

REVIEW

Periodontal Inflammation as a Modifiable Contributor to Low-Grade Systemic Inflammation: A narrative review

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ABSTRACT

Periodontitis is a dysbiotic, host-mediated inflammatory disease in which active lesions may intermittently deliver microbial and inflammatory stimuli into the bloodstream. This critical narrative review examined the PubMed/MEDLINE and Cochrane Library databases, supplemented by backward citation tracking. Systematic reviews, randomized trials, longitudinal and Mendelian randomization studies, consensus reports, and mechanistically informative studies were prioritized. Periodontitis is associated with elevated systemic inflammatory biomarkers, particularly C-reactive protein (CRP). Intensive periodontal treatment can trigger a brief acute inflammatory response, followed over weeks to months by modest reductions in CRP and small short-term improvements in glycated hemoglobin levels among individuals with type 2 diabetes. One randomized trial supports improved endothelial function, but this is an intermediate outcome. Cardiovascular and respiratory associations remain susceptible to shared risk factors, exposure misclassification, and residual confounding. Available trials were not designed or powered to determine whether periodontal therapy reduces the risk of myocardial infarction, stroke, cardiovascular mortality, chronic obstructive pulmonary disease progression, or other major systemic events. Therefore, periodontal therapy should be recommended for established oral health benefits and integrated risk factor management, and biomarker changes should not be presented as proof of systemic disease prevention.

Keywords: periodontitis, periodontal inflammation, systemic inflammation, C-reactive protein, periodontal treatment

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Introduction

Periodontitis is a chronic, multifactorial inflammatory disease associated with dysbiotic dental biofilms and is characterized by the progressive destruction of the tooth-supporting apparatus. The 2017 World Workshop framework classifies the disease by stage and grade, integrating severity, complexity, progression, risk factors, and anticipated treatment needs [1]. In this review, periodontitis denotes a clinical disease; periodontal inflammation denotes its biologically active inflammatory state; and periodontal disease is used only when a cited source applies that broader term. This distinction is important because a history of attachment or bone loss does not necessarily indicate current inflammatory activity.

The anatomical interface between a dysbiotic subgingival biofilm, ulcerated pocket epithelium, and dense periodontal microvasculature provides biologically plausible routes for transient bacteremia, dissemination of microbial products, spillover of inflammatory mediators, endothelial activation, and immune cell priming [2]. These mechanisms are biologically plausible; however, they do not establish independent causation or prove that periodontal treatment prevents major systemic clinical events.

Existing reviews and consensus reports have generally emphasized the following components of the field: mecha-

nistic pathways [2], cardiovascular associations and recommendations [3,4], diabetes [3,5], and treatment effects on CRP [6,7]. Unlike disease- or outcome-specific syntheses, this review uses active periodontal inflammation as the organizing exposure and evaluates each inference at four levels: biological plausibility, observational association, surrogate or intermediate modification, and major clinical outcomes. Therefore, its contribution is interpretive rather than another quantitative estimate of effect. This study aimed to identify evidence supporting clinical communication and the unjustified extrapolation from biomarkers to disease prevention.

Methods

A narrative search was conducted in PubMed/MEDLINE and the Cochrane Library for publications from January 2000 to April 2026. The core PubMed strategy combined ("Periodontitis"[MeSH Terms] OR periodontitis [Title/Abstract] OR "periodontal inflammation"[Title/Abstract] OR "periodontal disease"[Title/Abstract]) with ("systemic inflammation"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR interleukin-6[Title/Abstract] OR "tumor necrosis factor"[Title/Abstract]). Separate outcome searches were conducted for cardiovascular disease, atherosclerosis, diabetes, HbA1c, respiratory disease, COPD, periodontal treatment, endothelial function, glycaemic control, biomarkers, and clinical outcomes. The search filters were adjusted for the Cochrane interface.

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Backward citation tracking was used to retain seminal studies when foundational to the topic.

Records were screened by title and abstract, and when needed, by full text. Mechanistic studies were included if they provided evidence of pathways linking periodontal inflammation to systemic outcomes (e.g. animal models and in vitro studies of bacterial products). Systematic reviews, trials, and consensus documents informed clinical claims; longitudinal and genetic-instrument studies informed causal interpretation; and mechanistic studies supported plausibility only. Case reports, abstract-only reports, opinion pieces, non-English reports, and studies that relied only on tooth loss without periodontal ascertainment were excluded. The selection was purposive and iterative, consistent with a narrative review. Statistical power was assessed relative to the prespecified endpoint, effect size, variability, design, and precision, rather than to a fixed sample-size threshold.

The review was developed with reference to the SANRA principles [8]. No protocol was registered, and no exhaustive dual screening, quantitative synthesis, PRISMA flow chart, formal study-level risk-of-bias assessment, or GRADE evaluation was undertaken. Evidence was appraised qualitatively by study design, directness, confounding, selection and measurement bias, consistency, follow-up, precision, and outcome level (biomarker, intermediate phenotype, and major clinical event).

Periodontitis as a dysbiotic inflammatory disease

Subgingival pathogenicity arises from communities rather than from a single organism. Socransky et al. (1998) linked microbial complexes with probing depth and bleeding [9], and the keystone-pathogen model showed how low-abundance species, such as *P. gingivalis*, can disrupt host-microbial homeostasis and sustain an inflammation-dependent dysbiotic community [10]. Therefore, periodontal pathogens act within polymicrobial networks.

Tissue destruction reflects a dysregulated host response to persistent microbial challenges. Neutrophils, macrophages, epithelial cells, fibroblasts, lymphocytes,

and osteoclasts participate in lesions rich in IL-1 β , IL-6, TNF- α , prostaglandin E2, matrix metalloproteinases, and RANKL. Complement/Toll-like receptor crosstalk can sustain inflammation while impairing bacterial clearance [11], and Th17/IL-17 signaling and neutrophil extracellular traps may amplify inflammation and bone loss [12,13]. This host-microbe interaction should not be reduced to "periodontal infection", because microbial presence alone does not define systemic exposure.

The inflamed periodontium as a measurable biological surface

Clinical attachment loss and bone loss reflect accumulated damage, whereas bleeding on probing and suppuration reflect current inflammatory activity. PISA estimates the root-surface area of the bleeding pocket epithelium and has been proposed as a patient-level measure of the active periodontal inflammatory burden [14,15]. This may link site-level probing and bleeding with the tissue surface, through which microorganisms, antigens, or mediators can access the circulation.

PISA is an estimate and has not been validated against gold-standard measures of systemic inflammatory exposure. PISA does not directly measure epithelial ulceration, microbial translocation, or systemic exposure. It depends on full-mouth probing, bleeding assessment, examiner calibration, and assumptions about root morphology [14,15] and does not capture microbial composition, epithelial permeability, or host and vascular responsiveness. PISA and bleeding on probing are useful research descriptors but are not validated predictors of systemic events.

Mechanistic routes from periodontal to systemic inflammation

Periodontal lesions may generate systemic signals through overlapping routes rather than a linear pathway. Figure 1 summarizes the progression from dysbiotic biofilms and inflamed pocket epithelium to systemic dissemination, inflammatory signaling, and clinical associations. The final step represents an association, not proof of causation.

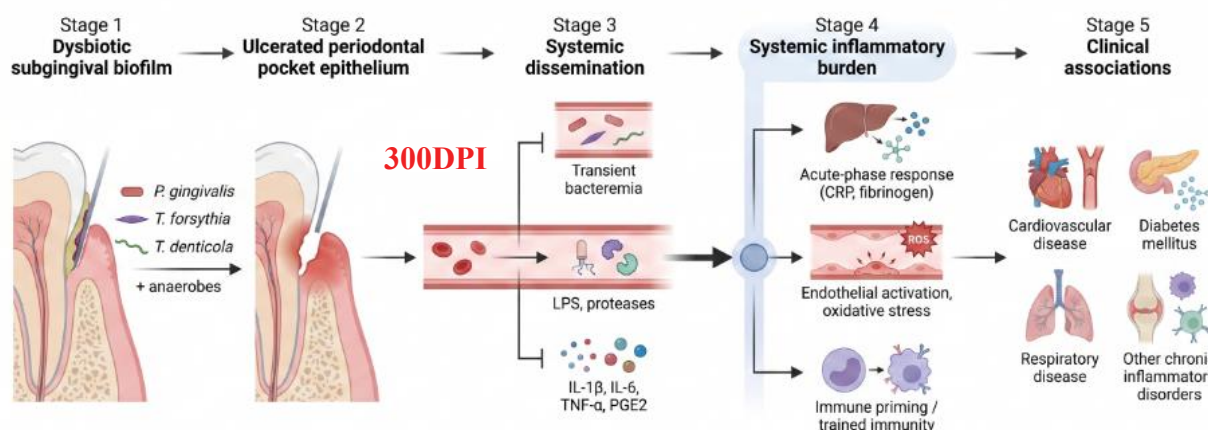


Figure 1. Multilevel pathways may link periodontal inflammation with low-grade systemic inflammation. The illustrated clinical associations represent observational findings and do not establish causation or prove that periodontal treatment prevents these outcomes. Created with BioRender. Beresescu FG (2026). <https://BioRender.com/0urbtzy>.

Tooth brushing and dental extraction can produce transient bacteremia [16]. Inflamed pocket epithelium may increase recurrent exposure to bacterial cells and products, including lipopolysaccharides, gingipains, outer membrane vesicles, and bacterial DNA, thereby activating immune, endothelial, platelet, and hepatic pathways [2,11]. Most episodes of bacteremia are brief, and the detection of bacterial DNA does not prove the persistence of viable organisms. The cumulative dose and patient-specific consequences of this treatment remain unclear.

Periodontal lesions contain cytokines, chemokines, complement fragments, and matrix-degrading enzymes. IL-6-driven hepatic acute-phase signaling plausibly links local inflammation to circulating CRP or fibrinogen. Periodontal improvement has been associated with subsequent reductions in serum inflammatory markers [17], whereas intensive therapy may trigger an immediate acute-phase response before subsequent improvement [18]. These observations describe distinct biological phases of the disease. Consequently, an elevated biomarker in an individual patient cannot be attributed to periodontitis without contextual assessment, and a post-treatment decrease cannot establish a reduced risk of a major clinical event.

Microbial products, cytokines, and oxidative stress may promote endothelial adhesion, monocyte recruitment, reduced nitric oxide bioavailability, and prothrombotic signaling [2,4]. Repeated *P. gingivalis* challenge accelerated atherosclerosis in apolipoprotein E-deficient mice [19], supporting plausibility but not human causality. In a randomized trial, intensive treatment caused acute endothelial dysfunction and systemic inflammation, followed by improved endothelial function at six months [20]. However, this surrogate improvement does not prove fewer myocardial infarctions or strokes.

Th17/IL-17 signaling and neutrophil extracellular traps may amplify this inflammation [12,13]. An exploratory study reported monocyte reprogramming compatible with trained immunity; however, replication and clinical validation are needed [21]. This finding is mechanistically informative; however, its persistence, magnitude, and systemic clinical consequences remain uncertain.

Systemic biomarkers: interpretive value and limitations

CRP is the most extensively studied circulating marker. A meta-analysis found higher concentrations in periodontitis than in controls with heterogeneous case definitions and designs [6]. A meta-analysis of randomized trials found a mean CRP reduction of 0.69 mg/L at six months (95% CI, 0.40-0.97 mg/L lower), high heterogeneity, and limited longer-term evidence [7]. An earlier synthesis found similar trends [22]. This supports a modest short-term change in biomarkers, not a durable clinical benefit.

This inference should be limited to the biomarker level. CRP may lie on a causal pathway, reflect parallel inflammation, or simply mark the total inflammatory burden;

its reduction is not equivalent to preventing major clinical events. IL-6 and TNF-alpha are also nonspecific and sensitive to sampling conditions, metabolic state, comorbidities, and assay platforms. CRP, IL-6, and TNF-alpha levels are influenced by numerous factors, including adiposity, smoking, diabetes, infection, medication, circadian variation, and socioeconomic status.

Future studies should combine accurate phenotyping of periodontal inflammation with pre-specified systemic outcomes and repeated biomarker sampling. Pathway-based panels may be more informative than isolated analytes if they are analytically validated and interpreted without multiplicity-driven overstatements.

Cardiovascular disease: association, intermediate outcomes, and causality

Prospective studies have yielded different estimates of coronary risk. An early cohort study reported higher coronary disease and mortality among participants with dental disease [23], whereas an analysis of 8,032 dentate adults found no convincing adjusted association [24]. In the INVEST, periodontal microbiota correlated with carotid intima-media thickness [25]. A later meta-analysis supported the association with cardiovascular disease but identified heterogeneous periodontal definitions and residual confounding [26].

Intervention evidence mostly concerns surrogate outcomes. One randomized trial showed initial inflammatory and endothelial deterioration, followed by improved endothelial function at six months [20]. PAVE established feasibility in secondary cardiovascular prevention but was not designed to estimate event reduction [27]. Mendelian randomization found no effect of genetically predicted periodontitis on ischemic stroke, coronary artery disease, or subclinical atherosclerosis [28]. However, genetic liability may not reflect current inflammatory activity.

The evidence includes biological plausibility, observational associations vulnerable to confounding, possible improvements in selected surrogates, and insufficient evidence that periodontal therapy reduces the risk of major cardiovascular events [3,4]. Periodontitis should be treated for oral health and integrated risk factor care, not as a cause-specific cardiovascular prevention strategy.

Diabetes mellitus: bidirectionality and treatment effects

Diabetes and periodontitis have a bidirectional relationship [3,5]. Hyperglycemia, AGE-RAGE signaling, oxidative stress, altered neutrophil function, impaired repair, and cytokine dysregulation increase susceptibility to periodontal disease. In contrast, severe periodontal inflammation may contribute to systemic inflammatory and insulin-resistant states. Longitudinal data have linked severe periodontitis with poorer glycemic control [29], and a small intervention study reported lower TNF-alpha and HbA1c levels after treatment [30].

Trials are not uniform. A large, randomized trial improved periodontal status without significant six-month HbA1c benefit [31]. In contrast, a 2022 Cochrane review found moderate-certainty HbA1c reductions of 0.43 percentage points at three to four months and 0.30 at six months [32]. Evidence at 12 months came from a single study. A 2025 meta-analysis reported similar short-term effects with substantial three-month heterogeneity [33]. Responses may vary with baseline HbA1c levels, medical treatment, adiposity, smoking, periodontal severity, intervention, and maintenance.

Mendelian randomization did not support the effect of genetic liability for periodontitis on glycemic traits or type 2 diabetes risk [34]. This does not negate the adverse effects of diabetes on periodontal health or short-term treatment-related HbA1c changes. However, it limits the claim that periodontitis independently causes diabetes. Periodontal therapy remains indicated for oral health and may offer modest ancillary glycemic improvement; however, it does not replace diabetes care or prevent diabetic complications.

Respiratory disease and other chronic conditions

For respiratory diseases, aspiration of oral microorganisms and inflammatory material is a more direct proposed route than cytokine spillover, particularly in frail or hospitalized individuals, those with dysphagia, and those with chronic lung disease. NHANES III showed an association between periodontal disease and chronic respiratory disease [35]. A meta-analysis reported associations with asthma, COPD, and pneumonia but emphasized the heterogeneity among these associations [36].

Shared factors, including smoking, age, socioeconomic disadvantage, medication, frailty, and access to care, complicate causal interpretation, especially for COPD [3,35,36]. Evidence that periodontal treatment prevents COPD progression or major respiratory outcomes is insufficient. Associations with kidney disease, rheumatoid arthritis, inflammatory bowel disease, adverse pregnancy outcomes, cognitive decline, and neurodegeneration may reflect shared pathways or residual confounding factors. These conditions were outside the scope of the focused clinical appraisal and should not be combined into a single causal oral-systemic mechanism.

Clinical implications and interdisciplinary management

Periodontal assessment should distinguish between active inflammation and accumulated damage. Bleeding on probing, suppuration, probing depth, attachment level, bone loss, plaque control, smoking, glycemic status, and maintenance history provide complementary information. Although the PISA score may summarize the inflammatory surface area in research, it is not a validated systemic risk score [14,15].

Patient communication should be precise: periodontal treatment improves oral health and may reduce CRP or

modestly improve short-term HbA1c in selected populations [7,32,33]. It has not been shown to prevent myocardial infarction, stroke, diabetes, COPD, or mortality. Periodontal care complements, rather than replaces, medical risk factor management.

Interdisciplinary care is justified by shared risk factors and opportunities for case detection. Oral health professionals can support smoking cessation, document medical risk indicators, and recommend assessments when history or findings suggest uncontrolled systemic risk. Clinicians can ask about gingival bleeding, tooth mobility, hygiene, and dental attendance and refer for periodontal evaluation when indicated [3]. This coordination supports established prevention and disease management without claiming that periodontal therapy prevents systemic diseases.

What periodontal treatment changes - and what remains unproven

Periodontal therapy is indicated to control dysbiotic biofilms and inflammation and preserve teeth, function, and quality of life. The EFP S3 guidelines recommend stepwise behavior change, supragingival control, subgingival instrumentation, management of residual sites, and supportive care [37]. Decisions should reflect the diagnosis, stage, and grade, patient preferences, comorbidities, and procedural safety.

The systemic effects are time- and outcome-dependent. Intensive instrumentation can transiently increase inflammatory markers and impair endothelial function [18,20]. Later, CRP may decline [7,22], endothelial function may improve [20], and HbA1c may decrease modestly in patients with diabetes [32,33]. These biomarker or intermediate changes do not justify altering evidence-based periodontal therapy to target a systemic endpoint alone. Treatment intensity and staging should follow periodontal guidance in consultation with the patient's physician when systemic conditions, such as diabetes or cardiovascular disease, are present.

Whether reducing periodontal inflammation changes the incidence or progression of major systemic diseases remains unclear. Most trials targeted biomarkers or surrogates, with insufficient follow-up and event counts to assess cardiovascular, respiratory, renal, and neurodegenerative clinical outcomes. Periodontal care should be presented as a necessary oral treatment with possible ancillary systemic effects, not proven systemic disease prevention. Insufficient event evidence is also not proof of an effect.

Critical appraisal, limitations, and research priorities

Evidence limitations vary by design. Mechanistic and animal studies support plausibility but are indirect for human events; cross-sectional studies cannot establish temporality; and cohorts remain vulnerable to exposure misclassification, healthy user effects, and residual confounding. Randomized periodontal trials better estimate biomarker

or intermediate changes. However, intervention heterogeneity, selective outcome reporting, short follow-up periods, and few clinical events limit extrapolation to incidence or mortality rates. Mendelian randomization reduces confounding factors but depends on instrument validity and represents lifelong genetic liability rather than active inflammation. Meta-regression confirms that design differences contribute to heterogeneous systemic outcomes after periodontal therapy [38].

This review was restricted to English-language literature and did not include exhaustive dual screening, a registered protocol, a PRISMA flow diagram, a formal risk-of-bias assessment, GRADE, or quantitative synthesis. Selection and qualitative weighting may therefore reflect author

judgment, and eligible reports may have been excluded. The endpoint-specific evidence, principal threats to inference, and boundaries of clinical interpretation are summarized (Table I).

Figure 2 distinguishes mechanistic plausibility, observational association, modification of biomarkers or intermediate phenotypes, and effects on major clinical outcomes. Evidence at one level cannot be automatically extrapolated to the next. Current evidence supports biological plausibility, epidemiological associations, and selected short-term surrogate changes after periodontal treatment, whereas effects on major systemic clinical events remain unproven (Figure 2).

Prior reviews have provided quantitative estimates of

Table I. Endpoint-specific evidence and boundaries for clinical interpretation.

Evidence domain	What the evidence support	Principal limitations	Appropriate clinical interpretation
Systemic inflammatory biomarkers	Periodontitis is associated with higher CRP levels. A randomized trial meta-analysis found a mean reduction of 0.69 mg/L at six months [6,7,22].	Heterogeneous definitions, assays, sampling, and comorbidity; biomarkers are non-specific; long-term evidence is limited.	Supports a modest short-term biomarker response, not a durable clinical benefit or systemic disease prevention.
Endothelial function	One trial reported acute deterioration after intensive treatment, followed by improved function at six months [20].	One influential trial; flow-mediated dilation is an intermediate outcome; no clinical event inference is possible.	Supports an intermediate vascular effect, not fewer myocardial infarctions or strokes.
Glycemic control in type 2 diabetes	Cochrane estimates were -0.43 percentage points at three to four months and -0.30 at six months; one large trial was null [31,32].	Variable diabetes care, baseline HbA1c, periodontal treatment, and maintenance; sparse 12-month evidence [32,33].	A modest, short-term adjunctive improvement is possible; periodontal therapy neither replaces diabetes care nor prevents complications.
Cardiovascular clinical events	Observational studies support this association; PAVE established feasibility; and Mendelian randomization did not support a direct effect [23-28].	Residual confounding, exposure misclassification, surrogate outcomes, and trials not designed for major events were also considered.	Periodontal therapy is appropriate for oral health and shared risk care, but not for preventing proven cardiovascular events.
Respiratory outcomes	Observational evidence links periodontal measures to COPD, pneumonia, and asthma; aspiration is biologically plausible [3,35,36].	Confounding factors include smoking, age, frailty, dysphagia, and access to care; heterogeneous definitions; and insufficient intervention evidence.	Supports oral care and referral when indicated; does not claim that treatment prevents COPD progression or pneumonia.

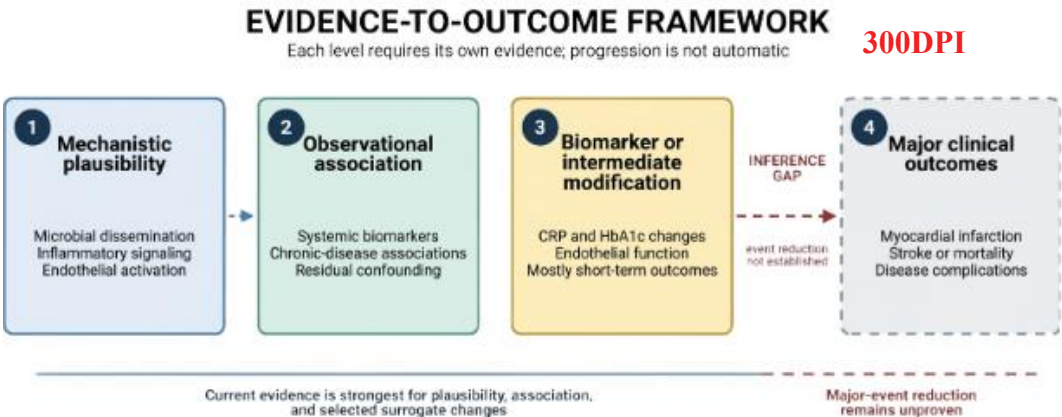


Figure 2. Four-level framework for interpreting evidence linking periodontal inflammation with systemic outcomes. Created in BioRender. Beresescu, F. G. (2026) <https://BioRender.com/2nmbsfw>

individual outcomes [2-7]. The present review contributes a cross-outcome framework that separates evidence of biomarker or intermediate modification from evidence of major event reduction. This boundary is essential for proportionate clinical and educational communications.

Future studies should use full-mouth periodontal definitions, calibrated repeated measurements, pre-specified systemic outcomes, adequate sample size calculations, and

sufficient follow-up. Biomarker studies should standardize sampling and connect trajectories to clinically interpretable endpoints. Longitudinal cohorts, negative controls, mediation analyses, valid genetic instruments, and pragmatic trials can strengthen causal inferences. Intermediate endpoints should be prespecified, mechanistically justified, and validated against clinical outcomes, rather than treated as substitutes.

Conclusions

Periodontal inflammation is a plausible source of intermittent microbial and inflammatory stimuli and is associated with higher systemic biomarker levels. Intensive treatment may briefly increase these markers; over the following weeks or months, therapy is associated with modest reductions in CRP and small short-term improvements in HbA1c in type 2 diabetes. Changes in endothelial function are also intermediate outcomes. These findings support surrogate modification rather than the prevention of major systemic diseases.

For cardiovascular and respiratory diseases, mechanistic and observational evidence is informative; however, residual confounding and insufficient event-focused trials preclude firm causal claims. Whether periodontal treatment reduces myocardial infarction, stroke, cardiovascular mortality, COPD progression, or other major events remain unknown. Periodontal care is a necessary oral treatment with possible ancillary systemic effects, but it has not been proven to prevent systemic disease. The absence of event-trial evidence means that claims of systemic disease prevention remain unproven and should not be made in clinical practice.

Abbreviations

AGE, advanced glycation end product; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HbA1c, glycated hemoglobin; IL, interleukin; NET, neutrophil extracellular trap; PISA, periodontal inflamed surface area; RAGE, receptor for advanced glycation end products; RANKL, receptor activator of nuclear factor kappa-B ligand; TNF-alpha, tumor necrosis factor-alpha.

Author Contributions

FGB (Conceptualization, Methodology, Funding acquisition, Writing - original draft); AB (Data curation, Formal analysis, Resources, Supervision, Validation, Writing - review and editing).

Conflict of Interest

The authors declare no conflict of interest.

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