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ORIGINAL ARTICLE

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Is there a difference in the oxidative stress levels between type 2 diabetic individuals with and without periodontitis? Systematic review

Existe diferença nos níveis de estresse oxidativo entre indivíduos com diabetes tipo 2 com e sem periodontite? Revisão Sistemática

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ABSTRACT

Objective: The authors' aim in this systematic review was to verify the scientific evidence for difference of oxidative stress biomarkers in individuals with type 2 diabetes mellitus with and without periodontitis. **Material and Methods:** Observational studies, baseline data of prospective and interventional studies were searched on the following databases: Virtual Health Library, Web of Science, PubMed, Embase, Scopus, Cochrane Library, Opengrey and Google Scholar. The electronic search was performed in June 01, 2020 until May 17, 2024 with alerts until June 01, 2024. The quality assessment and the certainty of the evidence of the included studies were evaluated through Fowkes and Fulton's checklist and GRADEpro Guideline Development Tool. **Results:** Of 988 relevant articles, the authors included 9 studies for the final analysis. Among those studies, 4 cross-sectional, 3 case-control, and 2 interventional studies were included. The analysis of non-randomized clinical trials properly reported most of the criteria analyzed in Summary questions (Bias, Confounding and Chance) as present in 3 studies. In six studies confounding factors were no detected. Due to the variation in the study results and clinical/methodological heterogeneity, a meta-analysis was not appropriate. The studies reported high concentrations of oxidizing agents and low antioxidants levels in individuals with type 2 diabetes mellitus and periodontitis when compared to with no periodontitis. **Conclusion:** Considering the few studies found, the methodological flaws, few markers studied and absence homogeneity in the evaluation of redox balance markers, as well as, the very low certainty of the evidence among included studies, it was not possible to determine whether there are or not differences in the oxidative stress levels in individuals with type 2 diabetes with and without periodontitis, and therefore, further prospective observational and interventional studies are recommended.

KEYWORDS

Diabetes mellitus non-insulin dependent; Periodontitis; Periodontal diseases; Oxidative stress; Antioxidants; Free radicals.

RESUMO

Objetivo: O objetivo dos autores nesta revisão sistemática foi verificar a evidência científica para a diferença de biomarcadores de estresse oxidativo em indivíduos com diabetes mellitus tipo 2 com e sem periodontite. **Material e Métodos:** estudos observacionais, dados de base de estudos prospectivos e intervencionistas foram pesquisados nas seguintes bases de dados: Biblioteca Virtual em Saúde, Web of Science, PubMed, Embase, Scopus, Cochrane Library, Opengrey e Google Scholar. A busca eletrônica foi realizada no período de 01 de junho de 2020 até 17 de maio de 2024, com alertas até 01 de junho de 2024. A avaliação da qualidade e a certeza da evidência dos estudos incluídos foi realizada através da lista de checagem Fowkes and Fulton's e da Ferramenta de desenvolvimento de diretrizes GRADEpro. **Resultados:** Dos 988 artigos relevantes, os autores incluíram 9 estudos para a análise final. Entre esses estudos, foram incluídos 4 estudos transversais, 3 de caso-controle e 2 de intervenção. A análise dos ensaios clínicos não randomizados relatou adequadamente a maioria dos critérios analisados nas questões resumo (Viés, Confundimento e Resultados ao caso) presentes em 3 estudos. Fatores de confusão não foram detectados em seis estudos. Devido à variação nos resultados do estudo e à heterogeneidade clínica/metodológica, não foi possível realizar uma meta-análise. Os estudos relataram altas concentrações de agentes oxidantes e baixos níveis de antioxidantes em indivíduos com diabetes mellitus tipo 2 e periodontite quando comparados a indivíduos sem periodontite. **Conclusão:** Considerando os poucos estudos encontrados, as falhas metodológicas, poucos marcadores estudados e ausência de homogeneidade na avaliação dos marcadores do balanço redox, bem como a baixíssima certeza da evidência entre os estudos incluídos, não foi possível determinar se há diferenças nos níveis de estresse oxidativo em indivíduos com diabetes tipo 2 associado e não à periodontite e, portanto, outras observações prospectivas e estudos de intervenção são recomendados.

PALAVRAS-CHAVE

Diabetes mellitus não insulino-dependente; Periodontite; Doenças periodontais; Estresse oxidativo; Antioxidantes; Radicais livres.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a significant risk factor for periodontitis and glycemic imbalance is the determining factor for bone loss that increases the risk and severity of periodontal disease [1]. The altered immunological response in T2DM influences periodontal diseases by altering the inflammatory responses, and periodontal wound healing. Additionally, it promotes the accumulation of advanced glycation end products (AGEs) that induce high levels of pro-inflammatory cytokines, and causes oxidative stress (OS) [2].

Oxidative stress occurs when, due to a higher concentration of reactive oxygen species (ROS) or a decrease in antioxidant capacity, there is a lack of homeostasis [3]. This can occur in several systemic conditions. According to the literature, the tissue destruction that occurs in periodontal diseases can be caused by the high production of ROS by inflammatory cells, leading to oxidative stress [4,5].

The increase in ROS of local and systemic forms found in these pathologies can significantly affect the functioning pattern of several tissues and is closely related to the comorbidities associated with T2DM [4-6]. The increase in oxidative damage [7,8] and lower levels of antioxidants [9,10] were found in patients with periodontitis compared to periodontally healthy individuals. The periodontal inflammatory condition can be explained by the local and systemic concentrations of some OS biomarkers [8].

Periodontitis and T2DM are diseases with characteristics of chronic inflammation and a permanent increase in OS [1,8]. However, no systematic review has assessed the level of OS biomarkers in type 2 diabetic individuals with and without periodontitis. Therefore, the aim of this systematic review was to answer the following question: Is there a difference in the level of OS in individuals with T2DM with and without periodontitis?

METHODS

Registration and protocol

This review was registered in the PROSPERO database under the protocol (https://www.crd.york.ac.uk/PROSPERO) ID: CRD42020190010, on August 7th, 2020 and was reported in accordance with the PRISMA checklist of systematic reviews and meta-analyses [11].

Eligibility criteria

The eligibility criteria were defined based on the PECO research strategy as follows:

1. Participants (P): T2DM individuals of both genders and without distinction in age and ethnicity. Studies including individuals with the following conditions were excluded: chronic kidney disease, malignant neoplasms, AIDS (Acquired Immunodeficiency Syndrome), pregnant or lactating women, immunosuppression by medication, autoimmune diseases, evidence of other systemic diseases ASA III and IV, smokers or former-smokers for less than twenty years, users of orthodontic appliances, history of use of steroidal or non-steroidal anti-inflammatory drugs in the last three months prior to the study and during research, use of antibiotics in the last six months prior to the study and during research, as well as individuals who underwent supra and subgingival scaling and/or periodontal surgery in the last 6 months before the investigation.
2. Exposure (E): Presence of Periodontitis. Selection criteria established: Probing depth (PD) ≥ 4mm, Clinical attachment level (CAL) ≥ 4mm, presence of biofilm and bleeding on probing (BOP) > 10%. The examination should be performed by calibrated examiners, performing a full-mouth periodontal examination (six sites per tooth), using the North Carolina periodontal probe.
3. Comparison (C): Absence of Periodontitis. Selection criteria established: PD ≤ 3mm, CAL ≤ 3mm, little or no biofilm, and BOP <10%. The examination should be performed by one or more calibrated examiners, performing a full-mouth periodontal examination (six sites per tooth), using the North Carolina periodontal probe.
4. Outcome (O): OS levels for different parameters, such as AGEs, calcium, catalase (CAT), glutathione reductase (GRd), iron, magnesium, malondialdehyde (MDA), nitric oxide (NO), oxidative stress index (OSI), protein carbonyl (Protein CO), small molecular antioxidant capacity (SMAC), superoxide dismutase (SOD), total antioxidant capacity (TAC), total oxidant status (TOS), vitamin C, zinc. If the outcomes of interest were not measured or not reported the studies were considered ineligible.

Information sources

A systematic search of the literature was conducted on the following electronic databases: MEDLINE using the PubMed, Scopus, Embase, Web of Science, Cochrane Library and Virtual Health Library (VHL). Other sources were consulted through OpenGrey and Google Scholar. The electronic search was initially performed in June 2020, and database alerts with the search strategy were created in each database and were set to retrieve newly published articles until May 17, 2024.

Literature search strategy

The search strategy included Medical Subject Headings (MeSH) terms, entry terms, free terms and keywords related to the aim of this review. No restrictions were placed on publication date or language. The strategy was developed using the boolean operators AND/OR, Medical Subject Headings (MeSH) terms, keywords, and other free terms related to "Diabetes mellitus, non-insulin dependent"; "Periodontitis, Periodontal diseases"; and "Oxidative stress, Antioxidants, Free radicals, Oxidants". The strategy was first idealized for Pubmed search engine use and then, adapted to each database according to their syntaxes rules. Specific search strategies were developed for each database (Appendix 1) with no restrictions on language or date. In addition, filters regarding VHL (virtual health library) database to LILACS and BBO collections were applied. A manual search was carried out among the selected articles. Experts in the field were identified in the Scopus database by the "Analyze results tool" and contacted for ongoing studies or unpublished results regarding the focused question, using e-mail contact for up to five attempts. The search strategy was organized and carried out by an expert librarian (D.M.).

Articles from Google Scholar covered the first 100 matches and were then manually processed to check if possible eligible papers were missed from the main database search engines. When necessary, articles published in languages other than English, Spanish, and Portuguese

were translated using the Google® Translate Tool [12].

Selection process

Observational studies and baseline data of prospective/interventional studies, with the variables of interest, were included. Reviews, case reports, case series, expert opinions, and animal studies were excluded.

The retrieved articles were exported to Endnote® Web [13] to list, organize and remove duplicates. Authors and co-authors of studies that were not retrieved in the full text were contacted by e-mail up to five attempts, from June 2020 to May 17, 2024.

All titles, abstracts, and full-text reading of the articles were independently analyzed by two reviewers (W.J.M.L. and C.C.M.) to determine whether they met the eligibility criteria. Whenever differences occurred between them, a consensus should be reached. When a study of interest had no abstract available, the study had its full text assessed for eligibility decision. At this stage, articles that did not meet the eligibility criteria were excluded. Next, selected articles were read in full. If a study had a sample overlapping with other studies and the same methodology criteria assessed, the least complete study was excluded. Whenever the two reviewers were unsure about the inclusion/exclusion of any publication, a discussion with a third reviewer (L.C.M.) was taken to solve any disagreement. After full-text examination were registered the reasons for exclusion of articles.

Data collection process/ data items

Data extraction regarding authors, year and country of the study, characteristics of participants (sample size, sample age, and T2DM duration in years), exposure (diagnostic criteria for periodontitis), body fluid collected (serum, saliva, and gingival crevicular fluid), assessment methods to oxidative stress parameters and statistics outcomes of interest (inferential and descriptive data) were extracted independently by 2 researchers (W.J.M.L. and C.C.M.). Any differences between the two examiners were solved by a third investigator (L.C.M.).

When missing data were detected, the corresponding author was contacted through electronic mail for up five consecutive weeks. In case there were no return from the authors to identify data in graphs, It was used the digital program WebPlotDigitizer online [14] to identify data in graphs from authors who did not respond to emails. Another author confirmed the accuracy of extracted data.

Quality assessment

The internal validity of the included studies was evaluated according to adaptations of Fowkes and Fulton's [15] critical appraisal of published research guidelines (Appendix 2).

Effect measure

Due to the variability of the sample size between the studies, an adaptation was performed to determine the central value and variance of the samples. For outcomes, mean and standard deviation were used.

Synthesis methods and certainty of evidence assessment

Narrative syntheses were conducted for the results reported on each oxidative stress parameter. The certainty of evidence was determined using the Grading of Recommendations, Assessment, Development, and Evaluation Pro software (GRADEpro Guideline Development Tool) for the synthesized results on each OS parameter [16]. The risk of bias, inconsistency, indirectness, suspicion of publication bias, presence of a large effect, dose-response gradient, and plausible confounders were the items considered to rate the overall certainty of evidence [17,18]. All the judgments were adapted to qualify the evidence synthesized in a narrative way [19].

RESULTS

Study selection

A total of 988 studies were identified and retrieved: 956 from the database search, 8 from the alerts, and 24 from other sources. The main databases used as sources for studies were VHL (n=282) and PubMed (n=239), followed by Web of Science (n=192), Embase (n=83), Scopus (n=72), Cochrane Library (n=50), opengrey (n=0), and additional records identified through Google Scholar (n=24). The 295 duplicated titles/abstracts were eliminated through EndNote Software, and 76 through manual exclusion.

All titles and abstracts (n=617) were analyzed and 585 were excluded according to the study criteria, resulting in 32 remaining studies, which were assessed for eligibility. Twenty-three were excluded due to the following reasons: absence of group T2DM without Periodontitis (n=21), research participants with more than one systemic disease (n=1), and an article that contained a part of an included study in this systematic review (n=1) (Appendix 3).

Regarding the records identified by other resources, the first one hundred matches from the 35700 results in Google Scholar were selected for the study, and none were recorded in Opengrey. There were found 36 duplicate records, which were manually removed, and another 64 records were excluded after title/abstract reading. Alerts were set by June 01, 2024 in Databases, and eight articles were retrieved. However, they did not meet the inclusion criteria for eligibility. Study selection process is shown in the flowchart (Figure 1). Nine articles were screened for the final analysis.

Study characteristics

The included studies were conducted in institutions such as universities, clinical centers, or hospitals in three different countries (Table I). Among those studies, 4cross-sectional[21,25,27,28],3case-control[23,24,26] and 2 interventional [20,22] studies were included. In all studies, low levels of antioxidants were evaluated as primary outcome. Studies varied greatly regarding age, ranging from 20 years [23] to 71 years [20].

Periodontal parameters, plaque index (PI), BOP, PD, and CAL, were reported for periodontitis diagnosis, represented as mean and standard deviation [20-25,27] or by mean percentage [26,28]. The patients in the included studies had chronic periodontitis, according to

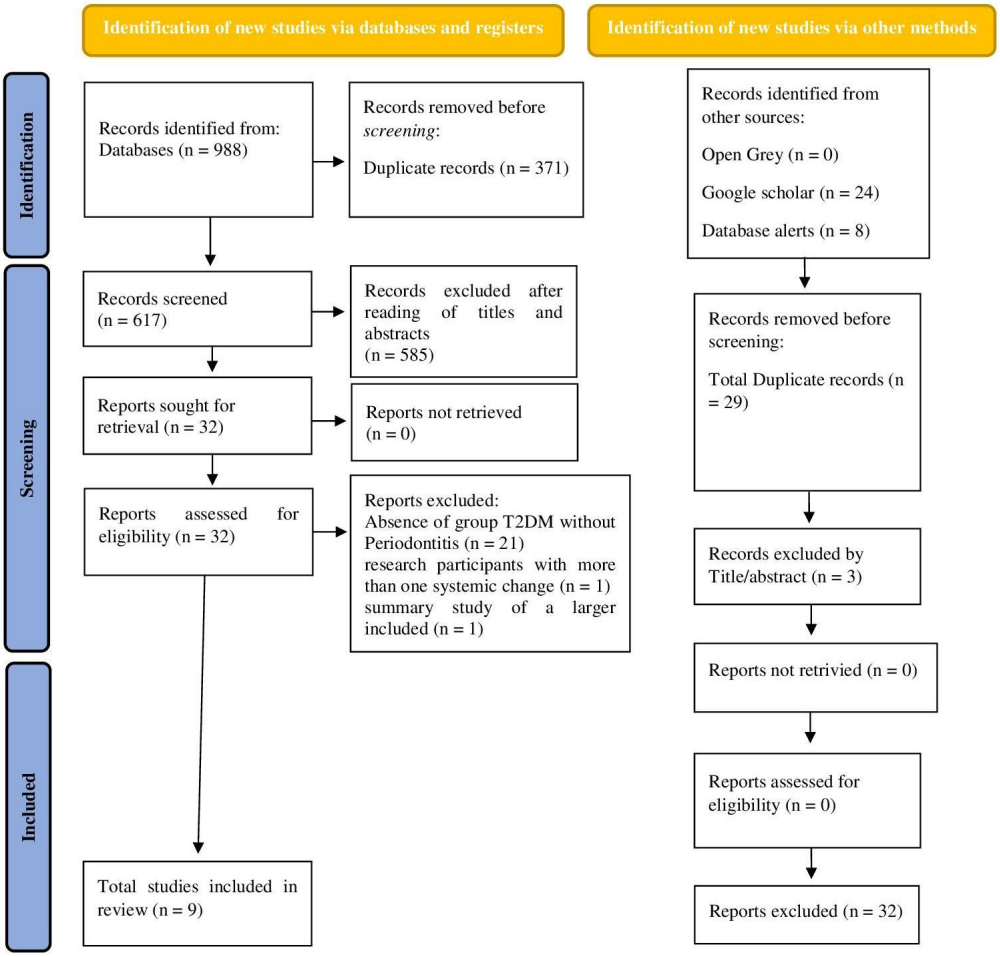

Figure 1. Flowchart diagram of literature search according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, published in 2020.

Table I - Characteristics of the sample and data collection of the 9 included studies.

Author et al. / year / Country	Study design	Characteristics of Subjects			Exposure	Outcomes		Numeric Data	
		Sample size	Sample age (Mean±SD)	Diabetes duration in years (Mean±SD)	Diagnostic criteria for periodontitis	Body fluid	Oxidative Stress Parameters (Assessment method)	Oxidative stress markers (Mean±SD) T2DM	T2DM + P
Allen et al. (2011) [20]/ Ireland	Cross-sectional	T2DM: 20 T2DM + P: 20	T2DM: 55±7 T2DM + P: 56±7	T2DM: 5.7±16.9 T2DM+P: 7.0±14.5 They should be on dose of oral hypoglycemic drugs, Anti-inflammatories, statins, ace inhibitors, β-blockers and diuretics.	- More than 16 teeth with periodontal pockets > 4mm in at least 6 sites. Probing depth (mm) Plaque index (%) Bleeding on probing (%)	Serum	Small molecule antioxidant capacity (Chemiluminescence) Protein carbonyl (ELISA)	523.4±111.1 1.99±0.85	452.6±100.1 2.71±0.94
Latha et al. (2018) [21]/ India	Intervention	T2DM: 10 T2DM + P: 15	T2DM: 56.8±8.71 T2DM + P: 51.13±6.75	The subjects should have been diagnosed with type 2 diabetes for at least 5 years. They should be on stable dose of insulin/oral hypoglycemic drugs.	- More than 20 teeth with clinical attachment loss of ≥ 5mm in at least 30% of the sites. Probing depth (Mean±SD) Plaque index (Mean±SD) Bleeding on probing (Mean±SD) Clinical attachment loss (Mean±SD)	Saliva	Malondialdehyde (spectrophotometric method) Nitric Oxide (spectrophotometric method)	2.19±1.62 1.76±1.02	2.17±0.52 9.08±2.33

Note: All patients in the diabetes group were diagnosed based on the criteria of the World Health Organization (Fasting glucose ≥126 mg/dL, HbA1c levels >5,6% and oral glucose tolerance test ≥200 mg/dL). DNPH: 2, 4- dinitrophenylhydrazine method; T2DM: Type 2 diabetes mellitus individuals; T2DM + P: Type 2 diabetes mellitus with periodontitis individuals; ELISA: Enzyme-Linked Immunosorbent Assay; HbA1c: Glycated hemoglobin; Nitro-PAPS: pyridylazo-N-propyl-N-sulfopropylaminoPhenol method; NR: Not reported; OCPC method: o-Cresolphthalein Complexone method; P: Periodontitis; qPCR: Quantitative Real-Time polymerase chain reaction; † data obtained by WebPlotDigitizer online software.

Table 1 - Continued...

Author et al. / year / Country	Study design	Characteristics of Subjects			Exposure	Outcomes		Numeric Data	
		Sample size	Sample age (Mean±SD)	Diabetes duration in years (Mean±SD)	Diagnostic criteria for periodontitis	Body fluid	Oxidative Stress Parameters (Assessment method)	Oxidative stress markers (Mean±SD) T2DM	T2DM + P
Pendyala et al. (2013) [22]/ India	Case-control	T2DM: 30 T2DM+ P: 30	40-65 years	Time of diagnosis for T2DM was not informed. These patients were not under any oral hypoglycemic agents and/or insulin therapy	- More than 14 teeth with two or more tooth sites with PD ≥ 4 mm or CAL of 4 mm that bled on probing. Probing depth (mm) Clinical attachment loss (mm) Probing depth ≥ 4mm (%) Clinical attachment loss ≥4mm (%) Plaque index (%) Bleeding on probing (%)	Saliva	Total antioxidant capacity (spectrophotometric method)	1.24±0.18	0.40±0.09
Pushpa Rani et al. (2013) [27]	Cross-sectional	T2DM: 150 T2DM + P: 150	T2DM: 46.26 ± 10.02 T2DM + P: 44.42 ± 10.37	Diagnosed by a physician by means of oral glucose tolerance test, for at least the past 5 years	- More than 30% of the sites with CAL ≥ 3 mm and PD ≥ 5 mm, at least 2 teeth in each quadrant with the condition of 20 teeth in all the subjects. Probing depth (mm) Clinical attachment loss (mm)	Serum	Vitamin C (DNPH method) Zinc (Nitro-PAPS)	1.25±3.58 † 157.2±45.8	0.99±1.66 † 106.8±31.83

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Pushpa Rani (2015) [28]	Cross-sectional	T2DM: 150 T2DM + P: 150	T2DM: 46.26±10.02 T2DM + P: 44.42±10.37	Diagnosed by a physician by means of oral glucose tolerance test, for at least the past 5 years	- More than 30% of the sites with clinical attachment level (CAL) ≥ 3mm and probing depth (PD) ≥ 5 mm, at least 2 teeth in each quadrant with the condition of 20 teeth in all the subjects. Probing depth (mm) Clinical attachment loss (mm)	Serum	Calcium (OCPC) Iron (Ramsay's dipyridyl method) Magnesium (Absorbance of 520 nm, with Xylidyl Blue dye reagent kit) Zinc (Nitro-PAPS)	8.59±0.86 76.53±20.23 1.56±0.42 157.2±45.8	11.79±2.07 114.9±40.91 1.45±0.41 106.8±31.83
Shetty et al. (2016) [23] / Índia	Intervention	T2DM: 30 T2DM+ P: 30	25-60 years	Time of diagnosis for T2DM was not informed.	- More than 20 teeth present. Used the classification of Löe (1967) to periodontal disease: gingival index, plaque index and retention index. Gingival index (0, 1, 2 and 3) Probing depth (0, 1, 2 and 3) Retentetion index system (0, 1, 2 and 3)	Serum	Magnesium (semi-autoanalyzer)	1.01±0.28	0.92±0.23

Note: All patients in the diabetes group were diagnosed based on the criteria of the World Health Organization (Fasting glucose ≥126 mg/dL, HbA1c levels >5,6% and oral glucose tolerance test ≥200 mg/dL). DNPH: 2, 4- dinitrophenylhydrazine method; T2DM: Type 2 diabetes mellitus individuals; T2DM + P: Type 2 diabetes mellitus with periodontitis individuals; ELISA: Enzyme-Linked Immunosorbent Assay; HbA1c: Glycated hemoglobin; Nitro-PAPS: pyridylazo-N-propyl-N-sulfopropylaminoPhenol method; NR: Not reported; OCPC method: o-Cresolphthalein Complexone method; P: Periodontitis; qPCR: Quantitative Real-Time polymerase chain reaction; † data obtained by WebPlotDigitizer online software.

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								T2DM	T2DM + P
Takeda et al. (2006) [24]/ Japan	Cross-sectional	T2DM: 28 T2DM+ P: 69	57.8± 12.1	T2DM: 8.0±7.7 T2DM+P: 8.6±7.6 The control with medicaments was not informed.	- Subjects had ≥ 10 functional teeth and more than one tooth with CAL > 5 mm. Bleeding on probing (Presence or Ausence of bleeding within 5 to 20 seconds after probing) Probing depth (mm) Clinical attachment loss (%)	Serum	Advanced Glycation End-products (uninformed)	2.6±1.0	2.5±0.8

Note: All patients in the diabetes group were diagnosed based on the criteria of the World Health Organization (Fasting glucose ≥126 mg/dL, HbA1c levels >5,6% and oral glucose tolerance test ≥200 mg/dL). DNPH: 2, 4- dinitrophenylhydrazine method; T2DM: Type 2 diabetes mellitus individuals; T2DM + P: Type 2 diabetes mellitus with periodontitis individuals; ELISA: Enzyme-Linked Immunosorbent Assay; HbA1c: Glycated hemoglobin; Nitro-PAPS: pyridylazo-N-propyl-N-sulfopropylaminoPhenol method; NR: Not reported; OCPC method: o-Cresolphthalein Complexone method; P: Periodontitis; qPCR: Quantitative Real-Time polymerase chain reaction; † data obtained by WebPlotDigitizer online software.

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Trivedi et al. (2014) [25]/ Índia	Case-control	T2DM: 30 T2DM+ P: 30	20-65 years, categorizaded (≤40 years and >40 years)	T2DM: 4.33±3.44 T2DM+P: 5.53±4.05 Were controlled diabetics being treated with stable doses of oral hypoglycemic agents and / or insulin by an endocrinologista.	- Patients with two or more tooth sites with probing depth ≥ 4mm or clinical attachment loss (CAL) ≥ 4mm that bled on probing. - Minimum number of teeth not informed. Plaque index (Presence or Ausence) Gingival index (Presence or Ausence) Probing depth (mm) Clinical attachment loss (mm)	Saliva	Malondialdehyde (spectrophotometric method) Superoxide dismutase (Mc Cord and Fridovich) Catalase (Mc Cord and Fridovich) Glutathione reductase (Mc Cord and Fridovich)	1.91±1..72 13.45±2.80 0.04±0.04	10.79±8.07 14.08±4.28 0.04±0.03
						Serum	Malondialdehyde (spectrophotometric method) Superoxide dismutase (Mc Cord and Fridovich) Catalase (Mc Cord and Fridovich) Glutathione reductase (Mc Cord and Fridovich)	13.73±2.79 13.01±5.55 19.05±5.88 0.06±0.03 6.28±4.96	18.33±7.47 15.91±6.98 26.84±12.1 0.06±0.03 12.15±6.11

Note: All patients in the diabetes group were diagnosed based on the criteria of the World Health Organization (Fasting glucose ≥126 mg/dL, HbA1c levels >5,6% and oral glucose tolerance test ≥200 mg/dL). DNPH: 2, 4- dinitrophenylhydrazine method; T2DM: Type 2 diabetes mellitus individuals; T2DM + P: Type 2 diabetes mellitus with periodontitis individuals; ELISA: Enzyme-Linked Immunosorbent Assay; HbA1c: Glycated hemoglobin; Nitro-PAPS: pyridylazo-N-propyl-N-sulfopropylaminoPhenol method; NR: Not reported; OCPC method: o-Cresolphthalein Complexone method; P: Periodontitis; qPCR: Quantitative Real-Time polymerase chain reaction; † data obtained by WebPlotDigitizer online software.

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Vincent et al. (2018) [26]/ India	Case-control	T2DM: 20 T2DM + P: 20	25-65 years	Participants diagnosed with type II DM by a diabetologist and under treatment with oral hypoglycemic drugs and diet control for a minimum of 6 months were included	- Minimum of 20 teeth present with at least 5 teeth in each quadrant, with a probing depth (PD) of ≥5mm with clinical attachment loss of ≥1mm in more than 30% of sites with mild to moderate periodontitis, and presence of >30% of sites with bleeding on probing. Plaque index Bleeding on probing Probing depth (mm) Clinical attachment loss (mm)	Gingival Fluid	Total antioxidant capacity (Erel O's novel automated method) Total oxidant status (Erel O's novel automated method) Oxidative stress index (Erel O's novel automated method)	0.77±0.27 7.84±1.50 1.00±0.52	0.69±0.19 10.05±3.26 1.39±0.62

Note: All patients in the diabetes group were diagnosed based on the criteria of the World Health Organization (Fasting glucose ≥126 mg/dL, HbA1c levels >5,6% and oral glucose tolerance test ≥200 mg/dL). DNPH: 2, 4- dinitrophenylhydrazine method; T2DM: Type 2 diabetes mellitus individuals; T2DM + P: Type 2 diabetes mellitus with periodontitis individuals; ELISA: Enzyme-Linked Immunosorbent Assay; HbA1c: Glycated hemoglobin; Nitro-PAPS: pyridylazo-N-propyl-N-sulfopropylaminoPhenol method; NR: Not reported; OCPC method: o-Cresolphthalein Complexone method; P: Periodontitis; qPCR: Quantitative Real-Time polymerase chain reaction; † data obtained by WebPlotDigitizer online software.

1999 AAP Classification [29]. The minimum number of teeth of the research participants in the included studies ranged from 10 [27] to 20 functional teeth [20,22,24].

Data on T2DM duration was introduced in years and expressed in mean and standard deviation. Most studies included participants diagnosed with T2DM for at least 5 years [20,21,23,25,28]. A study included participants with a minimum of 8 years of diagnosis for T2DM [27], other with participants at least 6 months of diagnosis [24], while two studies [22,26] did not report on this data.

The OS biomarkers were analyzed in more than one body fluid, including serum [21-23,25,27], saliva [20,23,26] and gingival fluid (GF) [24], and were expressed in mean and standard deviation, through different methods, comparing gold-standard or not. None of those studies directly cross-compared biomarkers findings between those body fluids.

Among the OS biomarkers studied a large number of antioxidants were evaluated such as SMAC [28], TAC [24,26], vitamin C [25], zinc [21,25], calcium [21], magnesium [21,22], CAT, SOD and GRd [23]. In addition, two oxidant agents were evaluated: NO [20] and iron [21]. Furthermore, biomarkers of cell damage due to OS were also evaluated, such as Protein CO [28], AGEs [27], MDA [20,23], TOS and OSI [24].

Only one study [23] evaluated the same biomarkers (MDA, SOD, CAT, and GRd) in blood and saliva, although no comparisons between findings from both fluids were compared, as mentioned before.

Quality assessment

For the quality assessment, the included studies were classified according to the risk of bias, confounding factors, and chance. Susceptibility to bias and results occurred by chance were observed in all analyzed studies [20-28]. Confounding factors were observed in 3 out of the 9 analyzed studies (Table II) [21,25,28]. According with the criteria used, there was no sound study.

Results of individual studies and synthesis

Some of the included studies demonstrated a significant correlation between high levels of oxidizing compounds and individuals with T2DM and periodontitis [20,21,27,28]. On the other hand, other studies presented a decrease in the levels of antioxidants in T2DM with periodontitis, when compared to T2DM without periodontitis [21-28]. Overall, the studies have shown that individuals with T2DM presented high OS levels, which are greater when associated with periodontitis.

Oxidants

In individuals with T2DM and periodontitis, Protein CO levels were higher compared with those without periodontitis. The same result of high levels was expressed for free radical damage markers (MDA, TOS, and OSI) in T2DM with periodontitis individuals when compared to T2DM individuals without periodontitis [20,23,24]. In T2DM with periodontitis individuals, the NO levels were higher than in T2DM without periodontitis [20]. Pushpa Rani [27] shown that elevated calcium and iron levels may be a contributing factor in many inflammatory conditions in T2DM with periodontitis individuals.

Antioxidants

The included literature demonstrated that Some antioxidants (SMAC, TAC, Vitamin C, Zinc, Magnesium, CAT, SOD, and GRd) were detected in low concentrations in individuals with T2DM with no periodontitis. Additionally, those levels were even lower in individuals with T2DM with periodontitis [21-26,28].

Due to the variation in the study results and clinical/methodological heterogeneity, a meta-analysis was not appropriate.

Certainty of evidence

The certainty of the evidence was rated as very low for all the syntheses. The risk of bias affected the evidence because the included studies had important methodological limitations that could have altered the results. The evidence on the outcomes of MDA and TAC was inconsistent since there was variation in the reported effects by the studies. The item imprecision was also affected due to the reduced number of individuals included in the syntheses (less than the threshold of 400 recommended by GRADE) (Table III). The certainty of the evidence for the outcomes that included a single study (SMAC, Protein carbonyl, NO, Vitamin C, Zinc, Ca, Iron, AGEs, SOD, CAT, GRd, TOS, OSI) was lowered due to the risk of bias and impression (insufficient

Table II - Quality assessment according to Fowkes and Fulton

Guideline	Checklist		Allen et al. (2011) [20]	Latha et al. (2018) [21]	Pen-dyala et al. (2013) [22]	Pushpa Rani et al. (2013) [27]	Pushpa Rani (2015) [28]	Shetty et al. (2016) [23]	Takeda et al. (2006) [24]	Trivedi et al. (2014) [25]	Vincent et al. (2018) [26]
Study design appropriate to objectives?	Objective:	Common design:									
	Prevalence	Cross sectional	NA	NA	NA	0	0	NA	0	NA	NA
	Prognosis	Cohort	0	NA	NA	NA	NA	NA	NA	NA	NA
	Treatment	Controlled trial	NA	0	NA	NA	NA	0	NA	NA	NA
	Cause	Cohort, case-control	NA	NA	0	NA	NA	NA	NA	0	0
Study sample representative?	Source of sample		+	+	+	+	+	+	+	+	+
	Sampling method		+	+	+	+	+	0	+	+	+
	Sample size		+	++	+	+	+	+	+	+	++
	Entry criteria/exclusions		0	+	0	+	+	+	++	+	+
	Non-respondents		NA	NA	NA	NA	NA	NA	NA	NA	NA
Control group acceptable?	Definition of controls		++	0	0	++	++	++	++	+	++
	Source of controls		+	+	+	+	+	0	+	+	+
	Matching/randomisation		++	++	+	++	++	0	+	+	+
	Comparable characteristics		++	+	+	++	++	++	0	0	+
Quality of measurements and outcomes?	Validity		+	0	0	+	+	0	+	0	+
	Reproducibility		NA	NA	0	0	0	0	0	0	0
	Blindness		NA	NA	NA	NA	NA	+	NA	NA	NA
	Quality control		+	0	0	++	++	0	0	0	0
Completeness?	Compliance		NA	NA	NA	NA	NA	NA	NA	NA	NA
	Drop outs		NA	NA	NA	NA	NA	NA	NA	NA	NA
	Deaths		NA	NA	NA	NA	NA	NA	NA	NA	NA
	Missing data		0	0	0	0	0	0	0	0	0
Distorting influences?	Extraneous treatments		NA	NA	NA	NA	NA	NA	NA	NA	NA
	Contamination		NA	NA	NA	NA	NA	NA	NA	NA	NA
	Changes over time		NA	NA	NA	NA	NA	NA	NA	NA	NA
	Confounding factors		++	0	+	++	++	0	0	+	0
	Distortion reduced by analysis		++	0	++	++	++	0	0	+	0
Summary questions	Bias - Are the results erroneously biased in a certain direction?		YES	YES	YES	YES	YES	YES	YES	YES	YES
	Confounding - Are the any serious Confounding or other distorting influence?		YES	NO	NO	YES	YES	NO	NO	NO	NO
	Chance - Is it likely that the results ocurred by chance?		YES	YES	YES	YES	YES	YES	YES	YES	YES

Note: NA: not applicable; +: Minor problem; ++: Major problem; 0: No problem was assigned.

Table III - Assessment of the certainty of evidence (GRADE)

Certainty assessment							
N° of datasets	**Design of the studies**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Certainty**
Malondialdehyde							
2	Observational*	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ VERY LOW
Total antioxidant capacity							
2	Observational	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ VERY LOW
Magnesium							
2	Observational*	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕◯◯◯ VERY LOW

* Baseline data from intervention studies were considered. a. The certainty of the evidence was downgraded in one level because the studies had important methodological limitations and it is likely that they may have altered the results. b. The certainty of the evidence was downgraded by one level because the studies reported different effects. c. The certainty of the evidence was downgraded by one level due to the reduced number of individuals considered in the synthesis (less than the threshold of 400 recommended by GRADE).

number of individuals). Publication bias was considered unsuspected, and since the evidence was affected by some of the previously mentioned criteria, no item was considered to raise the certainty. The judgments issued for the evaluation of the certainty of the evidence for the outcomes involving more than one study are presented in Table II.

DISCUSSION

This systematic review aimed to synthesize the scientific evidence of studies on the association of OS biomarkers in individuals with T2DM with and without periodontitis. This systematic review was based on 9 not-sound studies and indicates that high levels of oxidizing agents and low concentration of antioxidants in T2DM are related with the presence of periodontitis when compared to individuals without periodontitis. This is the first systematic review with quality assessment on this topic.

After filing in PROSPERO, studies selection, and full reading, it was observed that some studies had diagnostic criteria for periodontitis of CAL ≥3mm [27,28] and, if they were excluded, some important data would be missing for the systematic review. So we decided to include them, considering that the registration of the present study was made based on the APP classification [29]. According to the actual Classification of Periodontal Diseases and Conditions [30], taking into consideration CAL, periodontitis is characterized by: CAL ≥3mm in interproximal areas of at least 2 non-adjacent teeth or in buccal or lingual/palatal, without it being due to: 1) traumatic gingival recession; 2) dental caries extending to the cervical area of the tooth; 3) presence of insertion loss on the distal face of a second molar and associated with poor positioning or extraction of the third molar; 4) endoperiodontal lesion draining through the marginal periodontium; or 5) occurrence of vertical root fracture. Thus, this parameter had to be changed for articles selection.

Data show that patients with T2DM and periodontitis have impaired glycemic status and exhibit significantly lowered B-cell function and higher levels of HbA1c and fasting glucose than matched patients without periodontitis [20]. Those chronic inflammatory conditions are generally thought to be associated with increased OS with phagocytes, particularly neutrophils. Those cells are implicated in periodontal disease pathogenesis as they induce the generation of an oxidative burst during phagocytosis and killing [26]. On the other hand, ROS are associated with microvascular complications of T2DM. It is also known that severe periodontal disease can lead to endothelial dysfunction, which justify the assessment of effect of coexisting T2DM and periodontitis on the levels of OS markers [20].

Periodontitis increases plasma biomarkers of OS as evidenced by the finding of reduced SMAC combined with increased levels of protein CO, which is a marker of protein oxidation. In the co-occurrence of T2DM and periodontitis, there is higher alterations in levels of these OS

biomarkers. This suggests signs of enhanced OS in serum of T2DM with periodontitis individuals, showing that periodontitis has a negative effect on the already compromised oxidative status of T2DM patients [28]. Vincent et al. [26] shown high levels of TOS in T2DM with periodontitis group when compared to periodontitis without T2DM encouraging the aforementioned data.

Role of nitric oxide system in T2DM is few studied and controversial to scientifics research, demonstrating higher level, low level, or no change. In chronic inflammatory processes, where activity of PMNs, macrophages, and endothelial cells is elevated, such as in periodontitis, the expression of iNOS is increased. The positive relationship between iNOS, inflammatory cytokines and other mediators reveals an immune-activated state due higher NO production. Thus, it might be higher in individuals with T2DM and chronic periodontitis when compared to without periodontitis cells [20].

MDA is the major and commonly studied product of polyunsaturated fatty acid peroxidation that is shown to rise following OS. Glycated collagen has been shown a role in lipid glycoxidation compared to normal collagen that results in increased MDA in serum and tissues of diabetic subjects [20]. In T2DM individuals with periodontitis, MDA was reported to be higher when compared to individuals without periodontitis [23].

It was reported that TAC levels in GCF was lower in patients with T2DM and periodontitis, compared to individual with only T2DM. The decrease in TAC levels reported could be attributed to elevated ROS levels that must be neutralize causing depletion of antioxidants, in addition to presence hyperglycemia, which is the primary cause of inflammation in T2DM individuals [24]. In another study, the comparison of the TAC in saliva revealed lower antioxidant levels in T2DM with periodontitis compared to non-diabetic individuals with periodontitis [26].

Excessive glucose levels induce free radical production and enhance OS by increased formation of AGEs. These pathologic mechanisms in T2DM with the preexisting periodontal disease could be responsible for exacerbated periodontal destruction seen in diabetics [24]. Takeda et al. [24] reported that AGEs were significantly related to periodontal deterioration associated with T2DM, showing that their level may be a suitable biomarker to reflect periodontal status in those patients.

Micronutrients are regulated by homeostatic processes and function as antioxidant in the control of damage caused by ROS [31]. Calcium and iron play an essential role in regeneration, for coping with OS and for an adequate immune response, but dysregulation these micronutrients (high levels) in the serum may promote the development and progression of oxidative stress [32]. It has been reported that the mean calcium level in T2DM with periodontitis individuals was significantly higher when compared to systemically and periodontally healthy individuals. It was also demonstrated that an increased serum iron levels in T2DM with periodontitis can act as pro-oxidant agents, which are responsible for the formation of ROS [28].

Additionally, it was reported that T2DM with periodontitis had lower zinc levels than those individuals with T2DM without periodontitis [21,25]. Zinc deficiency promotes the activation of N-methyl-D-aspartate (NMDA) receptors, which increase the intracellular concentration of calcium. In conditions where zinc is deficient, the NADPH oxidase enzymes and nitric oxide synthase are activated, favoring the production of reactive species of oxygen and nitrogen [33].

Being an essential dietary nutrient, vitamin C is important for many enzyme reactions. It is an electron donor, and this property might account for all its known functions, such as water-soluble antioxidant in humans and protects from oxidative damage under conditions of increasing oxygen concentrations and apoptosis [34]. Pushpa Rani et al. suggests that decreased vitamin C levels are associated with an increased risk for the development of oxidative stress in type 2 diabetes mellitus with periodontitis, considering that the antioxidant activity of ascorbic acid involves transfer of hydrogen rather than an electron [25].

Magnesium it is a cofactor of several antioxidant enzymes, including SOD, one of the most important antioxidant enzymes [35] and it has been demonstrated that magnesium supplement has a beneficial effect on periodontitis [36]. Furthermore, low magnesium levels may favor the onset and progression of T2DM, frequently seen in these patients [21,37]. Pushpa Rani [28]demonstrated that magnesium

mean levels in T2DM without periodontitis and non-T2DM with periodontitis individuals were greater than the ones found for T2DM with periodontitis individuals and those findings were corroborated in another investigation [22].

The enzyme SOD is a key antioxidant that catalyzes the dismutation of superoxide (O_2^-), generating hydrogen peroxide (H_2O_2). The products CAT, GRd and GPx accelerate H_2O_2 reduction in water [38]. Trivedi et al. demonstrated that SOD, CAT and GRd activities were higher in T2DM with periodontitis group compared with T2DM without periodontitis group. In periodontitis, SOD, CAT and GRd levels are low due antioxidant depletion, to ongoing free radical activity and destruction of protective antioxidant species [23].

Clinical investigations must always focus on correct matching for gender, age, and periodontal status to reduce potential confounding factors. Latha et al. [20], Pendyala et al. [26], Takeda et al. [27] and Trivedi et al. [25] follow these restrictions and the distribution of age and gender was similar between groups, suggesting that they were well matched. Thus, their results might present greater validity and relatively fewer confounding factors.

The analysis of non-randomized clinical trials properly reported most of the criteria analyzed in Summary questions (Bias, Confounding and Chance) as present in 3 studies. In six studies [20,22-24,26,27] confounding factors were no detected. Shetty et al. [23] defined their study as a randomized clinical trial, but it has four groups (i.e., T2DM with periodontitis, T2DM without Periodontitis, non-T2DM with periodontitis, and systemically and periodontally healthy) with distinct interventions (scaling and root planning, and oral hygiene instructions), and there is no random allocation of groups/ treatment. In summary, their results are inconsistent and the evidence regarding OS biomarkers, T2DM and periodontitis relationship is lacking strong evidence.

Of the nine included studies, three assessed biomarkers in saliva and this suggests its potential relevance as an important alternative biological fluid [20,23,26]. Included studies in this systematic review are following the expected direction of the association, that there is difference in OS levels between T2DM individuals with and without periodontitis. These studies reported the relationship between high levels of oxidizing compounds or decrease of antioxidants in T2DM with periodontitis individuals, when compared to T2DM without periodontitis individuals. Therefore, these data suggest that periodontitis has a negative influence on OS in T2DM and recognize that an early diagnosis of periodontitis may be important for prevention of a negative impact on the OS biomarkers.

However, considering the few studies found, the methodological flaws, few markers studied and absence homogeneity in the evaluation of redox balance markers, as well as, the very low certainty of the evidence among included studies, ie there was no sound studies included in this systematic review, these results should be viewed with caution. Therefore, it was not possible to determine whether there are or not differences in the oxidative stress levels in individuals with T2DM associated with periodontitis and further prospective observational and interventional studies are recommended.

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Author's Contributions

WJML: Conceptualization, Validation, Formal Analysis, Investigation, Methodology, Resources, Data Curation, Writing – Original Draft Preparation. CCM: Conceptualization, Validation, Investigation, Methodology, Visualization, Writing – Review & Editing. GAMV: Validation, Formal analysis, Methodology, Visualization, Writing - Review & Editing. DM: Methodology, Visualization, Data Curation, Writing – Review & Editing. LCM: Conceptualization; Formal Analysis, Funding Acquisition, Methodology, Resources, Visualization, Writing – Review & Editing. MCMB: Conceptualization, Data Curation, Formal Analysis; Investigation; Methodology, Supervision, Writing – Review & Editing. CMSB: Conceptualization, Funding Acquisition, Investigation, Methodology, Supervision, Validation, Visualization, Writing – Original Draft Preparation; Writing – Review & Editing, Project Administration. CS: Data Curation; Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Validation,

Visualization, Writing – Original Draft Preparation, Writing – Review & Editing, Project Administration.

Conflicts of Interest

The authors have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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Regulatory Statement

This systematic review was conducted through a search strategy in electronic databases. The search was restricted to publications in peer-reviewed journals, in which approval for ethics committee were obtained in their original work.

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Appendix 1. Electronic database and search strategy

MEDLINE	(Diabetes Mellitus[Mesh] OR Diabetes Mellitus[Tiab] OR Diabetes Mellitus, Type 2[Mesh] OR Diabetes Mellitus Non Insulin Dependent[Tiab] OR Diabetes Mellitus Stable[Tiab] OR NIDDM[Tiab] OR MODY[Tiab] OR Maturity Onset Diabetes[Tiab] OR Type 2 Diabetes[Tiab] OR Diabetes Type 2[Tiab]) AND (Periodontal Diseases[Mesh] OR Periodontal Disease*[Tiab] OR Periodontitis[Mesh] OR Periodont*[Tiab] OR Aggressive Periodontitis[Mesh] OR Aggressive Periodont*[Tiab] OR Chronic Periodontitis[Mesh] OR Chronic Periodont*[Tiab]) AND (Oxidative Stress[Mesh] OR Oxidative Stress*[Tiab] OR Antioxidants[Mesh] OR Antioxidant*[Tiab] OR Antioxidant effect*[Tiab] OR Free radicals[Mesh] OR Free radicals[Tiab] OR Oxidants[Mesh] OR Oxidant*[Tiab] OR Oxidizing Agents[Tiab])
SCOPUS	TITLE-ABS-KEY(("Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "Diabetes Mellitus Non Insulin Dependent" OR "Diabetes Mellitus Stable" OR NIDDM OR MODY OR "Maturity Onset Diabetes" OR "Type 2 Diabetes" OR "Diabetes Type 2") AND (Periodontal Disease* OR Periodont* OR Aggressive Periodont* OR Chronic Periodont*) AND (Oxidative Stress* OR Antioxidant* OR Antioxidant effect* OR "Free radicals" OR Oxidant* OR "Oxidizing Agents"))
WEB OF SCIENCE	(("Diabetes Mellitus" OR "Diabetes Mellitus, Type 2" OR "Diabetes Mellitus Non Insulin Dependent" OR "Diabetes Mellitus Stable" OR NIDDM OR MODY OR "Maturity Onset Diabetes" OR "Type 2 Diabetes" OR "Diabetes Type 2") AND (Periodontal Disease* OR Periodont* OR Aggressive Periodont* OR Chronic Periodont*) AND (Oxidative Stress* OR Antioxidant* OR Antioxidant effect* OR "Free radicals" OR Oxidant* OR "Oxidizing Agents"))
COCHRANE	#1 MeSH descriptor: [Diabetes Mellitus] explode all trees #2 "Diabetes Mellitus" #3 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees #4 ("Diabetes Mellitus Non Insulin Dependent" OR "Diabetes Mellitus Stable" OR NIDDM OR MODY OR "Maturity Onset Diabetes" OR "Type 2 Diabetes" OR "Diabetes Type 2") #5 #1 OR #2 OR #3 OR #4 #6 MeSH descriptor: [Periodontal Diseases] explode all trees #7 Periodontal disease* #8 MeSH descriptor: [Periodontitis] explode all trees #9 Periodont* #10 MeSH descriptor: [Aggressive Periodontitis] explode all trees #11 Aggressive Periodont* #12 MeSH descriptor: [Chronic Periodontitis] explode all trees #13 Chronic Periodont* #14 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 #15 MeSH descriptor: [Oxidative Stress] explode all trees #16 Oxidative Stress* #17 MeSH descriptor: [Antioxidants] explode all trees #18 (Antioxidant* OR Antioxidant effect*) #19 MeSH descriptor: [Free Radicals] explode all trees #20 "Free radicals" #21 MeSH descriptor: [Oxidants] explode all trees #22 (Oxidant* OR "Oxidizing Agents") #23 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 #24 #5 AND #14 AND #23

Appendix 1. Continued...

LILACS and BBO	tw:(tw:((tw:((mh: "Diabetes Mellitus" OR mh: "Diabetes Mellitus, Type 2" OR "Diabetes Mellitus Tipo 2" OR "Diabetes Mellitus Non Insulin Dependent" OR "Diabetes Mellitus não dependente de insulina" OR "Diabetes Mellitus Stable" OR "Diabetes Mellitus estável" OR niddm OR dmndi OR mody OR "Maturity Onset Diabetes" OR "Diabetes com início na maturidade" OR "Type 2 Diabetes" OR "Diabetes tipo 2" OR "Diabetes Type 2" OR "Tipo 2 Diabetes"))) AND (tw:((mh: "Periodontal Diseases" OR "doenças periodontais" OR "periodontal disease" OR "periodontal diseases" OR "doença periodontal" OR "doenças periodontais" OR mh: periodontitis OR periodontite OR periodontitis OR periodontite OR mh: "Aggressive Periodontitis" OR "Periodontite Agressiva" OR "Aggressive Periodontitis" OR "Periodontite Agressiva" OR mh: "Chronic Periodontitis" OR "Periodontite Crônica" OR "Chronic Periodontitis" OR "Periodontite Crônica"))) AND (tw:((mh: "Oxidative Stress" OR "Estresse Oxidativo" OR oxidative stress* OR "Estresse Oxidativo" OR "Estresses oxidativos" OR mh: antioxidants OR antioxidantes OR antioxidant OR antioxidants OR antioxidante OR "antioxidant effect" OR "Antioxidants effects" OR "Efeito antioxidante" OR "Efeitos antioxidantes" OR mh: "Free radicals" OR "Radicais livres" OR "Free radicals" OR "Radicais livres" OR mh: oxidants OR oxidantes OR oxidants OR oxidant OR oxidante* OR "Oxidizing Agents" OR " agentes oxidantes")))) AND (db:("LILACS" OR "BBO"))) AND (type:("article"))
EMBASE	('diabetes mellitus':ti,ab,kw OR 'diabetes mellitus, type 2':ti,ab,kw OR 'diabetes mellitus non insulin dependent':ti,ab,kw OR 'diabetes mellitus stable':ti,ab,kw OR niddm:ti,ab,kw OR mody:ti,ab,kw OR 'maturity onset diabetes':ti,ab,kw OR 'type 2 diabetes':ti,ab,kw OR 'diabetes type 2':ti,ab,kw) AND ('periodontal disease*':ti,ab,kw OR periodont*:ti,ab,kw OR 'aggressive periodont*':ti,ab,kw OR 'chronic periodont*':ti,ab,kw) AND ('oxidative stress*':ti,ab,kw OR antioxidant*:ti,ab,kw OR 'antioxidant effect*':ti,ab,kw OR 'free radicals':ti,ab,kw OR oxidant*:ti,ab,kw OR 'oxidizing agents':ti,ab,kw)
OPEN GREY	Periodontitis and Diabetes and Antioxidants Periodontitis and Diabetes and Free radicals Periodontitis and Diabetes and Oxidants Periodontitis and Diabetes and Oxidative Stress Periodont* and Diabetes and Antioxidants Periodont* and Diabetes and Free radicals Periodont* and Diabetes and Oxidants Periodont* and Diabetes and Antioxidants Periodont* and Diabetes and Oxidative Stress Periodont* and Diabetes and Antioxidant* Periodont* and Diabetes and Oxidative Stress* Periodontitis and Diabetes and Antioxidant* Periodontitis and Diabetes and Oxidative Stress*
GOOGLE SCHOLAR	Periodontitis and diabetes type 2 and oxidative stress Periodontite e diabetes tipo 2 e estresse oxidativo

Appendix 2. Criteria's adopted to risk of bias classification (adapted from Fowkes and Fulton [15])

Study design appropriate to objective?	Prevalence - Cross-sectional	0 – if the study, or part of study, included in the present systematic review reported oxidative stress in type 2 diabetics with periodontitis and had a cross-sectional design
	Prognosis - Cohort	0 – if the study, or part of study, included in the present systematic review reported oxidative stress in type 2 diabetics with periodontitis and had a Cohort design
	Treatment - Controlled trial	0 - if the study, or part of study, included in the present systematic review evaluate some type of treatment related periodontitis or type 2 diabetes mellitus and measurement oxidative stress levels and had a controlled trial design
	Cause - Cohort, case-control, cross-sectiona	0 - if the study, or part of study, included in the present systematic review evaluate some type of relationship / association / risk reported of oxidative stress alteration in type 2 diabetics with periodontitis had a cross-sectional, case-control or cohort design, respectively.
Study sample representative?	Source of sample	(0) case group was obtained from various referral hospital (multicentre).
		(+) case group was composed of individuals from a reference center or referral hospital.
		(++) case group was obtained from unspecified locations.
	Sampling method	(0) probabilistic sampling (simple random, stratified, blocks).
		(+) did not use any type of randomization, but authors of the present systematic review judged that could not influence in outcome evaluation, as all eligible participants from a specific site/place were included.
		(++) did not use any type of randomization, but authors of the present systematic review judged that could influence in outcome evaluation by using a convenience sample.
	Sample size	(0) sample size calculation was described considering all variables and study groups.
		(+) did not perform sample size calculation but had a representative sample, using a sample size equal or higher than 97 subjects (median of samples from included studies).
		(++) did not mention such sample size calculation or representative sample, using a sample size lower than 97 subjects (median of samples from included studies).
	Inclusion/ exclusion criteria	(0) Selection criteria properly established. Periodontitis: PBS≥ 4mm, NCI≥ 4mm, presence of biofilm, bleeding on probing (> 10%) and presence of suppuration. Examination performed by a single calibrated examiner or more than one (calibrated), who underwent a complete periodontal examination (in the six sites of the teeth present), using a standard probe for the diagnosis of periodontitis (North Carolina 15mm).
		(+)Selection criteria established, but some criteria were not considered (do not mention one of the criteria for diagnosing periodontitis previously shown or the examiner is not calibrated).
		(++) Selection criteria loosely established or absence of two or more periodontitis selection criteria.
	Non-respondents	N. A. - the authors of the present systematic review judged that the non-respondent's rate could not influence in outcome evaluation.
Control group acceptable?	Definition of controls	(0) Selection criteria properly established. Absence of periodontitis: PBS≤ 3mm, NCI≤ 3mm, little or no biofilm, no or little bleeding on probing (<10%) and no suppuration. Examination performed by a single calibrated examiner or more than one calibrated, who underwent a complete periodontal examination (at the six sites of the teeth present), using a standard probe for the diagnosis of periodontitis (North Carolina 15mm).
		(+) Selection criteria established, but some criteria were not considered (do not mention one of the criteria for periodontal health shown previously).
		(++) Selection criteria loosely established. Absence of two or more selection criteria for periodontal health.
	Source of controls	(0) control group was obtained from various referral hospital (multicentre).
		(+) control group was composed of individuals from a reference center or referral hospital.
		(++) control group was obtained from unspecified locations.
	Matching/ randomization	(0) group control was paired according to gender, age and duration of diabetes.
	Comparable characteristics	(+) only matched by two of the criteria mentioned above.
		(++) control group was not paired.study mentioned that case and control groups were matching for sex, age and general health.
		(0) There is no difference between the groups regarding age, gender and duration of diabetes.
		(+) the groups are different only in relation to two criteria.
		(++) the groups are different in relation to age or duration of diabetes.
Quality of measurements and outcomes?	Validity	(0) Use of the gold standard method for determining the biomarker
		(+) adequate test, but it is not the gold standard.
		(++) Test not suitable.
	Reproducibility	(0) An experienced and calibrated evaluator and that there was acceptable reproducibility in the measurement of oxidative stress markers.
		(+) a trained evaluator, but the study's reproducibility analysis was not performed.
		(++) an uncalibrated evaluator, but the study was not reproducible or was not even mentioned in the study.
	Blindness	(0) Researcher who collected and analyzed samples were blinded to the study group.
		(+) Researcher who collected or analyzed the samples was blinded to the study group.
		(++) There was no blinding in any phase of the study.
	Quality control	(0) Adequate acquisition, processing and storage of samples. Adequate description of the parameters used to measure oxidative stress.
		(+) one of the points described above was neglected or not mentioned.
		(++) two or more points described above were neglected or not mentioned.

NA – Not applied.

Appendix 2. Continued...

Completeness?	Compliance	NA (question did not apply to study methodology)
	Dropouts	NA (question did not apply to study methodology)
	Deaths	NA (question did not apply to study methodology)
	Missing data	(0) The study reports the number of missing data (up to 30%) and the reasons. (or the absence of missing data).
		(+) the number of missing data is reported without explaining the reasons (with up to 30% of the missing data).
		(++) nothing is specified or there was a loss greater than 30%.
Distorting influences?	Extraneous treatments	NA (question did not apply to study methodology)
	Contamination	NA (question did not apply to study methodology)
	Changes over time	NA (question did not apply to study methodology)
	Confounding factors	(0) Presence of comorbidities: chronic kidney disease, high blood pressure, dyslipidemia, obesity and immunosuppressed by medication. Other metabolic changes. Age and gender. Duration of diabetes.
		(+) was assigned when 1 or 2 of these characteristics were present
		(++) if there were 3 or more.
	Distortion reduced by analysis	(0) Stratified data analysis was performed, or regression analysis considering possible confounding factors. Or, there was no need due to the absence of confounding factors.
		(+) adjustment of the analyzes was performed only in relation to some confounding factors.
		(++) there were confounding factors, but this was not considered in the analyzes.
Summary Questions	Bias - Are the results erroneously biased in a certain direction?	Yes / No
	Confounding - Are there any serious confounding or other distorting influences?	Yes / No
	Chance - Is it likely that the results occurred by chance?	Yes / No

NA – Not applied.

Appendix 3. Studies excluded and reason of the exclusion

Reason 1. Absence of group T2DM without Periodontitis
PUBMED
1. Arana C, et al. Increased salivary oxidative stress parameters in patients with type 2 diabetes: Relation with periodontal disease. Endocrinol, Diabetes Nutr. 2017; 64 (5):258-264.
2. Bazyar H, et al. The Impacts of Synbiotic Supplementation on Periodontal Indices and Biomarkers of Oxidative Stress in Type 2 Diabetes Mellitus Patients with Chronic Periodontitis Under Non-Surgical Periodontal Therapy. A Double-Blind, Placebo-Controlled Trial. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2020; 13: 19-29.
3. Duarte PM, et al. The expression of antioxidant enzymes in the gingivae of type 2 diabetics with chronic periodontitis. Archives of oral biology 2012; 57: 161-168.
4. El-Sharkawy H, et al. Propolis Improves Periodontal Status and Glycemic Control in Subjects With Type 2 Diabetes Mellitus and Chronic Periodontitis: A Randomized Clinical Trial. Journal of Periodontology 2016; 87 (12):1418-1426.
5. Gayathri S, et al. Effect of Initial Periodontal Therapy on Serum Nitric Oxide Levels in Chronic Periodontitis Patients with or without Type 2 Diabetes Mellitus. The Journal of Contemporary Dental Practice 2019; 20 (2):197-203.
6. Javid AZ, et al. Impact of resveratrol supplementation on inflammatory, antioxidant, and periodontal markers in type 2 diabetic patients with chronic periodontitis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2019; 13:2769-2774.
7. Javid AZ, et al. The effects of ginger supplementation on inflammatory, antioxidant, and periodontal parameters in type 2 diabetes mellitus patients with chronic periodontitis under non-surgical periodontal therapy. A double-blind, placebo-controlled trial. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2019; 12:1751-1761.
8. Koregol AC, et al. 8-Isoprostane in chronic periodontitis and type II diabetes: Exploring the link. Dental Research, Dental Clinics, Dental Prospects JODDD 2018; 12(4):252-257.
9. Koromantzos PA, et al. Effect of Non-Surgical Periodontal Therapy on C-Reactive Protein, Oxidative Stress, and Matrix Metalloproteinase (MMP)-9 and MMP-2 Levels in Patients With Type 2 Diabetes: A Randomized Controlled Study. Journal of Periodontology 2012; 83(1):1-10.
10. Lobão, WJM, et al. Redox biomarkers in saliva and nuclear abnormalities in jugal epithelial cells of individuals with type 2 diabetes mellitus and periodontitis. Arch Oral Biol 2024; 161:105915.
11. Masi S, et al. Mitochondrial oxidative stress, endothelial function and metabolic control in patients with type II diabetes and periodontitis: A randomized controlled clinical trial. International Journal of Cardiology 2017; 15 (271):263-268.
12. Mizuno H, et al. The effects of non-surgical periodontal treatment on glycemic control, oxidative stress balance and quality of life in patients with type 2 diabetes: A randomized clinical trial. PLoS ONE 2017; 12(11):1-17.
13. Patil VS, et al. Chronic Periodontitis in Type 2 Diabetes Mellitus: Oxidative Stress as a Common Factor in Periodontal Tissue Injury. Journal of Clinical and Diagnostic Research 2016; 10(4):12-16.
14. Pradeep AR, et al. 4-Hydroxy-2-nonenal, an oxidative stress marker in crevicular fluid and serum in type 2 diabetes with chronic periodontitis. Contemp Clin Dent. 2013; 4(3):281-285.
15. Sonoki, K, et al. Decreased Lipid Peroxidation Following Periodontal Therapy in Type 2 Diabetic Patients. J Periodontol. 2006; 77(11):1907-1913.
16. Thomas B, et al. A comparative evaluation of antioxidant enzymes and selenium in the serum of periodontitis patients with diabetes mellitus type 2. Contemp Clin Dent. 2013; 4(2):176-180.
17. Thomas B, et al. Serum levels of antioxidants and superoxide dismutase in periodontitis patients with diabetes type 2. Journal of Indian Society of Periodontology 2014; 18(4):451-58.
18. Zhu C, et al. The therapeutic role of baicalein in combating experimental periodontitis with diabetes via Nrf2 antioxidant signaling pathway. J Periodont Res. 2020; 55(3):381-391.
COCHRANE
1. Gholinezhad H, et al. Using Ginger Supplement in Adjunct with Non-surgical Periodontal Therapy Improves Metabolic and Periodontal Parameters in Patients with Type 2 Diabetes Mellitus (DM) and Chronic Periodontitis. A Double-Blind, Placebo-Controlled Trial. Journal of Herbal Medicine 2019; 20(100315).
VHL
1. Navarro MLR, et al. Niveles de proteína carbonilada y capacidad antioxidante total en pacientes con diabetes mellitus tipo 2 de reciente diagnóstico y enfermedad periodontal. Revista ADM 2019; 76 (4): 208-213.
2. Penagos AGV, Núñez VMM. Relación del estrés oxidativo con la enfermedad periodontal en adultos mayores con diabetes mellitus tipo 2. Revista ADM 2006; 63 (5):189-194.
Reason 2. research participants with more than one systemic disease
WEB OF SCIENCE
1. Bastos AS. Lipid Peroxidation Is Associated with the Severity of Periodontal Disease and Local Inflammatory Markers in Patients with Type 2 Diabetes. J Clin Endocrinol Metab 2012; 97 (8):1353-1362.
Reason 3. summary study of a larger included in this systematic review
EMBASE
1. Pushparani DS. Serum zinc and iron level in type 2 diabetes mellitus with periodontitis. International Journal of PharmTech Research, 2015; 7 (1):165-171.