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Literature Review Article

Heart tissue alterations in animal models of periodontitis – a systematic literature review

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Abstract

Introduction: The inflammatory process caused by periodontitis is associated with systemic repercussions and other non-communicable chronic diseases, including cardiovascular diseases. **Objective:** To conduct a systematic review on cardiac tissue alterations in animals with experimental periodontitis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) guidelines. **Material and methods:** The systematic literature search employed PubMed, SciELO, Medline, Lilacs, and Scopus databases. Experimental studies using animal models of experimental periodontitis that evaluated cardiac tissue were deemed eligible. The search strategy yielded 1548 articles, from which 13 experimental studies were selected based on the defined inclusion and exclusion criteria. They were then qualitatively analyzed and tabulated. Study quality was assessed using the Systematic Review Center for Laboratory Animal Experimentation (Syrcle) risk of bias tool for animal studies. **Results:** Studies showed cardiac tissue alterations induced by experimental periodontitis in animals, potentially leading to various pathological processes in the heart, characterized by elevated levels of oxidative stress biomarkers in cardiac tissue, increased serum levels of tumor necrosis factor-alpha (TNF-α), IL-1β, IL-10, and C-reactive protein (CRP), and histological changes in cardiac tissue. **Conclusion:** This review provides evidence regarding cardiac tissue alterations in animals with experimental periodontitis, suggesting that changes in cardiac tissue may occur in animals with this inflammatory condition; however, we found that the literature is limited. Therefore, further studies are necessary to validate and elucidate the mechanisms linking cardiovascular diseases to periodontitis.

Introduction

Periodontitis is a multifactorial chronic inflammatory disease associated with dysbiotic biofilm. It is characterized by the progressive destruction of tooth-supporting tissues. If untreated, it can lead to tooth loss [7]. More than 50% of the global population suffers from periodontitis. Its severe form ranks as the sixth most prevalent disease worldwide, affecting approximately 743 million people, or 11% of the human population [38]. The prevalence of periodontitis begins in late adolescence and peaks around the age of 55. Men and women are equally affected [42].

In addition to its local effects, periodontitis is associated with systemic changes and is considered a public health issue [19]. There is a well-established relationship between periodontal inflammation and systemic alterations such as cardiovascular diseases (CVDs) [31, 34], diabetes mellitus [13], Alzheimer's disease [26], chronic kidney disease [9], among others. One possible explanation for this association is that periodontitis generates low-grade inflammation, which may facilitate the development of other comorbidities [14]. Additionally, periodontitis is part of the non-communicable chronic diseases (NCDs) group. According to the Pan American Health Organization/World Health Organization, such diseases are the leading causes of death globally, with an estimated 31% of all deaths attributed to cardiovascular diseases alone [30].

The current scientific consensus is that chronic inflammatory diseases can induce a state of systemic inflammation, thereby increasing the risk of CVDs [23]. Recent studies show that the harmful effects of periodontitis are not limited to the oral cavity, but can also affect the entire organism [32]. Periodontitis is associated with systemic diseases such as CVDs, diabetes, and osteoporosis [41]. Some studies in the current literature already consider them as risk factors for CVDs, diabetes, and respiratory infections [35].

Preclinical studies demonstrate degenerative changes induced by periodontitis in the cardiac tissue of animals. Periodontitis acts as a chronic source of stress for cardiomyocytes, which may prompt myocardial inflammation, thus leading to cardiovascular dysfunction in the long term [21, 23, 25, 29, 36]. It is believed that systemic inflammation associated with the microbiota present in periodontal disease may contribute to the development of endothelial dysfunction [36].

However, the mechanism linking periodontitis to cardiac tissue remains unclear. Thus, this study aims to conduct a systematic review to evaluate cardiac tissue changes in animals with induced periodontitis.

Material and methods

A systematic review was conducted following the standards established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma) up to February 2024. The protocol was registered in Prospero (registration number CRD42022346153).

Focused question

The research question was formulated using the PICOT format – Population: animals with experimentally induced periodontitis; Intervention: methods for inducing experimental periodontitis in animals; Control: animals without periodontitis; Outcome of interest: changes in cardiac tissue of animals with experimental periodontitis; Study type: in vivo animal study. The resulting question was: "What are the alterations in the cardiac tissue of animals subjected to experimental periodontitis induction?".

Eligibility criteria

Only in vivo studies with experimentally induced periodontitis using animal models that analyzed cardiac tissue were considered eligible for this study. Studies published in languages other than English, Spanish, or Portuguese were excluded. Reviews, clinical trials in humans, and studies not addressing periodontitis and cardiac tissue were excluded. Studies that addressed periodontal disease but did not induce bone loss in their experimental models and/or lacked a control group were also excluded.

Search strategies

The search strategy was developed using the terms/keywords "Periodontitis" and "cardiovascular diseases" combined with the "AND" operator. The terms were chosen from the MeSH/DeCS[1] Thesaurus (supplementary table I). The search was conducted in the following databases: PubMed, SciELO, Medline, Lilacs, and Scopus, up to January 2024 (January 31, 2024). Alerts were set in the databases to identify studies published after the search date, up to February 2024. In addition to these databases, gray literature references were consulted.

[1] DeCS (Health Sciences Descriptors): a controlled vocabulary by Bireme/PAHO/WHO for standardizing descriptors in the indexing of scientific articles in health, similar to MeSH.

Study selection process

References from the consulted databases were aggregated and exported to the Rayyan® software, where duplicates were first identified and removed, as described in the PRISMA flow diagram (figure 1). The screening process consisted of two phases: initially, articles that contained the search strategy terms identified in MeSH/DeCS explicitly present in their title or abstract underwent title and abstract screening using the eligibility confirmation process. This initial phase was conducted by two independent reviewers (CRF and RTM), who classified studies as included/excluded. Those classified as irrefutable or questionable were re-evaluated by a third reviewer (GIK) for consensus. Articles classified as included proceeded to the second phase, in which the texts were fully read to confirm their eligibility (supplementary table II). Studies meeting all eligibility criteria were included and used for data extraction.

Data extraction

Data was extracted using a standardized Excel spreadsheet. From the included articles, the following data was extracted: author; year of publication; title; publication venue (journal); reference (DOI/PMID); study objective; animal model; experimental periodontitis model; duration of experimental periodontitis induction; sample size and comparison groups; variables analyzed; cardiac tissue outcomes (primary outcome of interest); other results; and conclusions. The collected information was organized into tables (table I and supplementary table II).

Risk of bias assessment

The methodological quality of evidence was assessed using the Syrcle tool for animal studies, recommended by Cochrane, to evaluate bias risk (table I). This assessment was conducted by two reviewers (CRF, GIK). For each bias domain, studies were classified as presenting a low, unclear, or high risk of bias. Discrepancies were discussed with a third reviewer for consensus (RTM). No studies were excluded based on the risk of bias.

Table I – Risk of bias assessment

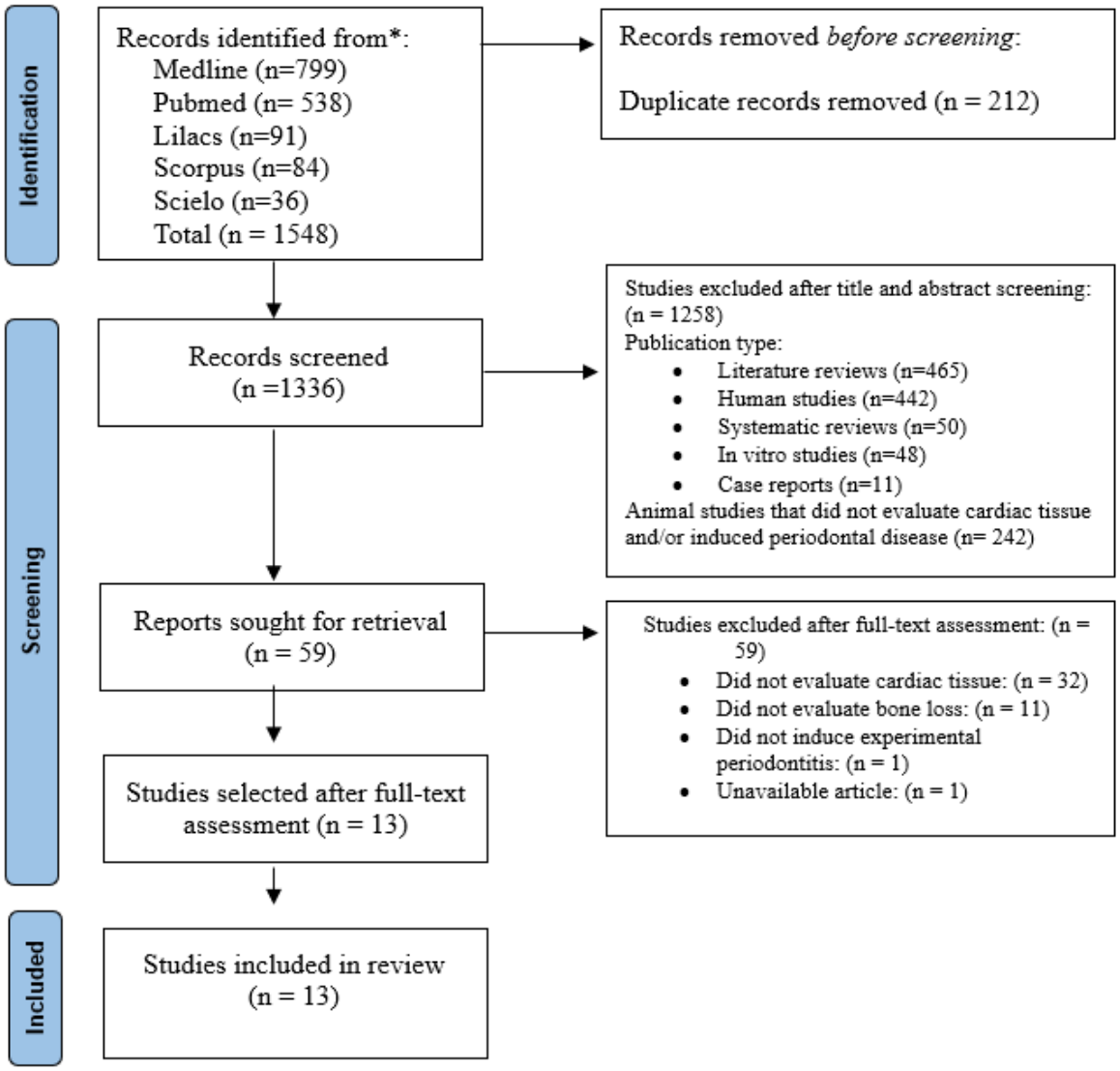
	Xiang *et al.* [40]	Elhaieg *et al.* [10]	Chen *et al.* [8]	Ribeiro *et al.* [32]	Yiğit *et al.* [44]	Kocaman *et al.* [21]	Köse *et al.* [25]	Köse *et al.* [23]	Köse *et al.* [24]	Özdem *et al.* [29]	Tomofuji *et al.* [36]	Herrera *et al.* [15]	Yu *et al.* [45]
Sequence generation	+	+	+	!	+	+	+	+	!	!	+	+	+
Baseline characteristics	+	+	+	+	+	+	+	+	+	+	+	+	+
Allocate concealment	!	!	!	!	!	!	+	!	!	!	!	!	!
Random housing	!	+	+	!	!	!	+	!	!	!	+	!	+
Blinding	!	+	!	!	!	!	!	+	!	!	+	!	!
Random outcome assessor	+	+	!	!	!	+	!	+	+	!	+	!	!
Blinding outcome assessors	+	!	+	!	!	+	!	+	+	!	+	!	!
Incomplete outcome	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective outcome reporting	+	+	+	+	+	+	+	+	+	+	+	+	+
Other sources of bias	+	+	+	+	+	+	+	+	+	+	+	+	+

+ Low risk of bias ! Risk of unclear bias - High risk bias

Results

Figure 1 depicts 1548 articles identified through electronic searches using keywords and additional filters (799 from Medline; 538 from PubMed; 91 from Lilacs; 84 from Scopus; and 36 from SciELO). Following the removal of duplicates and/or triplicates (n = 212), 1336 studies underwent title and abstract screening. 1258 studies were subsequently excluded, predominantly due to the wrong publication type (n = 1016) and the absence of cardiac tissue evaluation and/or periodontal disease induction (n = 242). A subsequent thorough examination of the remaining 59 publications' full text, excluded 46 studies. Finally, the 13 remaining studies were included in this review and deemed suitable for data extraction (figure 1).

Figure 1 – Prisma 2020 flowchart of search results



Study characteristics

The main characteristics of the studies were summarized and tabulated according to the following parameters, established by authors CRF and RTM: author/year of publication, animal model, experimental periodontitis model, induction time, comparison groups, methods of cardiac tissue analysis, and cardiac tissue results (outcome of interest) (table II).

Table II – Summary of study characteristics included

Author/ year	Animal model	Experimental periodontitis model	Follow-up time	Comparison groups	Methods of cardiac tissue analysis	Results
Xiang *et al.* [40]	Rats	Ligation of upper second molars followed by bi-daily application of a bacterial mixture (Porphyromonas gingivalis [Pg] and Aggregatibacter actinomycetemcomitans [Aa]) for 2 weeks.	4 weeks	Control group (n=7) Periodontitis group (n=7)	In vivo electrophysiological measurement; immunohistochemistry (RGS1 expression); histology (Hematoxylin-Eosin [HE] and Masson's Trichrome [TM] staining); Western blotting.	• RGS1 expression was significantly higher in the periodontitis group compared to the control. • Histology revealed extensive inflammatory cell infiltration in atrial tissues (HE staining) and fibrous deposits in the periodontitis group (Masson's trichrome).
Elhaieg *et al.* [10]	Rats	Ligation of the mandibular first molar.	5 weeks	Sham-operated group (Control group; n=8) Experimentally induced periodontitis group (IP; n=8)	Histological staining with Hematoxylin-Eosin (HE).	• The sham group exhibited normal myocardial structure. • The periodontitis group showed significant histopathological alterations, including myocyte degeneration, disorganized arrangement, and absence of nucleation, along with increased interstitial tissue and inflammatory infiltration around arterioles.

To be continued...

Continuation of table II

Author/ year	Animal model	Experimental periodontitis model	Follow-up time	Comparison groups	Methods of cardiac tissue analysis	Results
Chen *et al.* [8]	Rats	Ligation of the maxillary first molar and application of bacterial liquid locally.	4 weeks	Control group (Con group; n=8) Type I diabetes mellitus* group (DM group; n=8) Periodontitis group (PD group; n=8) Type I diabetes mellitus* with periodontitis group (DM + PD group; n=8) Artesunate 10 mg/ kg treatment group [DM* + PD + ART** (10 mg/kg); n=8] Artesunate 30 mg/ kg treatment group [DM* + PD + ART** (30 mg/kg); n=8] Artesunate 60 mg/ kg treatment group [DM* + PD + ART** (60 mg/kg); n=8] * Type I diabetes mellitus established by a single intraperitoneal injection of streptozotocin 60 mg/kg ** Artesunate: ART	Histological staining (HE, Masson, Sirius red, TUNEL), immuno-histochemistry (NF-KB, P38 MAPK, TGF-β, SMAD2, MMP9), quantitative RT-qPCR (NF-KB, ICAM-1, P38 MAPK, TGF-β, MMP9).	• Cardiac changes in DM and DM + PD groups: edema, cell degeneration, and disordered interstitial fibers. Significant apoptosis in cardiomyocytes in DM and DM + PD groups (TUNEL assay). • Higher expression of NF-KB, p38 MAPK, TGF-β, SMAD2, and MMP9 in DM and DM + PD groups, indicating inflammation, fibrosis, and apoptosis compared to the control. • Elevated mRNA expression of NF-KB, p38 MAPK, TGF-β, and MMP9 in the DM + PD group. Heart weights in DM and DM + PD groups were significantly reduced.
Ribeiro *et al.* [32]	Rats	Bilateral ligation of the mandibular first molar.	15 days	Spontaneously hypertensive group (SHR) with periodontal disease (SHR+PD; n= 5-7). SHR without periodontal disease (SHR+Sham; n = 5-7). WKY with periodontal disease (WKY + PD; n= 6-10). WKY rats without periodontal disease (WKY + Sham; n = 6-7).	Measurement of myocardial IL-1β concentration.	Experimental periodontitis increased myocardial IL-1β concentrations only in the SHR + PD group. A significant positive relationship was observed between mandibular bone loss, plasma nitrate (indirect measurement of nitric oxide), and myocardial IL-1β.

To be continued...

Continuation of table II

Author/ year	Animal model	Experimental periodontitis model	Follow-up time	Comparison groups	Methods of cardiac tissue analysis	Results
Yiğit *et al.* [44]	Rats	Ligation of the upper second molars	14 days	Control group (C;n=8) Periodontitis group (P; n=10) Periodontitis + caffeic acid phenethyl ester* (CAPE) group (PC;n=10) * Administered at a dose of 10 μmol/kg/day via intraperitoneal injection for 14 days	Determining the levels of MDA, GSH, and GSH-Px evaluated in cardiac tissue.	No significant differences in MDA levels were observed between groups C and P, with group P showing the highest levels. MDA levels returned to baseline after CAPE administration. Cardiac GSH and GSH-Px levels were significantly lower in group P compared to C and P + CAPE. CAPE treatment restored antioxidant levels.
Kocaman *et al.* [21]	Rats	Ligation on the right upper second molars	30 days	Control group (n=10) Periodontitis group (PD; n=10) Periodontitis + crocin* group (PD+Cr; n=10) * Received 100 mg/kg/day of oral crocin after ligation removal	Measurement of MDA levels in tissues; Measurement of tissue glutathione levels; Measurement of tissue SOD activity; Measurement of CAT tissue activity; Measurement of total tissue oxidant status; Measurement of total tissue antioxidant status; Tissue histopathology.	Periodontitis (PD) induced significant increases in TOS levels and reductions in antioxidant activity (GSH, SOD, CAT) in cardiac tissue compared to control and PD + crocin groups. No significant changes were observed in MDA levels between PD and control groups. Crocin treatment (PD + Cr) reduced MDA and TOS levels while enhancing antioxidant activity. Histological damage in the PD group included disorganized cardiomyocytes, hyalinization, vacuolization, and nuclear pyknosis, with a total damage score of 12. Crocin significantly reduced these damage parameters in the PD + Cr group.

To be continued...

Continuation of table II

Author/ year	Animal model	Experimental periodontitis model	Follow-up time	Comparison groups	Methods of cardiac tissue analysis	Results
Köse *et al.* [25]	Rats	Bilateral ligation of the mandibular first molar	5 weeks	Group control (n=8) Experimental periodontitis group (EP; n=8) Experimental periodontitis group with melatonin* treatment (Ep+Mel; n=8). *Melatonin administered intraperitoneally (10 mg/body weight) for 14 consecutive days after ligature removal.	Ventricular tissue analysis of malonyl aldehyde (MDA), glutathione (GSH), superoxide dismutation (SOD), catalase (CAT), matrix metalloproteinase-9 (MMP-9) and cardiac troponin-T (cTnT)	In the Ep group, the MDA level was significantly higher, and the levels of GSH, SOD, and CAT were slightly higher compared to the control group. MMP-9 and cTnT levels were higher in the Ep group compared to the control group. Melatonin caused a significant decrease in MDA, MMP-9, and cTnT levels compared to the Ep group. Melatonin did not cause significant changes in tissue antioxidant parameters (GSH, SOD, and CAT) compared to the control and Ep groups.
Köse *et al.* [23]	Rats	Bilateral ligation of the first molar	5 weeks	Control group (no ligature; n=9) Experimental periodontitis group (EP; n=9)	Histopathological analysis (triple Mallory staining modified from Crossman): Evaluation of inflammatory activity, cellular changes, cardiomyocyte cross-sectional area, and myocyte nuclear volume. Immunohisto-chemical analysis: NF-κB-p65 and β-MHC expression, cell density, and positive cell counts.	Cardiac tissue in the EP group demonstrated significant histopathological alterations, including cellular degeneration, collagen accumulation, inflammatory cell infiltration around arterioles, capillary endothelial changes, and perivascular fibrosis. NF-KB-positive cell counts were significantly higher in the EP group, and β-MHC positivity was more intense compared to the control group, indicating heightened inflammatory and molecular stress responses. Although the cross-sectional area of cardiomyocytes showed significant differences between groups, the volume of cardiomyocyte nuclei was not significantly altered.

To be continued...

Continuation of table II

Author/ year	Animal model	Experimental periodontitis model	Follow-up time	Comparison groups	Methods of cardiac tissue analysis	Results
Köse *et al.* [24]	Rats	Bilateral ligation of the mandibular first molar.	5 weeks	Control group (no ligature;n= 10) Experimental periodontitis group (EP; n=10)	Evaluation of left ventricular tissue levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), malondialdehyde (MDA), glutathione peroxidase (GSH-Px), total oxidant status (TOS), and total antioxidant status (TAS).	Markers of oxidative stress, including MDA, 8-OHdG, and oxidative stress index (TOS/ TAS ratio), were significantly elevated in the EP group compared to controls, indicating increased oxidative damage. However, antioxidant markers (GSH-Px, TAS) did not show statistically significant differences between the groups.
Özdem *et al.* [29]	Rats	Ligation of the upper second molars	4 weeks	Healthy + saline (Hs, n = 7) Healthy + melatonin* (Hm, n = 7) Periodontitis + saline (Ps, n = 8) Periodontitis + melatonin* (Pm, n = 8). * The melatonin was applied intraperitone-ally (10 mg/kg) every day for 2 weeks	Measurement of malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) levels in cardiac tissues.	SOD levels were similar between groups, while MDA in the Ps group was higher than in the Hs group. Furthermore, GSH-Px levels were higher and MDA levels were lower in Hm rats compared to Hs rats. The Pm group had lower MDA levels and higher GSH-Px levels compared to the P group.
Tomofuji *et al.* [36]	Rats	Topical application of bacterial pathogens [25 μg/μL *Escherichia coli* (*E. coli*) lipopolysac-charide (LPS) and 2.25 U/ μLStreptomy-ces griseus proteases]. LPS (0.5 μL × 3 times) and proteases (0.5 μL × 3 times) or pyrogen-free water (0.5 μL × 6 times) were introduced daily into the gingival sulcus of both upper first molars under anesthesia.	4 weeks	Periodontal inflammation* group (n=6); Received bacterial pathogens topically Control group** (n=6); Received pyrogen-free water topically	Histopathological analysis of cardiac tissue (hematoxylin and eosin); Measurement of tissue 8-hydroxy-2'-deoxyguanosine (8-OHdG).	Mitochondrial 8-OHdG levels were 2.01 times higher in the periodontal inflammation group than in the control group. However, no damage or inflammatory changes were observed in the cardiac tissue of either group.

To be continued...

Continuation of table II

Author/ year	Animal model	Experimental periodontitis model	Follow-up time	Comparison groups	Methods of cardiac tissue analysis	Results
Herrera *et al.* [15]	Rats	Ligation of the lower right first molar	3, 7 and 14 days	1.Sham groups (no ligature): oSham 3 days (S; n=10) Sham 7 days (S; n = 10) Sham 14 days (S; n = 10) 2.Sham + L-NAME groups (NO synthase inhibitor administered): Sham + L-NAME 3 days (S + L-NAME; n = 10) Sham + L-NAME 7 days (S + L-NAME; n = 10) Sham + L-NAME 14 days (S + L-NAME; n = 10) 3.Ligation groups (periodontitis-induced): Ligation 3 days (L; n = 10) Ligation 7 days (L; n = 10) Ligation 14 days (L; n = 10) 4.Ligation + L-NAME groups (periodontitis + NO synthase inhibitor): Ligation + L-NAME 3 days (L + L-NAME; n = 10) Ligation + L-NAME 7 days (L + L-NAME; n = 10) Ligation + L-NAME 14 days (L + L-NAME; n = 10) L-NAME treatment: Two weeks before ligature placement, animals received. L-NAME (200 mg/L in drinking water, equivalent to ~45-60 mg/kg/day). Treatment continued until euthanasia at 3, 7, or 14 days post-ligation.	TBARS (Thiobarbiturate Reactive Substances): Index of lipid peroxidation. Nitrotyrosine protein (NT): Marker of protein nitration. Myeloperoxidase activity (MPO): Marker of neutrophil infiltration.	Cardiac NT content increased significantly 7 days after ligature placement in normotensive rats. L-NAME treatment completely abolished ligation-induced cardiac NT. MPO activity was higher in the hearts of group ligation + L-NAME compared to the ligation-only group on day 3. On days 7 and 14 no significant changes in cardiac MPO were observed. Ligature-induced periodontitis did not induce significant changes in TBARS. No significant differences were found between groups in cardiac TBARS on the 7th or 14th day after ligature placement.

To be continued...

Continuation of table II

Author/ year	Animal model	Experimental periodontitis model	Follow-up time	Comparison groups	Methods of cardiac tissue analysis	Results
Yu *et al.* [45]	Dogs	Ligation on the second premolar of the mandible	90 days	Control group* (n=10) Periodontitis group* (n=12) * Before the ligation procedure and on days 30, 60, and 90 after ligation, a single atrial extrastimulation was performed in the right upper atrium, atrial septum (SA), and coronary sinus (CS), respectively for electrophysiological evaluation (to measure atrial refractoriness and the inducibility of AF)	Histopatho-logical analysis of cardiac tissues stained with hematoxylin and eosin.	The atrial effective refractory period was reduced, and atrial fibrillation inducibility progressively increased in the periodontitis group. The long and short-axis diameters of atrial cardiomyocytes in the periodontitis group were significantly larger than those in the control group. The number of inflammatory cells in the left atrial appendage, atrial septum, and right atrial appendage in the periodontitis group was higher than in the control group. The number of inflammatory cells in the ventricle of the periodontitis group was not statistically different from the control tissue. Myolysis affected some atrial cardiomyocytes from dogs with periodontitis. In the ventricles, cardiomyocyte hypertrophy and myolysis were not observed, and the inflammatory infiltration was not as general and severe as in the atria, therefore it was not statistically different from the control tissue.

Twelve out of the thirteen studies used rats as the animal model, with only one study [45] employing dogs. The majority of studies employed ligature-induced experimental periodontitis [8, 10, 15, 21, 23-25, 29, 32, 40, 44, 45]. Two studies [8, 40] utilized a combination of models; Chen *et al.* [8] used ligature combined with lipopolysaccharide (LPS) application (*Porphyromonas gingivalis*, Pg, ATCC BAA-308TM), while Xiang *et al.* [40] used ligature followed by bacterial mixture application comprising *Porphyromonas gingivalis* (Pg) and *Aggregatibacter actinomycetemcomitans* (Aa) on the ligature

thread. Only one study [36] did not use ligature as the primary method for inducing experimental periodontitis; instead, bacterial LPS and proteases applied to the gingival sulcus were chosen. There were also variations in experimental periodontitis induction protocols; the longest duration was 90 days [45], followed by 35 days [10, 23-25], 30 days [21], 28 days [8, 36, 40], 15 days [32], 14 days [29, 44], and 3, 7, and 14 days [15].

Alveolar bone loss analysis

Histomorphometric analysis to assess alveolar bone loss was conducted in six studies [21, 23-25, 36, 44]. Only two studies [8, 25] performed analysis using computed microtomography (μCT), allowing two- and three-dimensional results. In the other studies, data were obtained through morphometric analysis [10, 29, 32, 40] radiographic evaluation [10, 15, 24, 40], and macroscopic evaluation using a calibrated periodontal probe [45] to assess bone loss. All studies showed significant alveolar bone losses in the experimental periodontitis groups compared to the control groups.

Serological analyses

The inflammatory biomarkers evaluated in each study are summarized in table III.

Table III – Inflammatory biomarkers by study

References	Inflammatory biomarkers
Chen *et al.* [8]	CRP
Yiğit *et al.* [44]	IL-1β, IL-10, TNF-α
Köse *et al.* [23]	IL-1β, TNF-α, CRP
Tomofuji *et al.* [36]	CRP
Yu *et al.* [45]	CRP, TNF-α

Four studies evaluated C-reactive protein [8, 23, 36, 45]. Among these, two studies [23, 36] reported a significant increase in serum CRP levels due to periodontal inflammation. Chen *et al.* [8] did not find a statistically significant difference in serum levels between the periodontitis and the control groups. However, in Yu *et al.* [45], which assessed four different time points, differences were observed only after 60 and 90 days of periodontitis induction; similar results were found for serum TNF-α levels.

In the study by Yiğit *et al.* [44], which induced experimental periodontal disease for 14 days, a significant increase in serum TNF-α levels was evident when compared to the control group, while Köse *et al.* [23], which used an experimental periodontal disease induction time of 5 weeks, did not find this difference in animals with periodontitis.

When analyzing the inflammatory biomarker IL-1β, both studies [23, 44] used the ligature model and found significant differences between the periodontitis and the control groups. IL-10 was also significantly elevated in the presence of experimental periodontitis [44].

Yiğit *et al.* [44] analyzed lipid peroxidation levels by measuring MDA, GSH, and GSH-Px in serum; MDA levels increased, and the activity of basic antioxidant enzymes GSH and GSH-Px decreased in experimental periodontitis serum compared to the control group. Tomofuji *et al.* [36] evaluated serum levels of hexanoyl-lysine (HEL), a biomarker for early-stage lipid peroxidation, and found higher serum levels in the periodontal inflammation group compared to the control group. In the same study, serum LPS levels were evaluated, and no difference was found between the groups.

Kocaman *et al.* [21] conducted biochemical analyses showing indicators of serum bone destruction (C-telopeptide of type I collagen: CTx1; bone alkaline phosphatase: b-ALP) and cardiac tissue injury (lactate dehydrogenase: LDH and creatine kinase myocardial band: CK-MB). Serum levels of CTx1 were higher and b-ALP levels were lower in the periodontitis group compared to the control group. Significant elevations in LDH and CK-MB levels were observed in the periodontitis group.

Köse *et al.* [24] assessed the effects of periodontitis on serum paraoxonase-1 (PON-1) activity, which was significantly lower in rats with periodontitis compared to the control group.

Only one study [32] measured plasma nitrate levels (an indirect measurement of nitric oxide). The periodontitis group showed a significant increase in plasma nitrate levels in both evaluated rat strains (Wistar Kyoto: WKY and spontaneously hypertensive rats: SHR) with experimental periodontitis.

In the study by Chen *et al.* [8], other serological analyses were performed, such as terminal blood glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). However, none of those showed significant alterations between the control and periodontitis groups.

In the study performed by Köse *et al.* [23], lipid profile analysis was conducted, including total cholesterol (Tcho), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and HDL/LDL ratio. Significant differences were found in Tcho, LDL, triglycerides, and HDL/LDL.

Histological analyses of cardiac tissues

Histopathological evaluation was conducted in six studies [8, 10, 21, 23, 40, 45]. The primary significant histopathological findings observed with HE staining included: inflammatory cell infiltration [10, 23, 40], histopathological alterations including cell degeneration [10, 21, 23], collagen deposition [23, 40], and changes in cardiomyocyte diameter [45]. In the study conducted by Chen *et al.* [8], various staining techniques, including HE, Masson, PSR, and TUNEL (used to identify apoptosis in cardiomyocytes), were applied to analyze the cardiac tissue of rats that underwent 4 weeks of experimental periodontitis induction. The periodontitis group did not show significant changes compared to the control group in any of the stains performed; however, changes were found with the combination model of type I diabetes and periodontitis.

Immunohistochemical and immunoenzymatic analyses of cardiac tissue

Only three studies [8, 23, 40] performed immunohistochemical analyses of cardiac tissue. In the study by Köse *et al.* [23], immunohistochemical analyses of nuclear factor kappa B-p65 (NF-κB-p65) and beta-myosin heavy chain (β-MHC) were conducted. The number of cardiomyocytes positive for NF-κB-p65 and β-MHC significantly increased in the left ventricle tissue samples of rats with periodontitis. Chen *et al.* [8] performed a qualitative analysis of the expression of apoptosis and inflammatory pathway proteins in myocardial tissue through immunohistochemical staining of NF-κB, p38 MAPK, TGF-β, Smad2, and MMP9 to explore the relevant pathway mechanism. The periodontitis group showed higher expression levels of each protein than the control group, indicating that apoptosis, inflammation, and fibrosis occurred in the myocardium of the periodontitis group. In the same study, quantitative analysis of the gene expression of apoptosis and inflammatory pathways in myocardial tissue by RT-PCR was also performed. The mRNA expression levels of NF-κB, p38 MAPK, TGF-β, and MMP9 were significantly increased in the periodontitis group compared to the control group [8]. Xiang *et al.* [40] conducted immunohistochemical and western blotting analyses, revealing that the expression of the regulator of the G-protein signaling (RGS1) target gene was significantly higher in the periodontitis group compared to the control group.

ELISA (Enzyme-linked Immunosorbent Assay) analysis of cardiac tissue showed higher levels of matrix metalloproteinase-9 (MMP-9) and cardiac troponin-T (cTnT) in the periodontitis group compared to the control group [25]. Ribeiro *et al.* [32] demonstrated an increase in cardiac concentrations of IL-1β (ELISA) in the periodontitis group.

Analysis of oxidative stress biomarkers in cardiac tissue

Six out of the eleven included studies conducted oxidative stress biomarkers analysis in cardiac tissue [21, 24, 25, 29, 36, 44]. The most commonly used biomarkers were malondialdehyde (MDA) [21, 24, 25, 29, 44] glutathione (GSH) [21, 25, 44], superoxide dismutase (SOD) [21, 25, 29], glutathione peroxidase (GSH-Px) [24, 29, 44], catalase (CAT) [21, 25], total oxidant status (TOS) [21, 24], total antioxidant status (TAS) [21, 24], and 8-hydroxy-2'-deoxyguanosine (8-OHdG) [24, 36]. Table IV summarizes the biomarkers evaluated in each study.

Table IV – Oxidative stress biomarkers by study

References	Oxidative stress biomarkers
Kocaman *et al.* [21]	MDA, GSH, SOD, CAT, TOS, TAS
Yiğit *et al.* [44]	MDA, GSH, GSH-Px
Köse *et al.* [25]	MDA, GSH, SOD, CAT
Özdem *et al.* [29]	MDA, SOD, GSH-Px
Tomofuji *et al.* [36]	8-OHdG
Köse *et al.* [24]	MDA, GSH-Px, TOS, TAS, 8-OHdG

The level of MDA was significantly higher in the periodontitis groups than in the control groups in three studies [24, 25, 29]. Two other studies [21, 44] showed higher MDA levels than the control, but the elevation was not significant between the groups. Among the studies that evaluated GSH levels [21, 25, 44], none showed a significant increase compared to the control group. In contrast, Yiğit *et al.* [44] and Kocaman *et al.* [21] found reduced GSH levels compared to the control group. SOD levels in cardiac tissues, although increased in the study by Kose *et al.* [25], were not significant; in the study by Özdem *et al.* [29], they were similar between the groups. Conversely, in the study by Kocaman *et al.* [21], SOD levels were significantly reduced in the cardiac tissue of rats with induced periodontitis compared to the control group.

The GSH-Px biomarker did not show significant changes in the studies by Özdem *et al.* [29] and Köse *et al.* [24], while Yiğit *et al.* [44] observed significantly lower levels in the periodontitis group

compared to the control group. In the study by Köse *et al*. [25], CAT tissue levels were slightly increased compared to the control group but did not show a statistically significant difference. In contrast, Kocaman *et al*. [21] demonstrated that CAT and TAS levels were significantly reduced in the periodontitis group compared to the control group. In the study by Köse *et al*. [24], these levels were statistically higher in animals with periodontitis. TOS levels in the periodontitis group were significantly elevated compared to the control group [21, 24]. Köse *et al*. [24] determined the oxidative stress index (OSI) through the percentage ratio of TOS to TAS, and periodontitis caused a significant increase in OSI levels. Tomofuji *et al*. [36] analyzed the levels of 8-hydroxydeoxyguanosine (8-OHdG) in cardiac tissue, and the levels in the periodontitis group were 1.40 times higher compared to the control. In the study by Köse *et al*. [24], they were higher in the periodontitis group than in the control group.

Risk of bias analysis

When analyzing the ten items for risk of bias (table I), all included studies (n=13) presented a low risk of bias in three items: "baseline characteristics", "incomplete outcome", "selective outcome reporting", and "other sources of bias". However, the topics "allocation concealment" (n=12), "blinding" (n=10), "random housing" (n=9), "random outcome assessor" (n=7), and "blinding outcome assessors" (n=7) had the most uncertain risks. Only three studies showed uncertain risks in the "sequence generation" item. It is worth noting that some studies lacked information to judge the domains.

Discussion

This review sought to evaluate the alterations in cardiac tissue resulting from periodontitis in experimental studies conducted on animal models. The studies included in this review used different interventions to induce experimental periodontitis (ligature alone, ligature + bacteria, bacteria alone) and all observed alveolar bone loss.

Among the thirteen included studies, there was significant variation in methodology and methodological quality, making standardization challenging. There are various models for inducing experimental periodontitis; however, regardless of study design, outcome measures, animal models, and type of periodontal disease induction, our results indicate that experimental periodontitis is associated with changes in cardiac tissue.

Studies that assessed cardiac tissue histopathologically [8, 10, 21, 23, 40, 45] found infiltration of inflammatory cells [8, 10, 23] and histopathological changes including cellular degeneration [10, 21, 23], collagen deposition [23, 40], and changes in cardiomyocyte diameter [45]. These findings indicate that periodontitis has the potential to cause pathological changes in heart tissue, and therefore may have the potential to exacerbate cardiovascular problems and/or increase the risk of CVDs.

In the study by Chen *et al*. [8], different staining techniques (HE, Masson, PSR, and TUNEL [cardiomyocyte apoptosis]) were used to evaluate cardiac tissue. The periodontitis group showed no significant changes compared to the control in any of the stains performed; however, changes were found with the combined model of type I diabetes and periodontitis. In the study by Ziebolz *et al*. [46], using HE staining of atrial and ventricular tissues collected from patients undergoing aortic valve surgery with periodontitis, cardiac tissue inflammation was evident with an increase in inflammatory cells migrating to the atrium and ventricular myocardium. Based on these results, we hypothesize that periodontitis exacerbates cardiac tissue damage resulting from other diseases that affect cardiac tissue.

Different findings were observed among the included studies, including alterations in oxidative stress biomarkers in cardiac tissue such as MDA, GSH [21, 25, 29, 44], SOD [21, 29, 44], GSH-Px [25, 29], CAT [21, 25], and TOS [21]. Oxidative stress results from the excessive and uncontrolled generation of free radicals under pathological conditions due to excessive activation of phagocytic cells. When there is an imbalance between the production of free radicals (or reactive non-radical species) and antioxidation, the primary induction of tissue degeneration occurs in diseases such as diabetes mellitus [22], chronic kidney disease [28], cardiovascular diseases [4], among others.

Experimental [23, 25, 29, 36] and clinical studies [3, 43] suggest that periodontitis is a chronic inflammatory disease associated with local and systemic oxidative stress. Clinical [16, 18] and preclinical studies [5, 27] have documented endothelial dysfunction associated with periodontitis, leading to decreased nitric oxide production [11, 16, 27].

In the study by Tomofuji *et al*. [36], the increase in LPO products in periodontal inflammation was found to contribute to oxidative DNA damage in the heart. Furthermore, oxidative stress induced

by inflammation can trigger various pathological processes in the heart. Studies indicate that pro-oxidation and reduced antioxidation can cause more cellular and tissue damage, linking periodontitis to different types of oxidative damage, including lipid [1, 6], protein [2], and DNA [6, 39] damage.

The activation of the inflammatory response was demonstrated, with a significant increase in acute phase proteins such as CRP [23, 45]. It is important to note that serum CRP levels may be a significant indicator of cardiovascular disease risk, particularly myocardial infarction [20]. Additionally, CRP appears to play an active role during endothelial dysfunction [45]. Clinical [16, 37] and preclinical [5, 12, 27] studies also associate periodontitis with endothelial dysfunction.

In this review, three studies [23, 44, 45] observed changes in pro-inflammatory cytokines. The studies that evaluated the impact of IL-1β, IL-10, and TNF-α levels found an elevation in serum levels [23, 44, 45]. It is noteworthy that pro-inflammatory cytokines aid in the recruitment of polymorphonuclear leukocytes. Periodontitis is linked to changes in peripheral inflammatory cell patterns, which may influence the connection of the disease with other common systemic diseases, such as cardiovascular disease [17]. In a systematic review aiming to analyze the effects of periodontal treatment on cardiovascular risk parameters in patients with atherosclerotic cardiovascular disease, periodontal treatment was found to improve some biochemical parameters involved in the development of atherosclerotic cardiovascular disease, including CRP, TNF-α, IL-6, fibrinogen, leukocytes, oxidized LDL, and VLDL-C [33].

Only one study [18] measured levels of matrix metalloproteinase-9 (MMP-9) and cardiac troponin-T (cTnT). The analysis of MMP-9 levels in rats with periodontitis showed that periodontitis-related inflammation disrupts the extracellular matrix balance of left ventricular cardiac tissue, and cTnT levels may indicate that periodontitis-related inflammation impairs the homeostasis and vascularization of ventricular cardiac tissue.

This review presents a somewhat limited synthesis of evidence due to the variety of animal models and experimental techniques used in the analyzed studies. Although the studies had the risk of bias scores ranging from low to unclear, the lack of reporting on blinding in animal model experiments may suggest significant bias. On the other hand, the absence of information about random allocation and concealment (not directly relevant to study designs and outcomes) does not represent selection or confounding bias. Nonetheless, there is consistency in the results indicating possible alterations in cardiac tissues resulting from experimental periodontitis in animals. A limitation of our review is the scarcity of included studies and the non-possibility of performing a meta-analysis. Additional research in experimental models of periodontitis and CVDs may help clarify the association between periodontitis and cardiovascular disease.

Limitations

The studies included in this review did not specify the sex of animals as a controlled or analyzed variable. Therefore, the analysis of potential sex-based differences in cardiac tissue alterations could not be explored, representing a limitation for the generalizability of the findings. Incorporating sex-based analyses may contribute to greater precision and reproducibility in future research within this field.

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References

1. Akalın FA, Baltacıoğlu E, Alver A, Karabulut E. Lipid peroxidation levels and total oxidant status in serum, saliva, and gingival crevicular fluid in patients with chronic periodontitis. J Clin Periodontol. 2007;34(7):558-65.

2. Baltacıoğlu E, Akalın FA, Alver A, Değer O, Karabulut E. Protein carbonyl levels in serum and gingival crevicular fluid in patients with chronic periodontitis. Arch Oral Biol. 2008;53(8):716-22.

3. Baltacıoğlu E, Kehribar MA, Yuva P, Alver A, Atagün OS, Karabulut E et al. Total oxidant status and bone resorption biomarkers in serum and gingival crevicular fluid of patients with periodontitis. J Periodontol. 2014;85(2):317-26.

4. Beer C, Blacker D, Hankey GJ, Puddey IB. Association of clinical and aetiologic subtype of acute ischaemic stroke with inflammation, oxidative stress, and vascular function: a cross-sectional observational study. Med Sci Monit. 2011;17(9):CR467-73.

5. Brito LC, DalBó S, Striechen TM, Farias JM, Olchanheski LR Jr, Mendes RT, et al. Experimental periodontitis promotes transient vascular inflammation and endothelial dysfunction. Arch Oral Biol. 2013;58(9):1187-98.

6. Canakçi CF, Canakçi V, Tatar A, Eltas A, Sezer U, Ciçek Y et al. Increased salivary level of 8-hydroxydeoxyguanosine is a marker of premature oxidative mitochondrial DNA damage in gingival tissue of patients with periodontitis. Arch Immunol Ther Exp (Warsz). 2009;57(3):205-11.

7. Caton JG, Armitage G, Berglundh T, Chapple ILC, Jepsen S, Kornman KS et al. A new classification scheme for periodontal and peri-implant diseases and conditions – introduction and key changes from the 1999 classification. J Clin Periodontol. 2018;45 Suppl 20:S1-S8. DOI:10.1111/jcpe.12935.

8. Chen Y, Liang C, Li J, Ma L, Wang B, Yuan Z et al. Effect of artesunate on cardiovascular complications in periodontitis in a type I diabetes rat model and related mechanisms. J Endocrinol Invest. 2023;46:2031-53.

9. Deschamps-Lenhardt S, Martin-Cabezas R, Hannedouche T, Huck O. Association between periodontitis and chronic kidney disease: systematic review and meta-analysis. Oral Dis. 2019;25(2):385-402. DOI:10.1111/odi.12834.

10. Elhaieg A, Farag A, Elfadadny A, Yokoi A, Hendawy H, Mandour AS et al. Effect of experimental periodontitis on cardiac functions: a comprehensive study using echocardiography, hemodynamic analysis, and histopathological evaluation in a rat model. Front Vet Sci. 2023;10:1327484. DOI: 10.3389/fvets.2023.1327484.

11. Ferlazzo N, Currò M, Isola G, Maggio S, Bertuccio MP, Trovato-Salinaro A et al. Changes in the biomarkers of oxidative/nitrosative stress and endothelial dysfunction are associated with cardiovascular risk in periodontitis patients. Curr Issues Mol Biol. 2021;43(2):704-15.

12. Fernandes D, Khambata RS, Massimo G, Ruivo E, Gee LC, Foster J et al. Local delivery of nitric oxide prevents endothelial dysfunction in periodontitis. Pharmacol Res. 2023;188:106616.

13. Genco RJ, Borgnakke WS. Risk factors for periodontal disease. Periodontol 2000. 2013;62(1):59-94. DOI: 10.1111/j.1600-0757.2012.00457.x.

14. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. Nat Rev Immunol. 2021;21(7):426-40. DOI: 10.1038/s41577-020-00488-6.

15. Herrera BS, Martins-Porto R, Campi P, Holzhausen M, Teixeira SA, Mendes GD et al. Local and cardiorenal effects of periodontitis in nitric oxide-deficient hypertensive rats. Arch Oral Biol. 2011;56(1):41-7.

16. Higashi Y, Goto C, Hidaka T, Soga J, Nakamura S, Fujii Y et al. Oral infection-inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease. Atherosclerosis. 2009;206(2):604-10.

17. Irwandi RA, Kuswandani SO, Harden S, Marletta D, D'Aiuto F. Circulating inflammatory cell profiling and periodontitis: a systematic review and meta-analysis. J Leukoc Biol. 2022;111(5):1069-96.

18. Joshipura KJ, Wand HC, Merchant AT, Rimm EB. Periodontal disease and biomarkers related to cardiovascular disease. J Dent Res. 2004;83(2): 151-5.

19. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, Marcenes W. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. J Dent Res. 2014;93(11):1045-53. DOI: 10.1177/0022034514552491.

20. Kodovazenitis G, Pitsavos C, Papadimitriou L, Deliargyris EN, Vrotsos I, Stefanadis C et al. Periodontal disease is associated with higher levels of C-reactive protein in non-diabetic, non-smoking acute myocardial infarction patients. J Dent. 2011;39(12):849-54. DOI: 10.1016/j.jdent.2011.09.005.

21. Kocaman G, Altinoz E, Erdemli M, Gul M, Erdemli Z, Zayman E et al. Crocin attenuates oxidative and inflammatory periodontitis-related cardiac tissue damage in rats. Adv Clin Exp Med. 2021;30(5):453-60. DOI: 10.17219/acem/123856.

22. Koromantzos PA, Makrilakis K, Dereka X, Offenbacher S, Katsilambros N, Vrotsos IA, 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. J Periodontol. 2012;83(1):3-10.

23. Köse O, Arabacı T, Gedikli S, Eminoglu DÖ, Kermen E, Kızıldağ A et al. Biochemical and histopathologic analysis of the effects of periodontitis on left ventricular heart tissues of rats. J Periodontal Res. 2017 Apr;52(2):176-85. DOI: 10.1111/jre.12380.

24. Köse O, Arabacı T, Yemenoglu H, Ozkanlar S, Kurt N, Gumussoy I et al. Influence of experimental periodontitis on cardiac oxidative stress in rats: a biochemical and histomorphometric study. J Periodontal. 2017;52:603-8.

25. Köse O, Kurt Bayrakdar S, Akyıldız K, Altın A, Arabacı T, Yemenoglu H et al. Melatonin improves inflammatory stress related to periodontitis in left ventricular cardiac tissues in rats. J Periodontol. 2020;91(11):1486-94.

26. Ma KS, Hasturk H, Carreras I, Dedeoglu A, Veeravalli JJ, Huang JY et al. Dementia and the risk of periodontitis: a population-based cohort study. J Dent Res. 2022;101(3):270-7. DOI: 10.1177/00220345211037220.

27. Mendes RT, Sordi R, Olchanheski Jr LR, Machado WM, Stanczyk CP, Assreuy J et al. Periodontitis increases vascular cyclooxygenase-2: potential effect on vascular tone. J Periodontol Res. 2014;49(1):85-92.

28. Oberg BP, McMenamin E, Lucas FL, McMonagle E, Morrow J, Ikizler TA et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int. 2004;65(3):1009-16.

29. Özdem M, Kırzıoğlu FY, Yılmaz HR, Vural H, Fentoğlu Ö, Uz E et al. Antioxidant effects of melatonin on cardiac tissue after experimental periodontitis induction in rats. J Oral Sci. 2017;59(1):23-9. DOI: 10.2334/josnusd.59.23.

30. Pan American Health Organization; World Health Organization. Covid-19 fact sheet – PAHO and WHO Office in Brazil. Brasília: PAHO/WHO; 2022 [cited 2022 Dec 1]. Available from: https://www.paho.org/en/topics/cardiovascular-diseases.

31. Priyamvara A, Dey AK, Bandyopadhyay D, Katikineni V, Zaghlol R, Basyal B et al. Periodontal inflammation and the risk of cardiovascular disease. Curr Atheroscler Rep. 2020;22(7):28. DOI: 10.1007/s11883-020-00848-6.

32. Ribeiro AB, Silva TM, Santos-Júnior NN, Castania JA, Fazan Jr R, Salgado HC. Short-term effect of ligature-induced periodontitis on cardiovascular variability and inflammatory response in spontaneously hypertensive rats. BMC Oral Health. 2021;21(1):515. DOI: 10.1186/s12903-021-01885-6.

33. Roca-Millan E, González-Navarro B, Sabater-Recolons MM, Marí-Roig A, Jané-Salas E, López-López J. Periodontal treatment on patients with cardiovascular disease: systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2018;23(6):681-90.

34. Sanz M, Marco Del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P et al. Periodontitis and cardiovascular diseases: consensus report. J Clin Periodontol. 2020;47(3):268-88. DOI: 10.1111/jcpe.13189.

35. Song X, Li J, Jiao M, Chen Y, Pan K. Effect of endoplasmic reticulum stress-induced apoptosis on the role of periodontitis in vascular calcification in a rat model. J Mol Histol. 2021;52(5):1097-104. DOI: 10.1007/s10735-021-09981-3.

36. Tomofuji T, Ekuni D, Irie K, Azuma T, Tamaki N, Maruyama T et al. Relationships between periodontal inflammation, lipid peroxide and oxidative damage of multiple organs in rats. Biomed Res. 2011;32(5):343-9. DOI: 10.2220/biomedres.32.343.

37. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M et al. Treatment of periodontitis and endothelial function. N Engl J Med. 2007;356(9):911-20.

38. Tonetti MS, Jepsen S, Jin L, Otomo-Corgel J. Impact of the global burden of periodontal diseases on health, nutrition and wellbeing of mankind: a call for global action. J Periodontol. 2017;88(3):441-6.

39. Villa-Correa YA, Isaza-Guzmán DM, Tobón-Arroyave SI. Prognostic value of 8-hydroxy-2'-deoxyguanosine and human neutrophil elastase/α1-proteinase inhibitor complex as salivary biomarkers of oxidative stress in chronic periodontitis. J Periodontol. 2015;86(11):1260-7.

40. Xiang J, Cao J, Shen J, Wang X, Liang J, Li X et al. Bioinformatics analysis reveals the potential common genes and immune characteristics between atrial fibrillation and periodontitis. J Periodontal. 2024;59:104-18.

41. Xuan Y, Gao Y, Huang H, Wang X, Cai Y, Luan QX. Tanshinone IIA attenuates atherosclerosis in *Porphyromonas gingivalis*-infected apolipoprotein E knockout mice. Inflammation. 2017;40(5):1631-42. DOI: 10.1007/s10753-017-0615-8.

42. World Health Organization. Global report on oral health: Towards universal health coverage for oral health by 2030. Geneva: WHO; 2022 [cited 2025 Jan 27]. Available from: https://iris.who.int/handle/10665/364538.

43. Yağan A, Kesim S, Liman N. Effect of low-dose doxycycline on serum oxidative status, gingival antioxidant levels, and alveolar bone loss in experimental periodontitis in rats. J Periodontol. 2014;85(3):478-89.

44. Yiğit U, Kırzıoğlu FY, Özmen Ö, Uğuz AC. Protective effects of caffeic acid phenethyl ester on the heart in experimental periodontitis against oxidative stress in rats. Dent Med Probl. 2021;58(3):335-41.

45. Yu G, Yu Y, Li YN, Shu R. Effect of periodontitis on susceptibility to atrial fibrillation in an animal model. J Electrocardiol. 2010;43(4):359-66.

46. Ziebolz D, Rost C, Schmidt J, Waldmann-Beushausen R, Schöndube FA, Mausberg RF et al. Periodontal bacterial DNA and their link to human cardiac tissue: findings of a pilot study. Thorac Cardiovasc Surg. 2018;66(1):83-90.