um menor índice CPOD dependendo do controle glicêmico. Sugere-se que pacientes com DM tipo 2 podem ter mais cárie dental que indivíduos com DM tipo 1 como consequência de dividir fator de risco com a doença cárie. Diabéticos descompensados tem maiores chances de ter cárie dentaria quando comparados com indivíduos compensados, provavelmente pela falta de monitoramento médico e nutricional. Não foram coletados dados suficientes para confirmar a correlação entre cárie dental e doença periodontal em pacientes diabéticos.

ABSTRACT

DE LIMA, Ana Karolina Almeida. Dental caries in patients with Diabetes Mellitus: a systematic review and meta-analysis. 2019. Undergraduate Course Final Monograph (Undergraduate Course in Dentistry) – Department of Dentistry, School of Health Sciences, University of Brasília.

This systematic review and meta-analysis aimed to assess the relationship between dental caries and Diabetes Mellitus (DM). PubMed, LILACS, Web of Science, Scopus, Cochrane, and Livivo, databases were searched, as well as “grey literature” on Google Scholar, ProQuest, and Open Grey. A manual search of references lists of included studies was also performed. The inclusion of studies, data extraction, and risk of bias were performed by 2 reviewers through the reading of title and abstract and full article. A third reviewer was consulted in case of conflicts. Five different meta-analyses were conducted: 2 based on the dental caries reported in the studies (prevalence and DMFT) in patients with diabetes mellitus and non-diabetics; 2 based on the dental caries reported in studies (prevalence and DMFT) with the type of glycaemic index control; and the last one regarding the prevalence of root caries in DM and the control group. From 3.300 titles retrieved, 27 studies were included after meeting the inclusion criteria. The meta-analysis results supported no statistically significant differences in the prevalence of dental caries between DM and non-DM (OR=1.79; 95% CI 0.74-4.34; p=0.20; I^2=93%); higher DMFT index in the DM group in comparison with non-DM group (MD=1.71; 95% CI 1.08-2.33; p<0.00001; I^2=55%); T2DM individuals presented higher prevalence of root caries in comparison with non-DM individuals (OR=3.17; 95% CI 1.19-8.49; p=0.02; I^2 = 70%); Uncontrolled glycemic patients presented higher prevalence (OR=6.75; 95% CI 3.65-12.50; p<0.00001; I^2=34%) and DMFT index (MD=2.61; 95%

CI 1.14-4.08; p=0.0005; I^2=75%) when compared with controlled glycemic individuals. In conclusion, although DM patients presented higher DMFT index than non-diabetic individuals, caries disease can be influenced by the level of glycemic control. T2DM patients may have more dental caries than T1DM individuals as consequence of sharing a risk factor with dental caries. Uncontrolled DM patients are more likely to have dental caries when compared with controlled DM individuals, probably because of the lack of nutritional and medical monitoring. Not enough data was recorded to confirm a correlation between dental caries and periodontal disease.

SUMÁRIO

ARTIGO CIENTÍFICO

Este trabalho de Conclusão de Curso é baseado no artigo científico:
DE LIMA, Ana Karolina Almeida; AMORIM DOS SANTOS, Juliana; LIMA, Adriano de Almeida de; STEFANI, Cristine Miron; DAME-TEIXEIRA, Naile. Dental Caries in patients with Diabetes Mellitus: a systematic review and meta-analysis.
Apresentado sob as normas de publicação da Revista Caries Research.

FOLHA DE TÍTULO

Dental Caries in patients with Diabetes Mellitus: a systematic review and meta-analysis

Cárie em pacientes com Diabetes Mellitus: uma revisão sistemática e metanálise

Ana Karolina Almeida DE LIMA
Juliana AMORIM DOS SANTOS
Adriano de Almeida de LIMA
Cristine Mirom STEFANI
Naile DAME-TEIXEIRA

Department of Dentistry, Faculty of Health Sciences, University of Brasilia, Distrito Federal, Brazil

Keywords: Dental Caries; Diabetes Mellitus; Periodontal disease; Systematic review; Meta-analysis.

Short title: Dental caries and diabetes

Corresponding author
Nailê Damé-Teixeira
Department of Dentistry – Faculty of Health Science
Campus Universitário Darcy Ribeiro
University of Brasilia – Brasilia-DF
Post code: 70910-900
Phone: +55 61 3107 1802
e-mail: nailedame@hotmail.com

RESUMO

Dental Caries in patients with Diabetes Mellitus: a systematic review and meta-analysis

This systematic review and meta-analysis aimed to assess the relationship between dental caries and Diabetes Mellitus (DM). PubMed, LILACS, Web of Science, Scopus, Cochrane, and Livivo, databases were searched, as well as “grey literature” on Google Scholar, ProQuest, and Open Grey. A manual search of references lists of included studies was also performed. The inclusion of studies, data extraction, and risk of bias were performed by 2 reviewers through the reading of title and abstract and full article. A third reviewer was consulted in case of conflicts. Five different meta-analyses were conducted: 2 based on the dental caries reported in the studies (prevalence and DMFT) in patients with diabetes mellitus and non-diabetics; 2 based on the dental caries reported in studies (prevalence and DMFT) with the type of glycaemic index control; and the last one regarding the prevalence of root caries in DM and the control group. From 3.300 titles retrieved, 27 studies were included after meeting the inclusion criteria. The meta-analysis results supported no statistically significant differences in the prevalence of dental caries between DM and non-DM (OR=1.79; 95% CI 0.74-4.34; p=0.20; I^2=93%); higher DMFT index in the DM group in comparison with non-DM group (MD=1.71; 95% CI 1.08-2.33; p<0.00001; I^2=55%); T2DM individuals presented higher prevalence of root caries in comparison with non-DM individuals (OR=3.17; 95% CI 1.19-8.49; p=0.02; I^2 = 70%); Uncontrolled glycemic patients presented higher prevalence (OR=6.75; 95% CI 3.65-12.50; p<0.00001; I^2=34%) and DMFT index (MD=2.61; 95% CI 1.14-4.08; p=0.0005; I^2=75%) when compared with controlled glycemic individuals. In conclusion, although DM patients presented higher DMFT index than non-diabetic individuals,

caries disease can be influenced by the level of glycemic control. T2DM patients may have more dental caries than T1DM individuals as consequence of sharing a risk factor with dental caries. Uncontrolled DM patients are more likely to have dental caries when compared with controlled DM individuals, probably because of the lack of nutritional and medical monitoring. Not enough data was recorded to confirm a correlation between dental caries and periodontal disease.

Keywords: Dental Caries; Diabetes Mellitus; Periodontal disease.

INTRODUÇÃO

A global trend of population aging has been associated with an increasing prevalence of chronic diseases such as Diabetes Mellitus (DM) [World Health Organization, 2011]. DM is a condition which has a considerable impact on quality of life and longevity of affected individuals [Mauri-Obradors et al., 2017]. It has become a worldwide epidemics: according to the International Diabetes Federation (IDF) [International Diabetes Federation, 2017], 424.9 million individuals were diagnosed with this disease, and over 4 million deaths could be estimated in individuals among 20-79 years. This metabolic disease is characterized by high blood glucose levels, which can lead to serious damages and complications in the whole organism. These complications are directly linked to the level of disease decompensation and the duration of the condition.

Oral manifestations of DM are commonly observed. Periodontal disease is one of the most common complications in diabetics. DM patients have three times more chance of presenting periodontitis than non-diabetic patients (non-DM) [Novotna et al., 2015]. In addition, people with poor glycemic control are more likely to develop severe forms of periodontal disease [Morita et al., 2012; Novotna et al., 2015], while periodontal disease can also impair the glycemic control [Negrato, and Tarzia, 2010]. Changes in the salivary flow and composition are also observed as oral manifestations of DM [Mauri-Obradors et al., 2017]. Saliva has a well-known protective role in dental caries [Seethalakshmi et al., 2016]. Then, DM can theoretically predispose to dental caries by causing an imbalance of the oral environment, which favours a cariogenic microbiota establishment.

The controversy about scientific evidence for increased risk of caries in diabetics has raged unabated. Previous studies have not considered the effects of glycemic control, which could be

linked to the lack of agreement between studies. It is possible that patients with good glycemic control take low levels of sugar due to medical and nutritional treatments and, consequently, their chances to develop caries may be reduced.

Two systematic reviews have been conducted to gather evidence of the oral health of diabetics [Ismail et al., 2015; Mauri-Obradors et al., 2017]. Mauri-Obradors *et al.* showed that 40% of studies found an increased caries level in DM, and this was credited to the low salivary flow. Such approach, however, has failed to address a systematic understanding due to a low number of included studies. Ismail *et al*. investigated the oral health status of children with type 1 DM (T1DM), concluding that T1DM causes a significantly altered salivary flow and buffering capacity, with increased risk of caries. However, no evidence was found regarding the relationship between caries disease and DM in adults.

Causal factors leading to dental caries in patients with DM remain speculative. Although extensive research has been carried out on DM and dental caries, no single meta-analysis exists which focused on whether there are higher or lower chances of DM patients present caries lesions, as well as the correlation between dental caries and the most prevalent oral disease in DM: periodontal disease. It justifies a systematic review and meta-analysis aiming to address all variants of dental caries in DM. Therefore, the purpose of this study was to answer four questions: Are diabetics more predisposed to present dental caries than non-DM?; Is there any difference in the occurrence of dental caries among patients with T1DM and type 2 DM (T2DM)?; Is there any difference in the occurrence of caries among controlled diabetes patients and uncontrolled diabetes patients?; Is there any correlation between periodontal diseases and dental caries in diabetics?

METODOLOGIA

Protocol and registration

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [Moher et al., 2009]. A protocol was designed and registered at the International Prospective Register of Systematic Review, PROSPERO, under the identification number CRD42018111057.

Eligibility Criteria

The acronym PECOS (Population; Exposition; Comparator; Outcomes and Studies) was used to design review questions:

- Population: 1) Patients diagnosed with T1DM OR T2DM; 2) Diabetics with good glycemic index control;
- Exposition: Diabetes Mellitus;
- Comparator(s)/control: Non-diabetics and/or different conditions of DM;
- Outcome measure(s): Prevalence or incidence of caries; DMFT; simultaneous prevalence or incidence of periodontitis.
- Types of Studies included: cross-sectional studies, case-control studies and cohort studies.

Inclusion criteria

Studies eligible for this review were observational studies (cross-sectional, case-control or cohort studies), with no restriction of publication period. Dental caries index should be provided in T1DM or T2DM, independently of glycemic index state, in comparison to non-DM or different conditions of DM. It was expected some evaluation of periodontal conditions as well.

Exclusion criteria

Exclusion criteria were: (1) reviews, letters, personal opinions, book chapters, conference abstract, randomized or non-randomized clinical trials, animal and *in vitro* studies; (2) studies performed in non-DM, patients with Sjögren syndrome or studies in which samples included patients with other severe systemic conditions; (3) studies in which DM were not the main systemic condition; (4) studies in which there were no control; (5) studies that evaluated periodontal diseases or salivary flow as the single outcome, and not dental caries; (6) studies performed in children, adolescents, or young adults/individuals under 35 years-old; and (7) studies published in languages not derived from Latin;

Data Sources and Search Strategy

The search process was performed in January 2019. Appendix 1 shows the search strategy. “Dental Caries, Periodontal Disease, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Glycemic Control” were used as main search elements, among other terms, that were adapted for each electronic database: MEDLINE *via* PubMed, LILACS, Web of Science, Scopus, Cochrane and Livivo. Grey Literature search was also performed in Google Scholar, ProQuest and OpenGrey. Moreover, reference lists from included studies were assessed to identify other articles that could be selected. No language or time restrictions were applied.

Duplicates were identified through *EndNoteWeb* (Clarivate Analytics, Mumbai) and then manually at *Rayyan qcri*® (Qatar Computer Research Institute, Qatar).

Study Selection and Data Extraction

Selection process was performed in two phases. First, titles and abstracts were screened by two independent and blinded reviewers (A.K.A.L and J.A.S). This phase was carried out in a

web application tool designed to systematic reviews (Rayyan®, Qatar Computing Research Institute). Any disagreement was discussed in a meeting with an expert and the coordinator (C.M.S and N.D.T). In a second phase, same independent reviewers (A.K.A.L and J.A.S) gathered all the included studies by reading full articles. Once the study was selected for the second phase and the full-text was not available in any way through online sources, it was performed a protocol in which an email requesting the full-text was sent to authors. Emails were sent every 3 days during 15 days. By the end of this protocol, a final request via COMUT was performed.

Data was extracted using a specific data extraction form (A.K.A.L and J.A.S). Any disagreement was discussed in a meeting with the expert and the supervisor (C.M.S and N.D.T). Authors were consulted to obtain any further information not available in the paper. When the study results were published more than once or results was detailed in multiple publications, the most complete data set from all sources was identified, and the data was included only once.

Risk of Bias and Quality Assessment

The risk of bias of each study was evaluated using the Meta-Analysis of Statistics and Review Instrument (MAStARI) for observational studies developed by the Joanna Briggs Institute [S et al., 2017]. Review Manager 5.3 was used to perform the risk of bias figure. It was carried out independently (A.K.A.L and J.A.S). Any disagreement was discussed in a meeting with the expert and the supervisor (C.M.S and N.D.T). The risk of bias was defined according to the percentage of positive answers. A high risk of bias was considered ≥49% “yes” answers. Studies with a moderate risk of bias were 50% to 69% of “yes” answers, and low risk of bias were ≥70% “yes” answers.

Data Analysis

Mean values of the main outcome was directly pooled with weighted mean differences (WMDs) and 95% confidence intervals. Statistical heterogeneity was estimated by the Chi-square test ($p<0.05$) and I-squared Index (I2), which enabled to assess the magnitude of the inconsistency. Values of the I2 over 50% were classified as high, 25% to 50% moderate and less than 25% as low.

Revman 5.3 (The Cochrane Collaboration, Copenhagen) was used for conducting the meta-analysis. Five meta-analyses were conducted to answer questions of this study:

- 2 meta-analysis based on dental caries reported in the studies (prevalence or DMFT) comparing DM and non-DM;
- 2 meta-analysis based on dental caries reported in studies (prevalence or DMFT) comparing different levels of glycemic index control;
- 1 meta-analysis comparing the prevalence of root caries in DM and non-DM.

RESULTADOS

Study Selection

Searches retrieved 3,300 titles through database searching (Cochrane, LILACS, Livivo, PubMed, Scopus and Web Of Science) and 311 titles through grey literature (Google Scholar, Open Grey and ProQuest). After removing duplicates, 2,424 titles remained for screening. Figure 1 shows the PRISMA flowchart depicting the identified, included, and excluded studies with reasons. After phase 1, n=109 studies remained for a full-text review, being 27 studies included in qualitative synthesis and 19 included in a quantitative synthesis (meta-analysis) (Fig.1). Fourteen non-available articles were searched via COMUT, but

only five of them were available. Unfortunately, we were not able to access credit purchases on the COMUT platform due to non-active covenant error (C005-000) and, therefore, all items were excluded due to unavailability. The reasons for exclusion of studies at the second phase are listed in Appendix 2.

Studies Characteristics

All 27 included papers were cross-sectional studies and were published from 1988 [Albrecht et al., 1988] to 2017 [Malvania et al., 2017]. Studies were conducted in 18 different countries, amongst them seven were conducted in India [Bharateesh et al., 2012; Goyal et al., 2012; Malvania et al., 2017; Nimbal et al., 2016; Ramana, and Rao, 2014; Seethalakshmi et al., 2016; Sharma et al., 2011] and four in the United States of America [Cherry-Peppers, and Ship, 1993; Lin et al., 1999; Tavares et al., 1991; Zielinski et al., 2002].

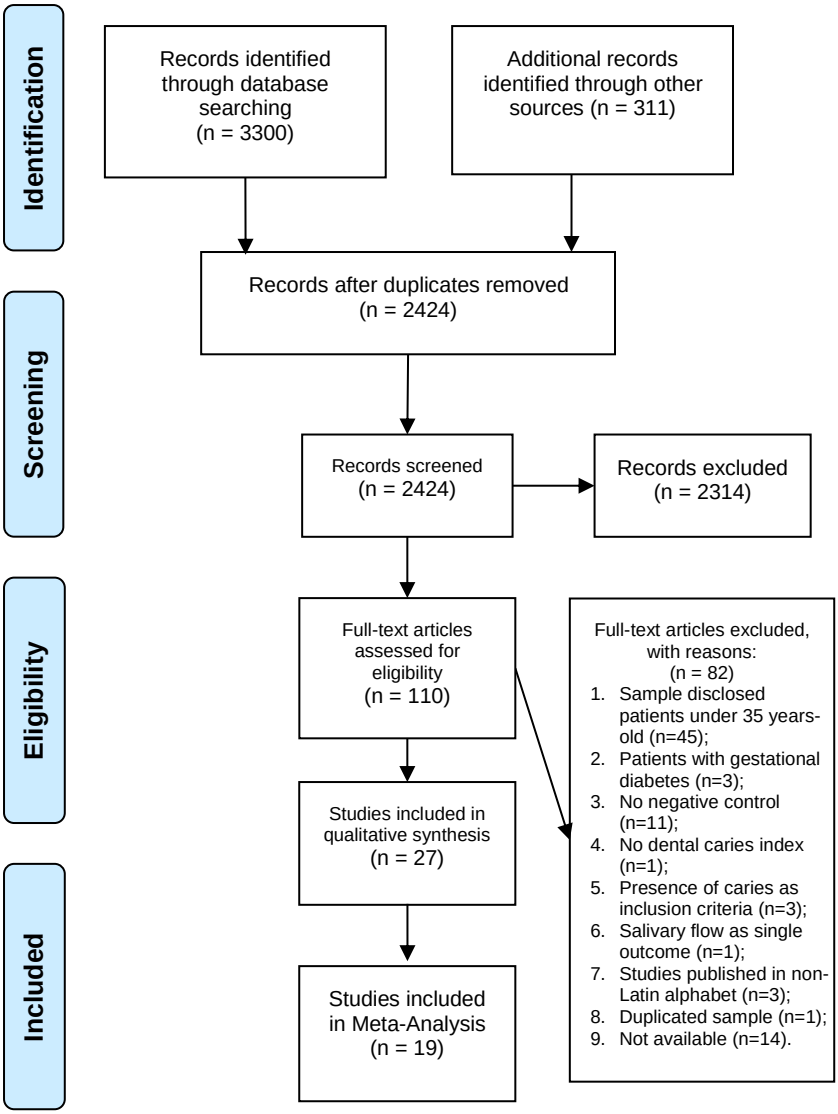

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart describing identified, included, and excluded studies with reasons.

Risk of bias within studies

The quality assessment of the selected studies was determined by Meta Analysis of Statistics Assessment and Review Instrument (MAStARI), and the critical appraisal tool for cross sectional studies was utilized (Appendix 3).

Fig. 2 shows a graph of the risk of bias assessed by RevMan 5.3. The overall risk of bias observed in the studies was 15% with high risk of bias, 18% with moderate risk and 66% with low risk. The highest risk of bias was observed in the definition of the inclusion criteria and an appropriate description of the study objects, while the lowest risk of bias was observed in the statistical analysis, revealing that overall the studies presented an appropriate analysis.

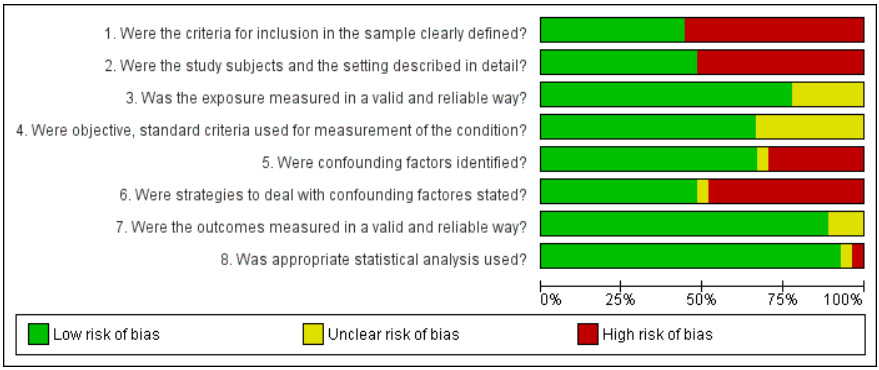

Fig 2. Evaluation of the risk of bias of each item of the instrument presented as percentages across all included studies.

Qualitative results of individual studies

Tables 1-4 show the studies characteristics. The results are shown below by the set of questions to be answered at this systematic review.

Table 1. Characteristics of studies that compare dental caries in diabetic and non-diabetic individuals (n=22).

Study Country	Gender (N)	Compared Groups	Age (mean ± sd/range) year-old	DM (N) T1DM T2DM	Control (N)	Caries index	Mean Caries Index DM	Mean Caries Index Control	Prev. Car. DM	Prev. Car. Control	Risk of Bias
Albrecht et al. *1988* Hungary	NR	A; B	35-65+ yo	810	214	1	NR	NR	NR	NR	🔴
Arrieta-Blanco et al. *2003* Spain	NR	A;B;C;D	40-70+ yo	47	44	1	16,93± 2,92	16,03±4,55	NR	NR	🟢
Bacic et al. *1989* Yugoslavia	NR	A; B; C; D	35-65+ yo	162	134	1	19,5±2,56	17,85±4,82	NR	NR	🟢
Bharateesh et al. *2012* India	234 F 366 M	A; B;	35-74 yo	300	300	NR	NR	NR	40,8 (13,6%)	96,9 (32,3%)	🔴
Iqbal et al. *2011* Pakistan	NR	A; B	NR	30	30	2	2.49	0.53	NR	NR	🟢
Lin et al. *1999* USA	22 F 20 M	B; D	54-86 yo	24	18	4	57.2 ± 33.8	79.7 ± 30.9	NR	NR	🟢

Ramana et al. *2014* India	123 F 205 M	A; B	41-80 yo	136		192	1	NR	NR	77 (56%)	104 (54%)	🟡
Seethalakshmi et al. *2016* India	30 F 10 M	A; B	NR	20		20	1	8.1±5.87	1.15±1.46	NR	NR	🟢
Tanriverdi et al. *2006* Indonesia	59 F 48 M	A; B	47.7±12.3 yo	82		25	NR	NR	NR	80 (97.56%)	10 (40%)	🔴
Cherry-Peppers et al. *1993* USA	NR	B; D	64.05 ± 5.44 yo	NA	11	43	3	53.8 ± 29.7	56.9 ± 33.9	**Root surface** 1.0 ± 1.2 **Coronary surface** 3.8 ± 9.5	**Root surface** 0.2 ± 0.5 **Coronary surface** 0.7 ± 1.7	🟡
Collin et al. *1998* Finland	22 F 43 M	B; D;	58-77 yo	NA	25	40	1	23.8±6.0	25.1±4.3	**Dental Caries** 15 (60%) **Root** 2,2±5,2 (%)	**Dental Caries** 22(55%) **Root** 2,5±5,2 (%)	🟢
Hintao et al. *2007* Thailand	105 F 103 M	B; D;	53.8 ± 0.71 yo	NA	105	103	2	3,8±0,2	3,3±0,3	**Root** 40% **Coronary** 83.8%	**Root** 18.5% **Coronary** 72.8%	🟢
Leung et al. *2008* China	282 F 243 M	B; D	63.85 ± 0.35	NA	364	161	1	16.8 ± 9.8	14.5 ± 8.6	NR	NR	🟢

Malvania et al. *2017* India	NR	B; D	35-74 yo	NA	120	120	1	2.43±2.88	0.74±1.27	88 (73.33%)	37 (30.83%)	●
Mohamed et al. *2013* Norway	278 F 179 M	B; D	52,6±10.5 yo	NA	154	303	1	NR	NR	**Dental Caries** 146 (94.8%) **Root** 81 (52.6)	**Dental Caries** 290 (95.7%) **Root** 120 (39.6)	●
Sandberg et al. *2000* Sweden	76 F 128 M	B; D	64.8±8.4 yo	NA	102	102	1	NR	NR	NR	NR	●
Sharma et al. *2011* India	NR	B; D	35-70 yo	NA	50	50	1	3.60±2.59	2.74±2.22	NR	NR	●
Soto et al. *2009* Colombia	NR	B; D	NR	NA	146	146	1	17.87±93.25	14.10±99.72	NR	NR	●
Sukmininggrum et al. *2013* Malaysia	NR	B; D	35-65 yo	NA	23	26	1	13.52±3.69	9.73±2.50	**Root** 17 (73.9%)	**Root** 6 (23%)	●
Tavares et al. *1991* USA	DM 38.8% F 61.1% M NDM 52.4% F 47.6% M	B; C	45-65 yo	88	NA	185	4p*	0.24 ± 0.14	0.28 ± 0.13	NR	NR	●
Vaziri et al. *2009* Iran	30 F 30 M	B; D	39-82 yo	NA	40	20	1	13.42 ± 5.09	10.55 ± 2.59	NR	NR	●

Zielinski et al. *2002* USA	42 F 30 M	B; D	DM 71±7 yo NDM 74±8 yo	NA	32	40	NR	NR	NR	19 (61%)	24 (60%)	●

Caries index: 1= DMFT; 2= DFT; 3= DMFS; 4= DFS. Compared groups: A = diabetics; B= non-diabetics; C= Type 1 Diabetics; D= Type 2 Diabetics. Gender (n female/ n male), Age (mean ± sd/range), T1DM= Type 1 Diabetics (n); T2DM= Type 2 Diabetics. Prev. Car = Prevalence of Dental Caries. NR: not reported; NA: not applied;

●: high risk of bias; ●: low risk of bias; ●: moderate risk of bias

*: DFS proportion

Table 2. Characteristics of studies that compare dental caries in type 1 and type 2 diabetics (n=1).

Study Country	Gender (N)	Compared Groups	Age (mean ± sd/range) year-old	DM (N) T1DM	DM (N) T2DM	Caries index	Mean Caries Index T1DM	Mean Caries Index T2DM	Prev. Car. T1DM	Prev. Car. T2DM	Risk of Bias
Weinspach et al. *2013* Germany	224 F 204 M	B; C; D	59.65 ± 13.65 yo	101	236	1	16.12 ± 7.58	18.80 ± 5.47	NR	NR	●

Caries index: 1= DMFT; 2= DFT; 3= DMFS; 4= DFS. Compared groups: A = Diabetics; B= non-diabetics; C= Type 1 Diabetics; D= Type 2 Diabetics. Gender (n female/ n male), Age (mean ± sd/range), Type 1 Diabetics (n); Type 2 Diabetics (n). T1DM = Type 1 Diabetes Mellitus; T2DM= Type 2 Diabetes Mellitus. Prev. Car = Prevalence of Dental Caries NR, not reported; NA, not applied;

●: high risk of bias; ●: low risk of bias; ●: moderate risk of bias

Table 3. Characteristics of studies that compare dental caries compensated and decompensated diabetics (n=8).

Study Country	Gender (N)	Compared Groups	Age (mean ± sd/range) year-old	DM (N) T1	DM (N) T2	CP (n)	DcP (n)	Caries index	Mean Caries Index CP	Mean Caries Index DcP	Prev. Car. CP	Prev. Car. DcP	Risk of Bias
Collin et al. *1998* Finland	22 F 43 M	B; D; E; F	58-77 yo	NA	25	11	14	1	NR	NR	5 (45,4%)	10 (66,7%)	●
Goyal et al. *2012* India	75 F 75 M	A; B; E; F	NR	100		50	50	1	4.52± 1.56	8.6± 4.01	NR	NR	●
Lin et al. *1999* USA	22 F 20 M	A; B; E; F	54-86 yo	24		9	15	4	63.4 ± 26.4	53.3 ± 38.0	NR	NR	●
Malicka et al. *2011* Poland	28 F 31M	D; E; F	45-79 yo	NA	59	28	31	1 3	22.03±7.29 90.89±48.19	24.90± 7.29 112.4± 43.75	NR	NR	●
Malvania et al. *2017* India	NR	B; D; E; F	35-74 yo	NA	120	47	73	1	0.62±1.01	3.46±3.16	20 (42.55%)	66 (90.41 %)	●

Mohamed et al. *2013* Norway	278 F 179 M	B; D; E; F	52,6±10.5 yo	NA	154	45	105	1	NR	NR	Root 22 (48.9%)	Root 57 (54.3%)	●
Nimbal et al. *2013* India	NR	E; F	NR	100		50	50	NR	NR	NR	8 (16%)	24 (48%)	●
Sharma et al. *2011* India	NR	B; D; E; F	35-70 yo	NA	50	33	17	1	3.45±2.26	3.88±3.12	NR	NR	●

Caries index: 1= DMFT; 2= DFT; 3= DMFS; 4= DFS. Compared groups: A = Diabetics; B= Nondiabetics; C= Type 1 Diabetics; D= Type 2 Diabetics; E= Controlled Glycemic Diabetics; F= Uncontrolled Glycemic Diabetics. Gender (n female/ n male), Age (mean ± sd/range), Type 1 Diabetics (n); Type 2 Diabetics (n). CP = Compensated Patients; DcP = Decompensated Patients. Prev. Car = Prevalence of Dental Caries NR: not reported; NA: not applied;

●: high risk of bias; ●: low risk of bias; ●: moderate risk of bias

Table 4. Characteristics of studies that analyzes the prevalence of dental caries and periodontal diseases in individuals with diabetes (n= 12).

Study Country	Gender (N)	Age (mean ± sd/range) year-old	DM (N) T1DM	DM (N) T2DM	Prevalence of Dental Caries in T1DM	Prevalence of Dental Caries in T2DM	Prevalence of Periodontal Disease in T1DM	Prevalence of Periodontal Disease in T2DM	Risk of Bias
Bharateesh et al. *2012* India	234 F 366 M	35-74 yo	300		41 (13,6%)		278 (92.6%)		🔴
Cherry-Peppers et al. *1993* USA	NR	64.05 ± 5.44 yo	NA	11	NA	Root surface 1.0 ± 1.2 Cervical 3.8 ± 9.5	NR	NR	🟡
Commisso et al. *2011* Italy	37 F 50 M	58-77 yo	NA	25	NA	9.2%	NA	Tooth Mobility 18% Gengivitis 58%	🟢
Hintao et al. *2007* Thailand	105 F 103 M	53.8 ± 0.71 yo	NA	105	NA	83.8%	NA	generalized periodontitis - 98.1%	🟢

Mohamed et al. *2013* Norway	278 F 179 M	52,6±10.5 yo	NA	154	NA	146 (94.8%) Root Caries 81 (52.6)	NA	Chronic periodontitis 133 (86.4)	●
Nimbal et al. *2016* India	NR	NR		100		32 (32%)		39 (39%)	●
Ramana et al. *2014* India	123 F 205 M	41-80 yo		136		77 (56%)	Pocket from 4mm	49 (36%)	●
Sandberg et al. *2000* Sweden	76 F 128 M	64.8±8.4 yo	NA	102	NA	NR	NA	Subjects with advanced periodontitis 44.8%	●
Sukminingrum et al. *2013* Malaysia	NR	35-65 yo	NA	23	NA	Root Caries 17 (73.9%)	NA	Teeth mobility 21 (91.30%)	●
Tanriverdi et al. *2006* Indonesia	59 F 48 M	47.7±12.3 yo		82		80 (97.56%)		74 (90%)	●

Weinspach et al. *2013* Germany	224 F 204 M	59.65 ± 13.65 yo	101	236	NR	NR	65 (64,3%)	212 (89,8%)	●
Zielinski et al. *2002* USA	42 F 30 M	DM 71±7 yo NDM 74±8 yo	NA	32	NA	19 (61%)	NA	Severe or moderate 23 (72%)	●

Gender (n female/ n male), Age (mean ± sd/range), Type 1 Diabetics (n); Type 2 Diabetics. T1DM = Type 1 Diabetes Mellitus; T2DM= Type 2 Diabetes Mellitus. Prev. Car = Prevalence of Dental Caries. NR: not reported; NA: not applied;

●: high risk of bias; ●: low risk of bias; ●: moderate risk of bias

Are diabetics more predisposed to have dental caries than non-DM?

Nine studies compared a DM group and a control non-DM group [Albrecht et al., 1988; Arrieta Blanco et al., 2003; Bacic et al., 1989; Bharateesh et al., 2012; Iqbal et al., 2011; Lin, 1999; Ramana, and Rao, 2014; Seethalakshmi et al., 2016; Tanriverdi et al., 2006]. These studies grouped DM patients, regardless of the type of diabetes or glycemia level.

All studies evaluated dental caries with DMFT, DFT or DFS index [Albrecht et al., 1988; Arrieta Blanco et al., 2003; Bacic et al., 1989; Iqbal et al., 2011; Lin et al., 1999; Seethalakshmi et al., 2016]. However, significant differences between groups were observed in only three of them ($p<0.05$) [Arrieta Blanco et al., 2003; Seethalakshmi et al., 2016; Lin et al., 1999]. The lowest mean value of DMFT index observed for DM patients was 8.1±5.87 [Seethalakshmi et al., 2016] and the highest was 19.5±2.56 [Bacic et al., 1989]. For non-DM patients, the lowest DMFT index observed was 1.15±1.46 [Seethalakshmi et al., 2016] and highest 17.85±4.82 [Bacic et al., 1989]. One study presented significant conclusions regarding the DMFT index, although it did not present a numerical value [Albrecht et al., 1988], revealing in the results that the DMFT index was always higher in the non-DM group, regardless the age group observed.

The components DFT and DFS were also presented: DFT= 2.49 for DM and 0.53 for non-DM [Iqbal et al., 2011] and DFS= 57.2±33.8 for DM and 79.7±30.9 for non-DM ($p=0.03$) [Lin, 1999].

Three studies compared the prevalence of caries in DM and non-DM, showing conflicting results [Bharateesh et al., 2012; Ramana, and Rao, 2014; Tanriverdi et al., 2006]. From those, one study revealed a significantly higher prevalence of dental caries in DM (97.56% against 40%) [Tanriverdi et al., 2006], while another showed higher prevalence of dental caries in the non-DM

(32.3% against 13.6%) [Bharateesh et al., 2012]. The third study showed no significant differences (prevalence of 56% in DM and 54% in non-DM)[Ramana, and Rao, 2014].

There were also studies that distinguish the results of non-DM and a specific type of DM. A study compared T1DM *versus* non-DM (DFS T1DM =0.24±0.14; DFS non-DM=0.28 ± 0.13) [Tavares et al., 1991]. Other 12 studies evaluated only T2DM comparing to a non-DM group [Cherry-Peppers, and Ship, 1993; Collin et al., 1998; Hintao et al., 2007; Leung et al., 2008; Malvania et al., 2017; Mohamed et al., 2013; Sandberg et al., 2000; Sharma et al., 2011; Soto, and Rodriguez, 2009; Sukminingrum et al., 2013; Vaziri et al., 2009; Zielinski et al., 2002]. The minimum DMFT mean observed for T2DM was 2.43±2.88 [Malvania et al., 2017] and maximum was 23.8±6.0 [Collin et al., 1998], while for the non-DM the minimum DMFT mean observed was 0.74±1.27 [Malvania et al., 2017] and the maximum was 25.1±4.3 [Collin et al., 1998]. Only four studies presented a statistically significant difference between groups ($p<0.05$) [Soto, and Rodriguez, 2009; Leung et al., 2008; Sukminingrum et al., 2013; Malvania et al., 2016]. A study compared T2DM and non-DM individuals with the DMFT index, but did not present any numerical values [Sandberg et al., 2002]. They affirm as result that no difference was found regarding the presence of caries lesions, however the T2DM presented more initial caries ($p=0.02$). Another study used the DMFS index [Cherry-Peppers, and Ship, 1993], revealing a mean of caries for T2DM of 53.8 ± 29.7 and 56.9 ± 33.9 for non-DM, being the only one in this group to report a higher caries index for non-DM.

Seven out of 12 studies showed a comparison of the prevalence of dental caries between T2DM and non-DM individuals [Cherry-Peppers, and Ship, 1993; Collin et al., 1998; Hintao et al., 2007; Malvania et al., 2017; Mohamed et al., 2013; Sukminingrum et al., 2013; Zielinski et al., 2002]. One study presented the prevalence of root caries (1.0±1.2 for T2DM and

0.2±0.5 for non-DM) and coronary caries (3.8±9.5 for T2DM and 0.7±1.7 for non-DM) [Cherry-Peppers, and Ship, 1993]. Another study presented the prevalence of only coronary caries between T2DM (83.8%) and non-DM (72.8%) [Hintao et al., 2007]. Four studies compared the prevalence of dental caries, in general [Collin et al., 1998; Malvania et al., 2017; Mohamed et al., 2013; Zielinski et al., 2002] of which the lowest prevalence observed was T2DM=60% [Collin et al., 1998] and non-DM=30.83% [Malvania et al., 2017] and the highest prevalence was T2DM=94.8% and non-DM=95.7% [Mohamed et al., 2013]. As for the prevalence of root caries, there was one study that presented it as mean prevalence (T2DM= 2.2±5.2% and non-DM= 2.5±5.2%) [Collin et al., 1998], and other three studies that presented it as percentage [Hintao et al., 2007; Mohamed et al., 2013; Sukminingrum et al., 2013], of which the lowest prevalence observed was 40% for T2DM and 18.5% for non-DM [Hintao et al., 2007]; and the highest prevalence of root caries observed was 73.9% in T2DM [Sukminingrum et al., 2013] against 39.6% in non-DM [Mohamed et al., 2013]. Of those, only Malvania et al. presented statistically significant results.

Meta-analysis showed no statistically significant difference in the prevalence of dental caries between DM and non-DM individuals (OR=1.79; 95% CI 0.74-4.34; p=0.20; I^2 = 93%) (Fig. 3), but it revealed higher mean of DMFT in DM individuals (MD=1.71; 95% CI1.08-2.33; p<0.00001; I^2=55%) (Fig. 4). Regarding root caries, the meta-analysis showed higher prevalence in T2DM when compared with non-DM (OR=3.17; 95% CI 1.19-8.49; p=0.02; I^2=70%) (Fig. 5).

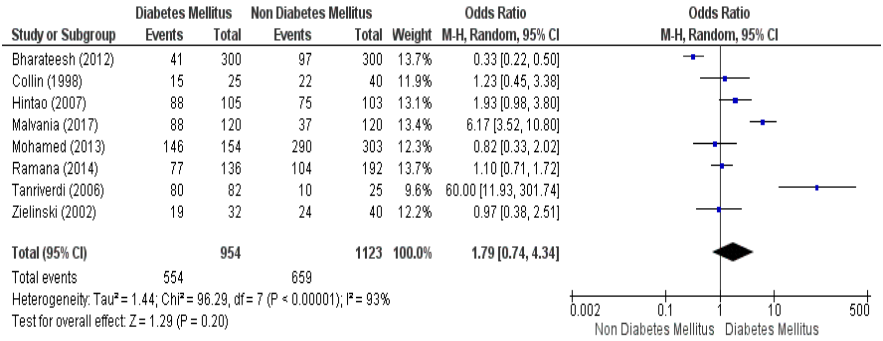

Fig 3. Forest plot of the prevalence of dental caries in DM *versus* Non-DM.

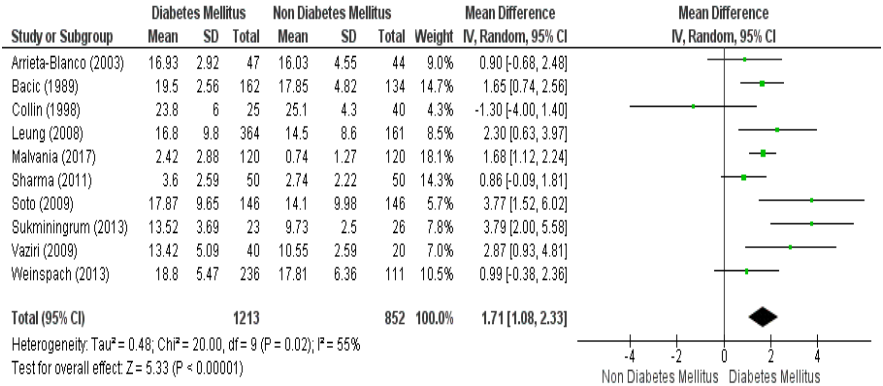

Fig 4. Forest plot of the DMFT in DM *versus* non-DM.

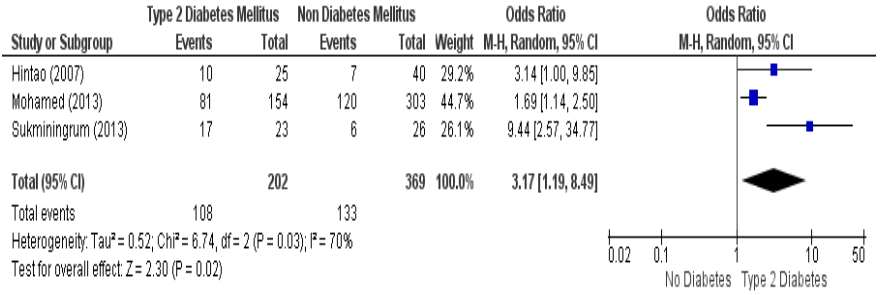

Fig 5. Forest plot of the prevalence of root caries in T2DM *versus* non-DM.

Is there any difference in the occurrence of dental caries among patients with T1DM and T2DM?

Studies that compared dental caries between T1DM patients and T2DM patients showed higher caries levels in T2DM patients [Arrieta Blanco et al., 2003; Bacic et al., 1989; Weinspach et al., 2013]. All of them used the DMFT index for the analysis. One study showed a DMFT index of 16.12±7.58 for T1DM and 18.80±5.47 for T2DM [Weinspach et al., 2013]. Individual data regarding the type of diabetes of the other studies were not recorded due to the range of age include children, adolescents or young adults [Arrieta Blanco et al., 2003; Bacic et al., 1989]. There isn't enough data for meta-analysis.

Is there any difference in the occurrence of dental caries among compensated and decompensated patients?

Nine studies approached for the difference of dental caries and periodontal disease between DM with different levels of glycemic control, considering compensated as good glycemic control state and decompensated as uncontrolled glycemic state [Collin et al., 1998; Commisso et al., 2011; Goyal et al., 2012; Lin, 1999; Malicka, and Kaczmarek, 2011; Malvania et al., 2017; Mohamed et al., 2013; Nimbal et al., 2016; Sharma et al., 2011]. The hypothesis of more caries when patients have uncontrolled glycemic control was confirmed, showing a relationship to the sugar intake as a common risk factor.

Six studies evaluated the glycemic index through glycosylated hemoglobin concentration (HbA1c) [Collin et al., 1998; Commisso et al., 2011; Malicka, and Kaczmarek, 2011; Malvania et al., 2016; Mohamed et al., 2013; Lin, 1999]. The value indicated as the limit to consider the DM individual as uncontrolled showed a variation between 9% [Collin et al., 1998; Lin, 1999] and 6% (7mmol/L) [Malvania et al., 2016]. Fasting

plasma glucose levels was also reported [Goyal et al., 2012; Sharma et al., 2011]. Goyal et al. applied fasting plasma glucose higher than 126mg/dl as a cuttoff for considering patients as uncontrolled. One paper did not distinguished the patients based on the glycemic levels (controlled or not) [Nimbal et al., 2016].

The minimum DMFT index detected in glycemic controlled patients was 0.62±1.01 [Malvania et al., 2017] and maximum was 22.03±7.29 [Malicka, and Kaczmarek, 2011]. The minimum DMFT index was 3.46±3.16 [Malvania et al., 2017] and maximum was 24.90±7.29 for uncontrolled DM patients [Malicka, and Kaczmarek, 2011]. The DFS index was also used and presented as mean 63.4±26.4 for the controlled patients compared to 53.3±38.0 for the uncontrolled DM patients [Lin, 1999]. Malicka (2011) displayed DMFS= 90.89±48.19 for the controlled and 112.4±43.75 for the uncontrolled DM patients [Malicka, and Kaczmarek, 2011].

There was a study that found a prevalence of 66.7% in uncontrolled DM patients [Collin et al., 1998]. Other two studies presented the value for both groups, one presenting 42.55% for controlled in contrast to 90.41% in uncontrolled DM patients [Malvania et al., 2017], and another presenting 16% in controlled and 48% in uncontrolled DM patients [Nimbal et al., 2016].

The prevalence of root caries between these groups was presented by another study, that showed 48.9% in controlled and 54.3% in uncontrolled DM patients [Mohamed et al., 2013].

Meta-analysis revealed that uncontrolled DM patients presented higher prevalence of dental caries in comparison to controlled ones (OR=6.75; 95% CI 3.65-12.50; $p<0.00001$; $I^2=34\%$) (Fig. 6), as well as a higher mean DMFT (MD= 2.61; 95% CI 1.14-4.08; $p=0.00005$; $I^2=75\%$) (Fig. 7).

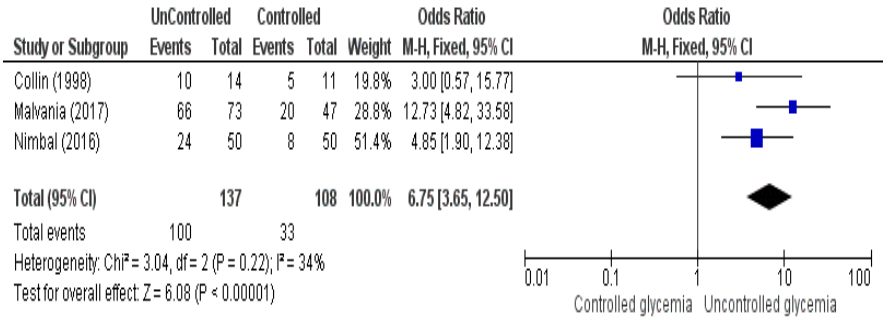

Fig 6. Forest plot generated by the meta-analysis of the prevalence of dental caries in controlled versus uncontrolled DM patients, assessed by Review Manager 5.3.

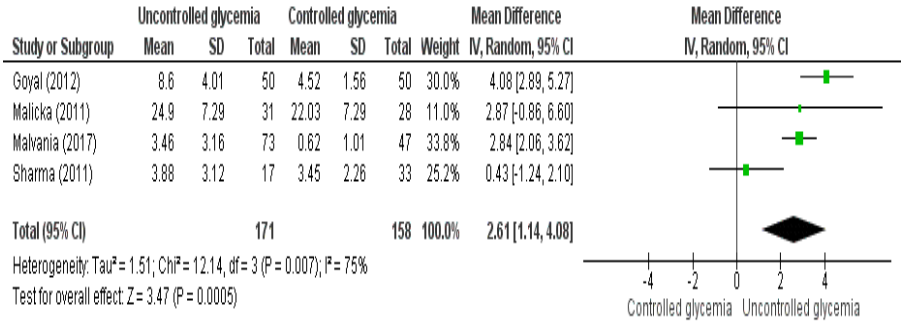

Fig 7. Forest plot generated by the meta-analysis of the DMFT in controlled versus uncontrolled DM patients, assessed by Review Manager 5.3.

Is there any correlation between periodontal diseases and dental caries in diabetics?

Eighteen studies performed an analysis of periodontal diseases in diabetics [Albrecht et al., 1988; Bharateesh et al., 2012; Cherry-Peppers, and Ship, 1993; Commisso et al., 2011; Hintao et al., 2007; Leung et al., 2008; Mohamed et al., 2013;

Nimbal et al., 2016; Ramana, and Rao, 2014; Sandberg et al., 2000; Seethalakshmi et al., 2016; Sharma et al., 2011; Soto, and Rodriguez, 2009; Sukminingrum et al., 2013; Tanriverdi et al., 2006; Tavares et al., 1991; Weinspach et al., 2013; Zielinski et al., 2002]. All studies observed higher prevalence or higher index of periodontal disease in DM in comparison with non-DM, except for one [Tavares et al., 1991]. The highest prevalence of generalized periodontitis observed among these studies was 98.1% in T2DM individuals [Hintao et al., 2007]. Regarding dental caries, the prevalence observed was 40% of root caries and 83.3% of coronary caries. Another study presented prevalence of periodontal diseases in diabetics of 92.6% [Bharateesh et al., 2012], showing 13.6% of dental caries prevalence in the same individuals. Other study found a prevalence of 91.30% of teeth mobility in T2DM, and equally high prevalence of dental caries (73.9%) (DMFT index = 13.52) [Sukminingrum et al., 2013]. This analysis showed no pattern of higher or lower caries prevalence related to presence of periodontitis in DM patients. Not enough data was applicable for a meta-analysis investigation.

DISCUSSÃO

DM is a chronic disease characterized by increasing blood glucose levels. Either hyperglycemia caused by T1DM or T2DM can lead to complications in several parts of the body [World Health Organization, 2016]. These complications mostly occur when high levels of glucose are not well controlled. In the oral cavity, patients with DM are more susceptible to have some diseases, such as periodontal disease. This systematic review and meta-analysis showed that patients with DM have more tooth affected by coronal and root caries when compared to non-DM,

and related to the level of glycemic control, patients with decompensated DM have more caries when compared to compensated ones. A final meta-analysis also showed higher prevalence of root caries in DM type 2 in comparison with no-DM patients. These findings may contribute to the field of oral health of DM patients, showing that not only the periodontal diseases but also caries should be analysed in patients with DM. Although most studies present low risk of bias, some studies does not present statistical analysis [Albrecht et al., 1988; Commisso et al., 2011; Sandberg et al., 2000] or did not isolated the numerical values by age for all outcomes, including a range of age that does not meet the interests of this systematic review [Arrieta Blanco et al., 2003; Bacic et al., 1989]. These studies usually have convenience samples, getting demand from hospitals and, therefore, may not present external validity.

We proposed to answer four PECOS questions in this study, which are discussed below.

ARE DIABETICS MORE PREDISPOSED TO HAVE DENTAL CARIES THAN NON-DM?

The mechanisms that support more caries in DM patients are not fully understood. It is important to point out that T2DM and caries have high levels of sugar intake as a common risk factor. It is also speculated that the reduction of the salivary flow, caused by polypharmacy or by the disease *per se*, increases the risk for dental caries in DM patients. Seethalakshmi et al. showed that DM patients had lower salivary pH [Seethalakshmi et al., 2016] and other differences in the composition of saliva are also expected. No statistically significant difference was observed in the prevalence of dental caries between DM and non-DM, however, the DMFT was higher in DM patients (fig. 3). Prevalence seems to have more disagreement than DMFT, which measure the extension of caries due to the history of the disease.

Overall, articles do not investigate the diet of the DM individuals, and that is probably why so many different outcomes and results can be observed in order to answer this question.

IS THERE ANY DIFFERENCE IN THE OCCURRENCE OF DENTAL CARIES AMONG PATIENTS WITH DM TYPE 1 AND DM TYPE 2?

Once DM is caused by a low or no insulin production via pancreas, the disease is known as type 1 DM. On the other hand, if this high glucose level is caused by incorrect use of insulin through the organism, it is a case of type 2 DM. The lifestyle of individuals with T2DM is considered as critical risk factors [Weinspach et al., 2013]. The results of this systematic review showed that individuals presenting T2DM presented higher DMFT than T1DM ones. Higher sugar intake is considered a common risk factor related to Dm and caries disease. T1DM individuals have multifactorial causes and it usually affects people of young age, the DM preventing them from having access to a diet rich in fermentable carbohydrates. On the other hand, T2DM is directly related to fewer risk factors, being high carbohydrate intake one of them. It is also known as the only crucial factor for the initiation of dental caries [Sheiham, and James, 2015]. From decades, the relationship between dental caries and the high sugar consumption and frequency was demonstrated [Gustafsson et al., 1953]. The results of the present study further support the idea that sugar restriction is important to the control of dental caries and also that caries disease can be considered an important oral sign of uncontrolled diabetes.

IS THERE ANY DIFFERENCE IN THE OCCURRENCE OF DENTAL CARIES BETWEEN COMPENSATED AND DECOMPENSATED PATIENTS?

The level of glycemic control can be measured with fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c). Even though FPG can be utilized for diagnostic of diabetes [Hong

et al., 2016], it can also be applied to evaluate the level of glycemic control of DM individuals. On the other hand, HbA1c can acquire, a more representative mean daily or long-term glycemic control than FPG, probably because of the glucose changing levels in HbA1c occur later than changes in FPG [Dekker et al., 2007]. In this review, two studies utilized FPG as a tool for evaluating of the glycemic control for DM individuals, and only one of those presented the numerical value adopted as limit (126mg/dl in medicated diabetic individuals) [Goyal et al., 2012]. HbA1c was more used, but a high diversity of the value imposed as the limit was observed (6% to 9%) which could modify the results.

Patients with DM are obligated to maintain a specific diet and to eat at regular hours and small quantities [Malicka, and Kaczmarek, 2011], which can modify the prevalence and caries index of this individuals when compared with those who do not maintain a medical and nutritional monitoring. In the present study, these patients had fewer caries than uncontrolled patients.

The knowledge of dental caries as a dysbiosis in the resident microbiota of patients with high sugar consumption [Marsh, 1994] could explain this outcome. Individuals with DM that maintain medical and nutritional monitoring probably intake fewer carbohydrates and, therefore, have a lower prevalence of dental caries. Likewise, the higher the blood glucose level, the lower the saliva secretion [Chávez et al., 2001]. It can significantly impact the risk of caries, since a decrease in the salivary flow tends to promote the growth of acidogenic microorganisms such as *mutans streptococci* [Miko et al., 2010]. With the decrease of the salivary flow, the concentration of mucin and glucose may increase [Negrato, and Tarzia, 2010]. It could also predispose the environment to dental caries. We believe that studies that did not find statistical differences between DM and non-DM could be the reflex of not distinguishing patients according to the level of glycemic control.

IS THERE A CORRELATION BETWEEN PERIODONTAL DISEASES AND DENTAL CARIES IN DIABETICS?

It is clear the correlation between periodontal disease and DM, and this study confirms the correlation between dental caries and DM. Since DM patients with severe periodontitis possess a proteolytic oral microbiota, the hypothesis is that these patients do not present dental caries. More studies are necessary in order to analyze if patients with DM and severe periodontal disease could present less dental caries. A study showed high prevalence of dental caries and periodontal disease as well [Mohamed et al., 2013], but no correlation could be performed. It is important to point out that the missing component of the DMFT index (more frequently used) can mislead the reality of cause of the tooth loss, that can be either related to dental caries or periodontal disease.

The diversity of caries index, and some without the missing component (DFS and DFT), unlabeled comparative for the achievement of the meta-analysis of this segment. For example, instead of using the DFS index, there was an article that used the proportion of DFS [Tavares et al., 1991], making it impossible to compare with another study that did use the DFS index [Lin, 1999]. An index that evaluates caries activity, such as the Nyvad index, would be more likely to demonstrate a real correlation between dental caries caused by DM.

LIMITAÇÕES

1. The age limitation observed in our study may have hampered the answer to the second focused question approaching the difference in the occurrence of dental caries among type 1 DM and type 2 DM.

2. Regarding the periodontal disease reporting throughout the studies, different case-definitions and clinical assessment for periodontal disease were used, so that the association between periodontal disease and dental caries occurrence was inconclusive.

3. Despite our endeavors to include studies with higher quality evidence, only cross-sectional studies could be included. Therefore, the odds ratio could have overestimated our results, as well as the risk of bias.

CONCLUSÃO

1. DM patients are more susceptible to have higher DMFT than non-DM individuals, but they are capable to have a lower DMFT relying on glycemic control. Also, T2DM individuals present more root caries than non-DM individuals.

2. T2DM patients may present more dental caries than T1DM individuals as a consequence of sharing dietary risk factors with dental caries.

3. Uncontrolled DM patients are more predisposed to have dental caries when compared with controlled DM individuals, probably because of the lack of nutritional and medical monitoring.

4. Not enough quality data was available to confirm a correlation between dental caries and periodontal disease in DM patients.

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None.

4. Author Contributions
Author contributions to this work are as follows: AKAL, JAS, CMS and NDT conceived and designed the study; AKAL and JAS performed the searches; AKAL, JAS, AAL, CMS, and NDT quality-checked, imputed, and processed the data; AKAL and AAL performed the statistical analysis; all authors interpreted the results and wrote, revised, and approved the manuscript.

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APÊNDICE

APÊNDICE 1 – SEARCH STRATEGIES ACCORDING TO DIFFERENT DATABASES, PERFORMED IN JANUARY 2019

Pubmed	#1 "dental caries"[MeSH Terms] OR "dental caries" OR "Dental Decay" OR "Carious Dentin" OR "Carious Dentins" OR "teeth carie" OR "teeth caries" OR "tooth caries" OR "teeth decay" OR "tooth decay" OR "dental decay" OR "Root Caries"[Mesh] OR "Cervical Caries";#2 ("Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "Diabetes Mellitus, Type 1"[Mesh] OR "Insulin Dependent Diabetes Mellitus 1" OR "Type 1 Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Type 2 Diabetes" OR "Diabetes Mellitus, Type 2"[Mesh]) OR ("glycemic index"[MeSH Terms] OR "Glycemic Control" OR "Blood Glucose"[Mesh] OR "glucose control" OR "Blood Glucose" OR "Blood Glucose Monitoring" OR "blood glucose control" OR "blood sugar");#1 AND #2
LILACS	#1 "dental caries" OR "dental decay" OR "carious dentin" OR "carious dentins" OR "teeth carie" OR "teeth caries" OR "tooth caries" OR "teeth decay" OR "tooth decay" OR "dental decay" OR "cervical caries" OR "Caries Dental" OR "Caries Dentales" OR "Manchas Blancas Dentales" OR "manchas blancas" OR "Cárie Dentária" OR "Cáries Dentárias" OR "Dente Cariado" OR "manchas (hipocalcificadas) brancas dentárias" OR "Manchas Brancas" OR "Caries Cervical" OR "Cárie radicular" OR "Caries radicular" OR "cárie cervical"; #2 "Diabetes Mellitus" OR "Insulin Dependent Diabetes Mellitus 1" OR "Type 1 Diabetes

	Mellitus" OR "Type 2 Diabetes Mellitus" OR "Type 2 Diabetes" OR "Diabete" OR "Diabete Melito" OR "Diabetes" OR "Diabetes Melito" OR "Diabetes Mellitus Tipo 1" OR "Diabetes Mellitus Inestable" OR "Diabetes Mellitus Insulinodependiente" OR "Diabetes Mellitus Insulino-Dependiente" OR "Diabetes Melitus Juvenil Inicial" OR "Diabetes Mellitus com Propensión a la Cetosis" OR "Dmid" OR "Diabetes Autoimmune" OR "Diabetes Mellitus de Inicio Súbito" OR "Diabetes Mellitus Instável" OR "Diabetes Mellitus Insulinodependente" OR "Diabetes Mellitus Insulino-dependente" OR "Diabetes Mellitus Dependente de Insulina" OR "Diabetes Mellitus de Início na Juventude" OR "Diabetes Mellitus com tendência à cetose" OR "Diabetes Autoimune" OR "Diabetes Mellitus de Início Súbito" OR "Diabetes Mellitus Tipo 2" OR "Diabetes Mellitus de Inicio Adulto" OR "Diabetes Mellitus resistente a la Cetosis" OR "Diabetes Mellitus no Insulinodependiente" OR "Diabetes Mellitus no Insulino-dependiente" OR "Diabetes Mellitus Estable" OR "DMNID" OR "Diabetes Mellitus de Inicio en la Madurez" OR "DMIM" OR "Diabetes Mellitus de Inicio Lento" OR "Diabetes Mellitus de Início no Adulto" OR "Diabetes Mellitus resistente a cetose" OR "Diabetes Mellitus não insulino-dependente" OR "Diabetes Mellitus não insulinodependente" OR "Diabetes Mellituso não dependente de insulina" OR "Diabetes Mellitus estável" OR "MODY" OR "Diabetes Mellitus de Início na maturidade" OR "Diabetes Mellitus de Início gradativo" OR "Glycemic index" OR "glycemic Control" OR "glucose control" OR "blood glucose" OR "blood glucose monitoring"

	OR "blood glucose control" OR "blood sugar" OR "Índice Glucémico" OR "índice Glicêmico" OR "Índice de Glucemia" OR "Índice de Glicemia" OR "Glucemia" OR "Glicemia" OR "Azúcar de la sangre" OR "Azúcar en la Sangre" OR "Glucosa de la sangre" OR "glucosa en la sangre" OR "glucosa sanguínea" OR "Açúcar do sangue" OR "Açúcar no sangue" OR "Glucemia" OR "Glucose do sangue" OR "Glucose no sangue" OR "Glucose sanguínea";#1 AND #2
Web of Science	(TS=((”Diabetes Mellitus” OR ”Insulin Dependent Diabetes Mellitus 1” OR ”Type 1 Diabetes Mellitus” OR ”Type 2 Diabetes Mellitus” OR ”Type 2 Diabetes”) OR ”glycemic index” OR ”Glycemic Control” OR ”glucose control” OR ”Blood Glucose” OR ”Blood Glucose Monitoring” OR ”blood glucose control” OR ”blood sugar”) AND (”dental caries” OR ”Dental Decay” OR ”Carious Dentin” OR ”Carious Dentins” OR ”teeth carie” OR ”teeth caries” OR ”tooth caries” OR ”teeth decay” OR ”tooth decay” OR ”dental decay” OR ”Cervical Caries”))
Scopus	(TITLE-ABS-KEY((”Diabetes Mellitus” OR ”Insulin Dependent Diabetes Mellitus 1” OR ”Type 1 Diabetes Mellitus” OR ”Type 2 Diabetes Mellitus” OR ”Type 2 Diabetes”) OR ”glycemic index” OR ”Glycemic Control” OR ”glucose control” OR ”Blood Glucose” OR ”Blood Glucose Monitoring” OR ”blood glucose control” OR ”blood sugar”) AND (”dental caries” OR ”Dental Decay” OR ”Carious Dentin” OR ”Carious Dentins” OR ”teeth

	carie" OR "teeth caries" OR "tooth caries" OR "teeth decay" OR "tooth decay" OR "dental decay" OR "Cervical Caries"))
Cochrane	#1 [mh "diabetes mellitus"] or "Diabetes Mellitus" or "Diabetes Mellitus, Type 1" or "Diabetes Mellitus, Type 2" or "Glycemic Control" or "glucose control" or "Blood Glucose" or "Blood Glucose Monitoring" or "blood glucose control" or "blood sugar"; #2 [mh "root caries"] or "Caries, Root" or "Caries, Cervical" or "Cary, Cervical" or "Cervical Cary" or "Cervical Caries" or "Carious Dentin" or "Carious Dentins" or "Dentin, Carious" or "Dentins, Carious" or "Dental Decay" or [mh "dental caries"] or "Caries, Dental" or "Decay, Dental"; #1 AND #2
Livivo	TI=((("Diabetes Mellitus" OR "Insulin Dependent Diabetes Mellitus 1" OR "Type 1 Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Type 2 Diabetes") OR "glycemic index" OR "Glycemic Control" OR "glucose control" OR "Blood Glucose" OR "Blood Glucose Monitoring" OR "blood glucose control" OR "blood sugar") AND ("dental caries" OR "Dental Decay" OR "Carious Dentin" OR "Carious Dentins" OR "teeth carie" OR "teeth caries" OR "tooth caries" OR "teeth decay" OR "tooth decay" OR "dental decay" OR "Cervical Caries"))
Google Scholar Web Search	allintitle: diabetes mellitus dental caries
Proquest	#1"dental caries" OR "Dental Decay" OR "Carious Dentin" OR "Carious Dentins" OR "teeth carie" OR "teeth caries" OR "tooth caries" OR "teeth decay" OR "tooth decay" OR "dental decay" OR "Root Caries" OR "Cervical Caries"; #2 ("Diabetes Mellitus"

	OR "Diabetes Mellitus, Type 1" OR "Insulin Dependent Diabetes Mellitus 1" OR "Type 1 Diabetes Mellitus" OR "Type 2 Diabetes Mellitus" OR "Type 2 Diabetes" OR "Diabetes Mellitus, Type 2") OR ("glycemic index" OR "Glycemic Control" OR "Blood Glucose" OR "glucose control" OR "Blood Glucose" OR "Blood Glucose Monitoring" OR "blood glucose control" OR "blood sugar"); AB=(#1 AND #2)
Open Grey	Dental Caries, Diabetes

APÊNDICE 2 – EXCLUDED ARTICLES AND REASONS FOR EXCLUSION (N=82)

Author, year	**Reason for exclusion**
Albrecht et al. 1991	9
Albrecht et al. 1991	9
Albrecht et al., 1987.	2
Almusawi et al., 2018.	1
Amalia et al., 2018.	1
Andrades et al., 2009.	1
Bahru et al. 1992	9
Bajaj et al., 2012.	3
Bakhshandeh et al., 2007.	1
Barrios M; Ceballos NV, 2010.	3
Barylo et al., 2018.	3
Ben Mami Ben Milled et al. 1998	9
Ben-Aryeh et al., 1993.	1
Bissong et al., 2015.	1
Boitor et al., 2016.	5
Buysschaert et al., 2018.	1
Chomicz et al., 2004.	4
Ciglar et al., 1991.	1
Ciglar et al., 2002.	1
Delmés et al., 2014.	3
Díaz-Romero et al., 2005.	2

Elovikova et al. 1989	9
Falk et al., 1989.	1
Garcia et al., 2016.	1
Ghorbani et al., 2018.	6
Gisbert Sellés et al. 1998	9
Goodson et al., 2017.	1
Gupta et al, 2014.	1
Hegde et al., 2014.	3
Hernández-Laguna et al. 2006	9
Hintao et al., 2007	8
Ilguy et al., 2007.	1
Jawed et al., 2011.	1
Jawed et al., 2012.	5
Jones et al., 1992.	1
Kakoei et al., 2015.	1
Kampoo et al., 2014.	1
Kanjirath et al., 2011.	1
Karjalainen, 2000	1
Kirk et al. 1991	9
Kneckt et al., 2000.	1
Koçöztürk et al., 2012.	1
Kogawa et al., 2016.	1
Lalla et al., 2004.	1
Latti et al., 2018.	1

Lima et al., 2017.	3
Lima-Aragão et al., 2016.	1
Lopez-Perez et al., 1996.	2
Machado et al., 2017.	1
Marlow et al., 2011.	3
Masudi et al. 2011	9
Miralles et al., 2002.	1
Miralles et al., 2006.	1
Moore et al., 2000.	3
Moore et al., 2001.	1
Motegi et al. 1975	9
Na et al., 2011.	7
Nunchievici et al. 2009	9
Ogawa, 1994	7
Patiño et al., 2008.	1
Peck et al., 2006.	3
Pohjamo et al. 1991	9
Pohjamo et al., 1995.	1
Punta et al., 2003.	3
Puttaswamy et al., 2017.	1
Ramli et al., 2016.	1
Reddy et al., 2018.	1
Robertson, 2011	1
Sensorn et al., 2012.	1

Shoaib et al., 2016.	1
Singh et al., 2016.	1
Song et al., 2017.	1
Soni et al., 2014.	3
Stojanovi et al., 2010.	7
Sukminingrum et al., 2013.	1
Suryaprabha et al., 2014.	5
Syrjälä et al., 2003.	1
Tenovuo et al., 1986.	1
Vaziri et al., 2009.	1
Willersharusen-Zonnchen et al. 1989	9
Yonekura et al., 2017.	1
Ziolkowska et al. 2006	9

1. Sample disclosed patients under 35 years-old (n=45); 2. Patients with gestational diabetes(n=3); 3. No negative control (n=11); 4. No dental caries index (n=1); 5. Presence of caries as inclusion criteria (n=3); 6. Salivary flow as the single outcome (n=1); 7. Studies published in languages not derived from Latin (n=3); 8. Duplicated population (n=1); 9. Not available (n=14).

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APÊNDICE 3 – RISK OF BIAS OF PRIMARY STUDIES ASSESSED BY META-ANALYSIS OF STATISTICS ASSESSMENT AND REVIEW INSTRUMENT (MASTARI1) CRITICAL APPRAISAL TOOLS.

Risk of Bias was categorized as **High** when the study reaches up to 49% score "yes", **Moderate** when the study reached 50% to 69% score "yes", and **Low** when the study reached more than 70% score "yes".

Question	*Answer**													
	Albrecht et al. 1988	Arrieta Blanco et al. 2003	Bacic et al. 1989	Bharateesh et al. 2012	Cherry-Peppers and Ship 1993	Collin et al. 1998	Comisso et al. 2011	Goyal et al. 2012	Hintao et al. 2007	Iqbal et al. 2011	Leung et al. 2008	Lin et al. 1999	Malicka and Kaczmarek 2011	Malvania et al. 2017
1. Were the criteria for inclusion in the sample clearly defined?	N	Y	N	N	N	Y	Y	N	Y	Y	Y	Y	N	Y
2. Were the study subjects and the setting described in detail?	N	Y	Y	N	N	Y	Y	N	Y	N	Y	Y	N	N
3. Was the exposure measured in a valid and reliable way?	U	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	U	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Were confounding factors identified?	N	N	N	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y
6. Were strategies to	N	N	N	N	N	Y	N	N	Y	N	Y	N	Y	N

deal with confounding factores stated?														
7. Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y
8. Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
% yes/risk	28/H	85/L	71/L	28/H	62/M	100/L	75/L	57/M	100/L	71/L	100/L	87/L	75/L	75/L

*NA=Not Applicable, Y=Yes, N=No, U=Unclear

Question	*Answer**												
	Mohamed et al. 2013	Nimbal et al. 2016	Ramana et al. 2014	Sandberg et al. 2000	Seethalakshmi et al. 2016	Sharma et al. 2011	Soto and Rodriguez 2009	Sukminingrum et al. 2013	Tanriverdi et al. 2006	Tavares et al. 1991	Vaziri et al. 2009	Weinspach et al. 2013	Zielinski et al. 2012
1. Were the criteria for inclusion in the sample clearly defined?	Y	N	N	N	Y	N	N	Y	N	Y	N	N	N
2. Were the study subjects and the setting described in detail?	Y	N	N	Y	N	N	Y	N	N	Y	Y	N	Y
3. Was the exposure measured in a valid and reliable way?	Y	U	U	Y	Y	Y	Y	Y	U	Y	U	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	Y	U	U	U	Y	U	U	Y	U	Y	U	Y	Y
5. Were confounding factors	Y	N	Y	Y	Y	Y	Y	N	U	Y	Y	Y	Y

identified?													
6. Were strategies to deal with confounding factores stated?	Y	N	Y	Y	N	Y	Y	N	U	Y	Y	Y	Y
7. Were the outcomes measured in a valid and reliable way?	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y
8. Was appropriate statistical analysis used?	Y	N	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y
% yes/risk	100/L	0/H	50/M	75/L	75/L	62/M	75/L	71/L	0/H	100/L	62/M	75/L	87/L

*NA=Not Applicable, Y=Yes, N=No, U=Unclear

[1]Meta Analysis of Statistics Assessment and Review Instrument (MAStARI). Joanna Briggs Institute Reviewers Manual. Australia: The Joanna Briggs Institute, 2014.

ANEXOS

NORMAS DA REVISTA

Revista: Caries Research

Systematic Reviews are literature reviews focused on research question that synthesizes all high-quality research evidence relevant to that question. Systematic reviews should be presented in the Introduction, Methods, Results, Discussion format. The subject must be clearly defined. The objective of Systematic Review should be to arrive at an evidence-based conclusion. The Methods section should give a clear indication of the literature search strategy, data extraction procedure, grading of evidence, and kind of analysis used. We strongly encourage authors to comply with the Preferred reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Title Page

The first page should contain a short and concise title plus a running head of no more than 80 characters. Abbreviations should be avoided.

Below the title, list all the authors' names as outlined in the article sample, which can be downloaded under Article Types. Each listed author must have an affiliation, which comprises the department, university, or organization and its location, city, state/province (if applicable), and country.

Place the full postal address of the corresponding author at the bottom of the first page, including at least one telephone number and e-mail address.

Keywords relevant to the article should be listed below the corresponding author information.

1. Abstract

The abstract should summarize the main points and reflect the content of an article. It should be written in a clear and simple way and be unstructured, set in 1 paragraph. Abbreviations used in the main text may be introduced and used. Use neither bibliographic references nor references to figures or tables in the Abstract. For the accepted length (word count), if applicable, consult the specific Author Guidelines.

2. Introduction

The Introduction should provide a summary of the background to the relevant field of research and the specific problems addressed and should state the hypotheses being explored as well as the main goal(s) of the study. Conclusions or findings should not appear in the Introduction.

3. Materials and Methods

The Materials and Methods section should clearly list all inclusion and exclusion criteria, methods of research, and variables evaluated and should state how outcomes were assessed. All terms should be adequately defined and statistical information should be sufficiently detailed so that a study can be repeated. We strongly encourage authors to comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

4. Results

The Results section should describe the most important findings of the study, analysis, or experiment. The most important results should be indicated, and relevant trends and patterns should be described.

5. Discussion/Conclusion

The Discussion/Conclusion should provide an evaluation of the results. There should be a clear discussion of the implications,

significance, and novelty of the results presented and whether the data support or contradict previous studies.

6. Appendix

Appendices may contain complementary information that was not integrated into the main text (tables, figures, and/or formulas). They may include references, which should be listed in the general reference list of the manuscript. However, tables and figures should be numbered separately.

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Supplementary Material directly relevant but not essential to the conclusions of the paper may be submitted in separate files. Further information on Supplementary Material can be found in the Guidelines for Authors.

8. Statements

All papers must contain the following statements after the main body of the text and before the reference list:

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In the Acknowledgement section, authors must include individuals and organizations that have made substantive contributions to the research or the manuscript. The exception is where funding was provided, which should be included in Funding Sources. Please refer to the Guidelines issued by the ICMJE to determine non-author contributors that should be included in the Acknowledgement section.

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Subjects (or their parents or guardians) have given their written informed consent.

The study protocol has been approved by the research institute's committee on human research.

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If the paper is not directly related to human or animal research, please include the statement "The authors have no ethical conflicts to disclose."

8.3. Disclosure Statement

Any financial interests (stocks, patents, employment, honoraria, or royalties) or nonfinancial relationships (political, personal, or professional) that may be interpreted as having influenced the writing of the manuscript must be declared in the Disclosure Statement.

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Examples

Papers published in journals:

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Chen C, Hu Z. ApoE polymorphisms and the risk of different subtypes of stroke in the Chinese population: a comprehensive meta-analysis. Cerebrovasc Dis. DOI: 10.1159/000442678.

Monographs:

Matthews DE, Farewell VT. Using and understanding medical statistics. 5th ed, revised. Basel: Karger; 2015.

Edited Books:

Cohen SR, Gardner TW. Diabetic retinopathy and diabetic macular edema. In: Nguyen QD, Rodrigues EB, Farah ME, Mieler WF, Do DV, editors. Retinal pharmacotherapeutics. Dev Ophthalmol. Basel: Karger; 2016. Vol. 55; p. 137–46.

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Karger Publishers [Internet]. Basel: Transforming Vesalius: The 16th-Century Scientific Revolution Brought to Life for the 21st Century [cited 2013 Feb 4]. Available from: http://www.vesaliusfabrica.com/en/new-fabrica.html.

10. Figure Legends

Fig. 1. Legend text.

Fig. 2. Legend text.

Please note that the figures themselves and all tables should be uploaded separately. They do not constitute a part of the manuscript file.

In-Text Citation

References in the text should be made up of the author(s)'s name(s) (up to 2 authors) followed by the year of publication. When there are more than 2 authors, the first author's name and 'et al.' should be used. When references are made to more than 1 paper by the same author, published in the same year, they should be designated as a, b, c, etc.

The reference list should be arranged alphabetically, then chronologically. In-text citations should always be ordered chronologically, e.g., [Rendulic et al., 2004; Jurkevitch, 2006].

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