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Review article

Periodontal inflammation indices in association to systemic diseases

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ABSTRACT

Objectives: Periodontitis is a multifactorial inflammatory disease that has been associated with several systemic inflammatory conditions. Periodontal inflammation indices are quantitative tools used to estimate the inflammatory burden of periodontitis and its potential systemic relevance. The aim of this review was to summarise and critically evaluate the current evidence on periodontal inflammation indices as connecting factors between periodontitis and systemic inflammatory diseases, and to assess their responsiveness to periodontal and systemic therapy.

Data and sources: This narrative review included intervention studies investigating patients with both periodontitis and systemic inflammatory diseases by monitoring the inflammatory status using a periodontal inflammation index. Relevant studies were identified through systematic searches across major electronic databases.

Results: The available evidence is limited and methodologically heterogeneous. Most studies focused on periodontal-inflamed-surface-area (PISA). Intervention studies using PISA have been reported in relation to diabetes mellitus, cardiovascular disease, rheumatoid arthritis, and chronic kidney disease. Several studies indicate that reductions in periodontal inflammatory burden following periodontal or systemic therapy may be accompanied by improvements in selected systemic inflammatory or disease-related parameters. However, these findings are inconsistent and often limited by small sample sizes, short follow-up periods, and inadequate control of confounding factors.

Conclusion: While periodontal inflammation indices provide a biologically plausible framework for quantifying inflammatory burden, the bidirectional relationship between periodontal and systemic inflammation, as well as the long-term impact of therapeutic interventions, remains incompletely understood.

Clinical significance: Periodontal inflammation indices may support the assessment of periodontitis as a contributor to systemic inflammatory burden. Although high-quality evidence is limited, periodontal therapy may represent a non-pharmacological adjunct in the management of certain systemic inflammatory diseases. Consequently, it may be worthwhile for various medical disciplines, researchers, and professional organisations to engage in comprehensive discourse and issue official statements concerning periodontal therapy as a primary and secondary prevention for systemic diseases.

1. Introduction

Periodontal disease is one of the most prevalent inflammatory diseases affecting 1.1 billion humans. With a prevalence of almost 62 % in dentate adults, periodontitis remains a worldwide public health problem [1,2]. It is an irreversible, chronic, multifactorial inflammatory disease caused by a dysbiotic biofilm, characterised by progressive destruction of the tissues that support the teeth [3]. Dysregulation of the immune response plays a major role in the pathogenesis of periodontitis [4]. Genetic [5–7] and lifestyle factors, particularly smoking and poor oral hygiene [8], influence susceptibility to periodontitis by facilitating the expression of bacterial pathogenicity. This interaction between a dysbiotic biofilm and periodontal tissues leads to inflammation. The area of the inflamed epithelial surface which persists during severe

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periodontitis is approximately the size of an adult's palm (Fig. 2) [9,10].

In this regard, periodontal inflammation plays a dual role. The inflammatory response is a physiological reaction aimed at protecting the organism against bacterial infections reaching deeper tissues [4]. However, when inflammation becomes deregulated and persistent, it can result in the irreversible destruction of periodontal tissue, leading to periodontitis and its symptomatic consequences, such as periodontal pockets, attachment loss, gingival recession, tooth mobility, tooth migration and tooth loss [4,11].

In a healthy state, the dentogingival junction acts as a semi-permeable barrier, allowing bacteria, whether planktonic or in biofilm form, to enter the bloodstream [12]. When a subgingival dysbiotic biofilm persists in direct contact with a pocket epithelium, local inflammation can affect systemic health [13]. It is assumed that the following mechanisms exist between periodontitis and systemic diseases. Firstly, periodontal biofilms and their endotoxins, such as gingipains and fimbriae, enter the bloodstream via an ulcerated periodontal pocket, invasive dental procedures like subgingival debridement [14], or even oral hygiene like brushing and flossing [15]. This can lead to systemic bacteraemia [16,17]. Subsequently, this appears to activate a series of cells, receptors, and signalling pathways, including dendritic cells, which play a pivotal role in the immune response and can also act as "transporter" for bacteria and their endotoxins [16]. Furthermore, gingipains from *Porphyromonas gingivalis* have been demonstrated to activate protease-activated receptors and toll-like receptors, leading to an increased inflammatory response involving the release of chemokines and pro-inflammatory cytokines such as interleukin-(IL)-6, prostaglandin E2 and thromboxane B2 [18]. Oral dysbiotic biofilms can affect distant organs directly through bloodstream dissemination, involving the direct migration of resident oral pathogens and their colonisation in distant organs [19]. In some case studies [20], these oral pathogens have been identified as the direct cause of bacterial endocarditis, acute post-streptococcal glomerulonephritis, and infective endocarditis-associated glomerulonephritis.

Secondly, locally produced pro-inflammatory mediators (e.g. cytokines such as IL-1β or matrix metalloproteases) can enter the systemic bloodstream directly via an ulcerated periodontal pocket, thereby affecting distant organs and disrupting the inflammatory equilibrium [21]. Indeed, patients with periodontitis have higher levels of circulating white blood cells and other systemic inflammatory parameters, such as C-reactive protein (CRP), than healthy subjects. Thus, inflammatory loads in the organism are modified. Conversely, systemic inflammation can affect periodontal health (Fig. 1) [22,23].

Thirdly, oral biofilms enter the gastrointestinal tract with saliva during swallowing and cause dysbiosis. This weakens the intestinal tight junctions of the intestinal epithelium. Bacterial translocation via portal vein circulation allows bacterial components, such as pathogen-associated molecular patterns, to enter e.g. the liver. This triggers endotoxemia and inflammatory processes [24,25].

Due to its broad impact, periodontitis has been associated with several systemic inflammatory diseases such as type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), rheumatoid arthritis (RA) and chronic kidney disease (CKD) in the recent decades [26,27]. However, as most studies are observational or cross-sectional in design, questions regarding causality cannot be conclusively answered. Assessing periodontitis as an independent risk factor for systemic diseases is further complicated by its recent association with multimorbidity [27,28]. Periodontitis and many systemic diseases share environmental, lifestyle, and genetic risk factors [8] as well as immunopathological pathways [16]. Diagnosing periodontitis during its active phase and identifying individuals at risk of developing severe forms of the disease presents challenges for clinicians and researchers alike. Advances in diagnostic techniques for periodontal diseases focus on identifying and quantifying the inflammatory load due to periodontal inflammation indices.

A recently published review by our group [29] provides a comprehensive overview of the pathogenic mechanisms and links between periodontitis and various systemic diseases, with a focus on systemic blood inflammation indices, which are thought to form a connection between the two diseases. However, the relationship between different periodontal inflammation indices and periodontitis remains poorly understood and warrants further investigation, as these indices could serve as potential markers of systemic inflammation in patients with systemic diseases. This is the first review to discuss the current literature on periodontal inflammation indices as a surrogate parameter to measure the inflammatory burden of periodontitis in relation to systemic inflammatory diseases.

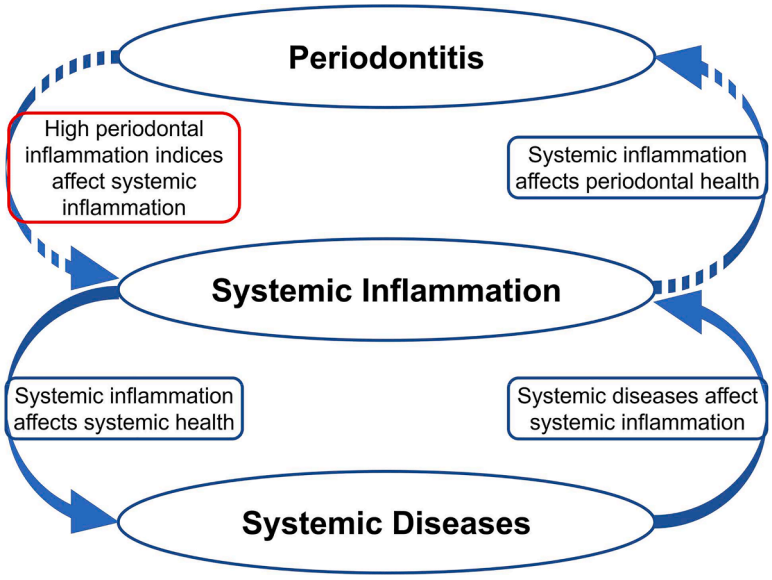

Fig. 1. Inflammation resulting from periodontitis has the potential to extend to a systemic level, thereby influencing the patient's overall inflammatory burden and systemic health [30]. Conversely, systemic diseases can influence systemic inflammation, which in turn may affect periodontal health [31]. Patients with periodontitis and therefore high periodontal inflammation indices may have elevated levels of circulating systemic inflammatory markers, increasing their risk of systemic diseases such as type 2 diabetes mellitus and cardiovascular disease. The present review will focus on the association between periodontitis and systemic diseases via periodontal inflammation indices. Figure modified after Walther et al. [29].

This narrative review includes periodontal inflammation indices such as periodontal inflamed surface area (PISA), periodontal epithelial surface area (PESA), PISA to PESA ratio, dentogingival epithelial surface area (DGES) and periodontal index for risk of infectiousness (PIRI). Furthermore, this review assesses the impact of periodontitis and its treatment on systemic inflammatory diseases, and vice versa, in order to identify causal relationships (Table 1 and 2).

2. Periodontal inflammation indices

Gingival bleeding is an evident manifestation of inflammation in the periodontal tissue. Its clinical monitoring is often inconsistent. Minor gingival bleeding is so frequently occurring that it tends to be overlooked by both patients and dental healthcare providers [32]. Except in cases of acute trauma, bleeding should invariably be interpreted as a sign of inflammation. Bleeding on probing (BOP) signifies a decrease in collagen density, an increase in blood vessel density and fragility and a reduction in periodontal pocket epithelial thickness and integrity [33–35]. The discontinuous, thin or fragile pocket epithelium may facilitate the entry of oral bacteria into the systemic blood circulation. Additionally, BOP is characterised by a dense infiltration of inflammatory cells, including neutrophils, lymphocytes, and macrophages [36–38]. As the most abundant type of leukocyte, neutrophils are central to inflammatory pathways, bridging innate and adaptive immunity, and are often described as a double-edged sword in the immune response [39]. The dentogingival epithelial surface, which encompasses the pocket epithelium in direct contact with the subgingival biofilm, acts as a crucial interface through which local inflammation can affect systemic health. The dentogingival junction represents the interface through which periodontal inflammation may exert systemic effects, which is known as bacteraemia. When microbial loads are minimal and gingival tissues are healthy, such bacteraemia poses minimal threat to host tissues and has low systemic impact [40,41]. This is due to the activity of the innate immune system in dentate mammals, which can respond well to and prevent the entry of bacteria through the dentogingival junction. As described above, severe periodontitis may result in a substantial inflamed epithelial surface. (Fig. 2) [9]. Consequently, locally produced pro-inflammatory mediators may enter the circulation. This contributes to an elevated inflammatory load at a systemic level, which can affect distant organs [30,40,42]. Studies have shown that patients with periodontitis exhibit higher systemic levels of various inflammatory markers, influenced by the composition of the oral microbiome [43]. This indicates increased low-grade systemic inflammation [22,29,44–47].

Multiple indices have been established in the clinical evaluation of gingival inflammation. Early in the literature, descriptive indices of gingival inflammation were introduced and were utilized in studies from the 1960s up to now. Russell developed the first index for periodontal

Table 1
Overview of periodontal inflammation indices.

Index	Calculation	Characteristics	Advantages	Limitations
Periodontal inflamed surface area (PISA)	For each tooth, PPD is combined with gingival margin to estimate the epithelial attachment level. Linear measurements are converted into root surface area using tooth-specific morphometric coefficients. The circumference of the tooth at the gingival margin is multiplied by the epithelial height to calculate epithelial surface area, which is then multiplied by the proportion of sites exhibiting BOP. The sum across all teeth yields the total inflamed surface area in mm^2 [10].	Quantifies the actively inflamed periodontal pocket epithelium as a continuous variable	Biologically plausible estimate of systemic inflammatory exposure; sensitive to periodontal therapy; allows dose–response analyses	Dependent on BOP assessment; may underestimate inflammation in gingival overgrowth or pseudopockets; requires calculation algorithms
Periodontal epithelial surface area (PESA)	Linear periodontal measurements (PPD or CAL) are converted into epithelial attachment height for each tooth. Tooth-specific root surface area data are used to calculate the total epithelial surface area lining the periodontal pocket. Values are summed across the dentition to obtain total epithelial surface area in mm^2, independent of inflammatory status [9,10,65].	Represents total pocket epithelial surface irrespective of inflammation	Provides an anatomical baseline for epithelial exposure; serves as denominator for relative indices	Includes both inflamed and non-inflamed epithelium; does not reflect inflammatory activity or vascularity
Dentogingival epithelial surface area (DGES)	Root surface area is estimated using morphometric data derived from average tooth dimensions. The proportion of root length corresponding to the sulcular, junctional and pocket epithelium is calculated based on CAL. Surface areas for all teeth are summed to estimate total dentogingival epithelial surface area in cm^2 [9].	Structural estimate of epithelial surface exposed to biofilm	Historically important anatomical concept; independent of BOP	Does not account for inflammation; based on population-derived morphometric assumptions; limited biological relevance for systemic inflammation
PISA/PESA ratio	Calculated by dividing total PISA by total PESA and multiplying by 100 to express the proportion of epithelial surface that is inflamed in % [58].	Relative measure of inflammatory burden per available epithelial surface	Normalises inflammation for individual anatomical differences; facilitates inter-individual comparisons	May obscure absolute inflammatory burden; limited normative data; interpretation requires concurrent reporting of absolute values
Periodontal Index for Risk of Infectiousness (PIRI)	Scores are assigned based on the number and depth of PPD exceeding predefined thresholds (scored 1–6) and the number and severity of furcation involvements (scored 1–4). The summed score categorises patients into low (0), moderate (1–5) or high (6–10) infectious risk groups [59,68].	Composite clinical risk score reflecting periodontal lesion severity	Simple and clinically applicable; incorporates PPD and furcation involvement	Does not convert linear measures into surface area; excludes BOP and inflammatory activity; indirect estimate of systemic risk

Abbreviations: PPD= pocket probing depth, CAL= clinical attachment level, BOP= bleeding on probing.

Table 2
PISA and systemic inflammatory diseases.

Parameter	Autor, year, reference, country	Study design	Number of participants, gender, age	Number of diagnosed participants	Treatment/ Intervention	Smoking status	Significant difference in age between groups	Significant difference in gender between groups	Main results of treatment/ intervention	Conclusion
Cardiovascular disease	Donders et al., 2022 [148], Netherland	follow-up pilot study	$n = 42$ (17 males, 25 females, mean age= 54y)	42 patients with/ without P [11]	group 1 ($n = 21$)= SRP+PMPR+OHI+ surgical therapy+ 3–4x SPT, group 2 ($n = 21$)= OHI+ 1–2x PMPR	included non-smokers, former smokers and smokers	n.s.	n.s.	PISA of group 1: baseline= 1,740mm^2; 1y= 295mm^2 ($p < 0.001$) Reactive Hyperemia Index of group 1: baseline= 2.5; 1y= 2.4 ($p = n.s.$) BP systolic of group 1: baseline= 129 mmHg; 1y= 125 mmHg ($p = n.s.$) PISA of group 2: baseline= 319mm^2; 1y= 284mm^2 ($p = n.s.$) Reactive Hyperemia Index of group 2: baseline= 2.5; 1y= 2.4 ($p = n.s.$) BP systolic of group 2: baseline= 123 mmHg; 1y= 121 mmHg ($p = n.s.$) Reactive Hyperemia Index of group 1 vs. group 2: $p = n.s.$	Periodontal therapy does not influence endothelial function
	Jockel-Schneider et al., 2018 [151], Germany	randomized, controlled clinical intervention single-center	$n = 55$ (mean age= 53y, gender not mentioned)	55 patients with P	group 1 ($n = 27$)= 500 mg amoxicillin + 500 mg metronidazole + SRP+PMPR+OHI+ 4x SPT, group 2 ($n = 28$)= SRP+PMPR+OHI+ 4x SPT,	included non-smokers, former smokers and smokers	n.s.	not mentioned	PISA of all patients: baseline= 865mm^2; 1y= 95mm^2 ($p < 0.001$) Pulse wave analysis of all patients: baseline= 8.92m/s; 1y= 8.85m/s ($p = n.s.$) Augmentation index of all patients: baseline= 23.8; 1y= 30.6 ($p = 0.04$) Aortic pulse pressure of all patients: baseline= 39.5 mmHg; 1y= 45.8 mmHg ($p = 0.011$) Changes in PISA between baseline and 12 m were correlated with changes of vascular parameters in all patients: pulse wave analysis: Kendall's tau= 0.208, $p = 0.025$ - augmentation index: Kendall's tau= 0.287, $p = 0.002$ - aortic pulse pressure: Kendall's tau= 0.225, $p = 0.015$ Changes between groups are not shown.	PISA is significantly correlated to vascular parameters
	Miyauchi et al., 2024 [61], Japan	prospective nonrandomized	$n = 288$ (190 males, 98 females, mean age= 68y)	288 patients with P and atrial fibrillation	group 1 ($n = 97$)= 2x SRP+PMPR+OHI after radiofrequency catheter ablation, group 2 ($n = 191$)= no periodontal therapy after radiofrequency catheter ablation	included non-smokers, former smokers and smokers	n.s.	n.s.	PISA of group 1: baseline= 614mm^2; 1.4y= 322mm^2 PISA of group 2: baseline= 311mm2, 1y= 277mm^2 PISA and atrial fibrillation recurrence within 12 months: 456mm^2 vs. 277mm2, $p = 0.001$ group 1 (treatment) significantly fewer atrial fibrillation recurrences than group 2 (non-treatment) after 12 m ($p = 0.04$), but differences throughout long follow-up period were n.s. receiver operating characteristic analysis for atrial fibrillation recurrence (area under the curve= 0.611, sensitivity= 39 %, specificity= 89 %): high-PISA (>615 mm^2) and low-PISA (<615 mm^2) high PISA: HR=2308 (95 %CI 1234–4315), $p = 0.009$ patients with high PISA and periodontal therapy showed significantly fewer atrial fibrillation recurrences ($p = 0.01$, log-rank test), multivariable Cox regression model: high PISA (>615 mm^2): HR= 2.022 (95 %CI: 1175–3479), $p = 0.01$ periodontal therapy: HR= 0.393 (95 %CI: 0.215–0.719), $p = 0.002$	Periodontal therapy and low PISA significantly improves atrial fibrillation ablation outcomes
	Pappe et al., 2025 [150], Germany	secondary sub-analysis of an RCT	$n = 36$ (13 males, 23 females, mean age= 59y)	80 patients with P and hypertension	group 1 = 16 weeks whole food plant-based diet,	included non-smokers, former	not mentioned	not mentioned	PISA of group 1: baseline= 125mm^2; 4m= 92mm^2 ($p = n.s.$) BP systolic of group 1: baseline= 135 mmHg; 4m= 131 mmHg ($p = n.s.$)	Whole food plant-based diet significantly improves PISA in CVD patients

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Table 2 (*continued*)

Parameter	Autor, year, reference, country	Study design	Number of participants, gender, age	Number of diagnosed participants	Treatment/ Intervention	Smoking status	Significant difference in age between groups	Significant difference in gender between groups	Main results of treatment/ intervention	Conclusion
					group 2= no change in diet	smokers and smokers			BP diastolic of group 1: baseline= 81 mmHg; 4m= 80 mmHg (p = *n.s.*) PISA of group 2: baseline= 142mm^2; 4m= 165mm^2 (p = *n.s.*) BP systolic of group 2: baseline= 136 mmHg; 4m= 135 mmHg (p = *n.s.*) BP diastolic of group 2: baseline= 80 mmHg; 4m= 78 mmHg (p = *n.s.*) PISA of group 1 vs. group 2 (4 m – baseline): $p = 0.001$ BP systolic or diastolic of group 1 vs. group 2 (4 m – baseline): p = *n.s.*	
	Seinost et al., 2020 [149], Austria	single-blinded randomized controlled trial	$n = 89$ (75 males, 14 females, mean age= 59y)	89 patients with severe P [218] and peripheral arterial disease	group 1 ($n = 30$)= one-stage full-mouth disinfection + 500 mg amoxicillin, 125 mg clavulanic acid, 500 mg metronidazole + OHI, group 2 ($n = 29$)= one-stage full-mouth disinfection + OHI, group 3 ($n = 30$)= OHI	included non-smokers, former smokers and smokers	n.s.	n.s.	PISA of group 1: baseline= 842mm^2; 3m= not mentioned ($p = 0.001$) BP systolic of group 1: baseline= 140 mmHg; 3m= not mentioned BP diastolic of group 1: baseline= 80 mmHg; 3m= not mentioned PISA of group 2: baseline= 764mm^2; 3m= not mentioned ($p = 0.001$) BP systolic of group 2: baseline= 145 mmHg; 3m= not mentioned BP diastolic of group 2: baseline= 80 mmHg; 3m= not mentioned PISA of group 3: baseline= 918mm^2; 3m= not mentioned BP systolic of group 3: baseline= 147 mmHg; 3m= not mentioned BP diastolic of group 3: baseline= 80 mmHg; 3m= not mentioned ^{18}F-FDG PET/C no change after 3 m in all groups (p = *n.s.*) no significant difference between PISA and ^{18}F-FDG PET/C (p = *n.s.*)	Periodontal therapy does not reduce vascular inflammation
Type 2 diabetes mellitus	Komatsu et al., 2022 [62], Japan	RCT	$n = 46$ (17 males, 29 females, mean age= 65y)	46 patients with T2DM and P stage 2 or 3, grade B	group 1= SRP + azithromycin, group 2= PMPR+OHI	included non-smokers	n.s.	n.s.	PISA of group 1: baseline= 884mm^2; 1m= 100mm^2; 3m= 94mm^2; 6m= 98mm^2; 9m= 66mm^2 ($p < 0.0001$) HbA1c of group 1: baseline= 7.4 %; 1m= 7.3 %; 3m= 7.2 %; 6m= 7.1 %; 9m= 7.1 % ($p < 0.001$) PISA of group 2: baseline= 884mm^2; 1M= 821mm^2 3m= 830mm^2; 6m= 828mm^2; 9m= 833mm^2 ($p < 0.01$) HbA1c of group 2: baseline= 7.3 %; 1m= 7.4 %; 3m= 7.5 %; 6m= 7.6 %; 9m= 7.4 % (p = *n.s.*) PISA group 1 vs. group 2: $p < 0.0001$ HbA1c group 1 vs. group 2: p = *n.s.* HbA1c showed a significant correlation with PISA in both groups ($r = 0.5963$, $p < 0.0001$) and in group 1 ($r = 0.4163$, $p = 0.043$) combined over 9 m, but no correlation was observed in group2 ($r = 0.0822$, p = *n.s.*)	Periodontal therapy and PISA are associated with T2DM and HbA1c
	Ramadhani et al., 2024 [99], Japan	secondary data analysis from a RCT	$n = 27$ (16 males, 11 females, mean age= 65y)	27 patients with T2DM (HbA1c ≥6.0 %) with stable diabetic treatment regimen and P	group 1= SRP + local antibiotic (10 mg minocycline) and 3x	included non-smokers	n.s.	significant difference	PISA of group 1: baseline= 293.7mm^2; 6m= 155.3mm^2 ($p < 0.01$) HbA1c of group 1: baseline= 7.0 %; PISA of group 2: baseline= 102.1mm^2; 6M= 59.6mm^2	Periodontal therapy and PISA are not associated with T2DM and HbA1c

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Table 2 (*continued*)

Parameter	Autor, year, reference, country	Study design	Number of participants, gender, age	Number of diagnosed participants	Treatment/ Intervention	Smoking status	Significant difference in age between groups	Significant difference in gender between groups	Main results of treatment/ intervention	Conclusion
					PMPR + local antibiotic, group 2= SRP and 3x PMPR				($p = 0.02$) HbA1c of group 2: baseline= 7.1 %; For both groups, the level of HbA1c tends to decrease over time, with no significant differences observed.	
	Xu et al., 2024 [100], China	RCT	$n = 49$ (24 males, 25 females, mean age= 56y)	49 patients with generalized severe chronic P [218] or stage III-IV generalized periodontitis [219] and diagnosed T2DM [226] for >2y	group 1= SRP + 500 mg amoxicillin and 200 mg metronidazole for 7d, group 2= SRP	included non-smokers	n.s.	n.s.	PISA of group 1: baseline= 1,962mm^2; 3m= 1,302mm^2 ($p < 0.01$) HbA1c of group 1: baseline= 7.95 %; 3m=7.42 % ($p = 0.004$) PISA of group 2: baseline= 1,926mm^2; 3M= 1,318mm^2 ($p < 0.01$) HbA1c of group 2: baseline= 7.6 %; 3m=7.22 % ($p = 0.001$) multivariable model: baseline PISA is not associated with decreased HbA1c levels after periodontal therapy	Periodontal therapy significantly improves glycaemic parameters (regardless of SRP+antibiotics or SRP alone)
Rheumatoid arthritis	de Pablo et al., 2023 [63], England	RCT	$n = 60$ (15 males, 45 females, mean age= 58y)	60 patients with generalized stage II–IV P [11] and RA [227] treated with DMARDs for ≥3 m and with a DAS28 ≥3.2 or a DAS28 score >5.1 unwilling to take biologics	group 1= OHI+SRP, group 2= OHI	included non-smokers, former smokers and smokers	not mentioned	not mentioned	PISA of group 1: baseline= 374mm^2; 3m= 195mm^2*; 6m= 105mm^2* Tender joint count of group 1: baseline= 12; 3m= 8*; 6m= 10* Swollen joint count of group 1: baseline= 2; 3m= 1*; 6m= 2* DAS28 of group 1: baseline= 4.98; 3m= 4.38*; 6m= 4.68* Ultrasound grey scale score of group 1: baseline= 5.8*; 3m= 4.6*; 6m= 4.3* Total ultrasound grey scale score of group 1: baseline= 9*; 3m= 5*; 6m= 8* Ultrasound power Doppler of group 1: baseline= 3.3*; 3m= 2.7*; 6m= 1.8* Total ultrasound power Doppler of group 1: baseline= 5.2; 3m= 3*; 6m= 4.2* PISA of group 2: baseline= 390mm^2; 3m= 380mm^2*; 6m= 305mm^2* Tender joint count of group 2: baseline= 13; 3m= 12*; 6m= 12* Swollen joint count of group 2: baseline= 3; 3m= 2*; 6m= 2.5* DAS28 of group 2: baseline= 5.32; 3m= 5.25*; 6m= 5.48* Ultrasound grey scale score of group 2: baseline= 6.6*; 3m= 5.1*; 6m= 5.4* Total ultrasound grey scale score of group 2: baseline= 10*; 3m= 9*; 6m= 9* Ultrasound power Doppler of group 2: baseline= 4.7*; 3m= 3.1*; 6m= 3.8* Total ultrasound power Doppler of group 2: baseline= 7.2; 3m= 6.8*; 6m= 6.2*	Periodontal therapy significantly improves overall RA disease activity
	de Smit et al., 2021 [186], Netherland	longitudinal observation	$n = 26$ (7 males, 19 females, mean age= 62.5y)	26 patients with RA [227] and gingivitis ($n = 16$) or moderate P ($n = 8$) or severe P ($n = 2$)	MTX vs. MTX + Anti-TNFα	included non-smokers and smokers	not mentioned	not mentioned	PISA of MTX group: baseline= 170mm^2, 2m= 180mm^2 ($p = n.s.$) PISA of Anti-TNFα group: baseline= 190mm^2, 3M= 190mm^2, 6M= 120mm^2 ($p = n.s.$) DAS28 of MTX group: baseline= 5.8, after 2m= 3.2 ($p < 0.01$)	MTX or anti-TNF therapy does not improve periodontal parameters

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Table 2 (*continued*)

Parameter	Autor, year, reference, country	Study design	Number of participants, gender, age	Number of diagnosed participants	Treatment/ Intervention	Smoking status	Significant difference in age between groups	Significant difference in gender between groups	Main results of treatment/ intervention	Conclusion
									DAS28 Anti-TNFα group: baseline= 5.3, after 3m= 2.8, after 6m= 3.3 ($p < 0.05$)	
	Kobayashi et al., 2023 [187], Japan	retrospective cohort study	$n = 50$ (4 males, 46 females, mean age= 55y)	50 patients with RA [227] and with/without P [191] treated with corticosteroids, conventional synthetic DMARDs, or non-steroidal anti-inflammatory drugs	high-PISA group ($\leq$75.2mm^2) vs. low-PISA group (>75.2mm^2) and no/ mild P vs. moderate/ severe P, all patients treated with biological DMARDs	included non-smokers, former smokers and smokers	n.s.	significant difference	PISA $\leq$75.2mm^2 group vs. >75.2mm^2 group: baseline= 27mm^2 vs. 238mm^2 clinical disease activity index: baseline= 18.3 vs. 17.9 ($p = n.s.$), 12 m changes= −12.7 vs. −10.4 ($p = n.s.$) tender joint count: baseline= 4.8 vs. 4.6 ($p = n.s.$), 12 m changes= −3.9 vs. −2.9 ($p = n.s.$) swollen joint count: baseline= 3.6 vs. 4.2 ($p = n.s.$), 12 m changes= −2.4 vs. −2.8 ($p = n.s.$) no/ mild P vs. moderate/ severe P: baseline= 83mm^2 vs. 195mm^2 clinical disease activity index: baseline= 18.8 vs. 17.3 ($p = n.s.$), 12 m changes= −13.8 vs. −8.7 ($p = 0.02$) tender joint count: baseline= 5.2 vs. 4.1 ($p = n.s.$), 12 m changes= −4.3 vs. −2.3 ($p = 0.01$) swollen joint count: baseline= 4.3 vs. 3.4 ($p = n.s.$), 12 m changes= −3.4 vs. −1.6 ($p = 0.03$) Periodontitis case definitions changes after 1 year of biological DMARD therapy by the Spearman's rank correlation coefficient= 0.4 ($p = 0.005$) Periodontitis case definitions changes after 1 year of biological DMARD therapy by a multiple regression analysis= 0.34 (CI: 1.91 to 9.23), $p = 0.0038$	Biological DMARD therapy significantly improves periodontal parameters but not PISA values and biological DMARD therapy is less effective in P patients
	Yamashita et al., 2020 [188], Japan	retrospective cohort study	$n = 54$ (5 males, 49 females, mean age= 55y)	54 patients with RA [227] and with P [191] treated with corticosteroids, conventional synthetic DMARDs, or non-steroidal anti-inflammatory drugs	high-PISA group (>79.1mm^2) vs. low-PISA group ($\leq$79.1mm^2), all patients treated with biological DMARDs	included non-smokers and former smokers	n.s.	n.s.	PISA >79.1mm^2 group vs. PISA $\leq$79.1mm^2 group: baseline= 229mm^2 vs. 31mm^2 clinical disease activity index: baseline= 16.4 vs. 20.4 ($p = n.s.$), 6 m changes= −8.8 vs. −15.8 ($p < 0.01$) tender joint count: baseline= 5.1 vs. 5.0 ($p = n.s.$), 6 m changes= −2.9 vs. −3.7 ($p = n.s.$) swollen joint count: baseline= 4.8 vs. 4.1 ($p = n.s.$), 6 m changes= −2.7 vs. −3.1 ($p = n.s.$) Multiple regression analysis revealed a significantly positive association between baseline PISA and changes in CDAI 6 months later ($p < 0.001$).	Biological DMARD therapy is less effective in P patients
Chronic kidney disease	Vachhani and Bhavsar, 2021, India [64], India	randomized, controlled, parallel-group, single-center pilot study	$n = 80$ (59 males, 21 females, mean age= 50y)	80 patients with moderate to severe P and CKD	group 1= OHI+SRP, group 2= OHI	included non-smokers, former smokers and smokers; no significant difference	n.s.	n.s.	PISA of group 1: baseline= 1772; 3m= 279; 6m= 249 ($p < 0.001$) eGFR of group 1: baseline= 17; 3m= 20; 6m= 25 ($p < 0.001$) UACR of group 1: baseline= 184; 3m= 169; 6m= 138 ($p < 0.001$) PISA of group 2: baseline= 1785; 3m= 1819; 6m= 1854 ($p < 0.001$) eGFR of group 2: baseline= 19; 3m= 17; 6m= 16 ($p < 0.001$) UACR of group 2: baseline= 191; 3m= 205; 6m= 218 ($p < 0.001$)	Periodontal therapy significantly improves CKD

Abbreviations: *P*= periodontitis, PISA= periodontal inflamed surface area, T2DM= type 2 diabetes mellitus, RA= rheumatoid arthritis, CKD= chronic kidney disease, OHI= oral hygiene instructions, SRP= scaling and root planing, PMPR= professional mechanical plaque removal, SPT= supportive periodontal therapy, BP= blood pressure [mmHg], FPG= fasting plasma glucose, eGFR= estimated glomerular filtration rate [mL/min/1.73 m^2], UACR= urine-albumin-to-creatinine-ratio [mg/gCr], DMARDs= disease-modifying antirheumatic drugs, DAS28= 28-joint disease activity score, MTX= methotrexate, anti-TNF= anti-tumor necrosis factor-α, *d*= day, *m*= month, *y*= year, CI= 95 % confidence interval, n.s.= not significant, *= values estimated from a figure, no exact values given in publication.

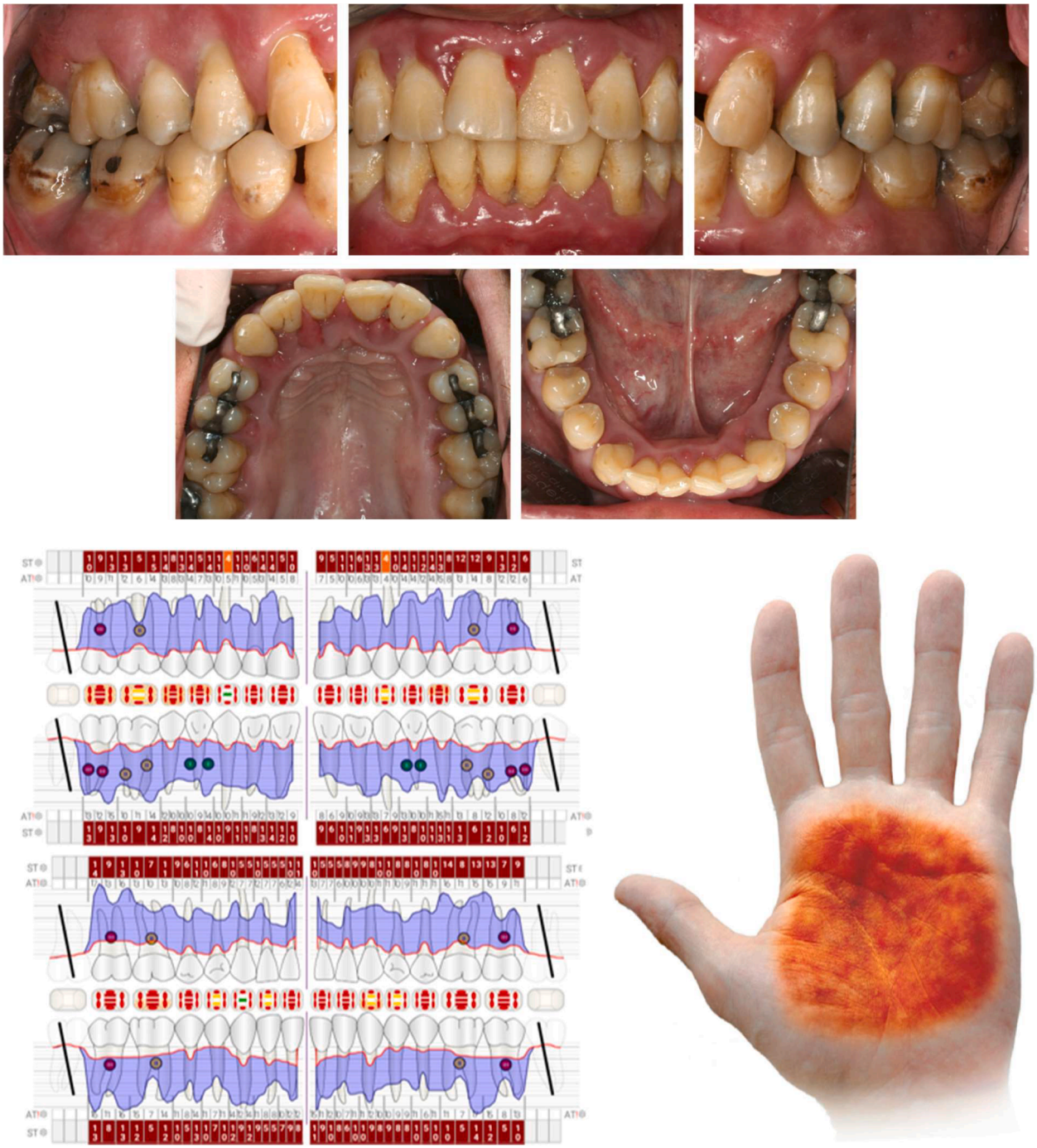

Fig. 2. Intraoral clinical picture and periodontal parameters of a patient suffering generalised periodontitis, stage IV and grade C. The PISA value is 5,777mm^2 and has been projected onto the palm of a hand to help the patient visualise it.
Abbreviations: ST= pocket probing depth, AL= clinical attachment level.

disease, the Periodontal Index in 1956 to facilitate the surveillance of periodontal disease. One of the Periodontal Index criteria was based upon the signs of periodontal inflammation [48]. The Gingival Index [49], the Sulcus Bleeding Index [50] and the Papilla Bleeding Index [51] are most routinely used tools for assessing inflammation. They base on scoring systems that are easily applicable in clinical settings and are effective for accurately evaluating the status of gingival inflammation during periodontal maintenance therapy. The Gingival Index and the Sulcus Bleeding Index include the colour of the gingival tissue and the (spontaneous) presence or absence of bleeding upon probing within the gingival sulcus or pocket. In contrast, the Papilla Bleeding Index focuses solely on the absence or the intensity of bleeding upon probing within the gingival sulcus at the papilla level, in the interproximal spaces. The indices provide an easily replicable assessment of clinical signs of gingival inflammation. High scores in all indices indicate generalized bleeding tendencies and thereby high levels of inflammation.

It is noticeable that BOP does not necessarily forecast periodontitis disease progression. Lang et al. [52] examining BOP as a predictor for periodontal disease progression revealed its low positive predictive value in forecasting the progression of periodontitis. The same group recommended, that the absence of BOP is a strong predictor of future stability [53]. This finding underlines the recommendation for the use of

BOP in daily clinical practice. However, it should be noted that this index has been used in many studies in a dichotomous way: ether "present or absent" of bleeding, thereby not verifying for the severity of gingival inflammation [54].

Numerous studies characterise periodontitis as a non-continuous process, employing cut-off points to classify patients as either unaffected or affected by mild, moderate or severe disease [55] or as stage I, II, III and IV [11]. Therefore, the classification of periodontitis does not measure the extent of inflamed periodontal tissue. Conversely, numerous studies that have associated periodontitis with systemic diseases, "quantify" periodontitis by a continuous variable, for instance, using mean pocket probing depth (PPD) or mean clinical attachment level (CAL). Although these are continuous variables, it does not automatically imply that they accurately quantify the total inflamed periodontal tissue.

Newer indices such as PISA, PESA, PISA to PESA ratio, DGES and PIRI quantify the amount of inflamed periodontal tissue in periodontitis (Table 1). Significant differences were found in IL-1α levels in the gingival crevicular fluid of healthy individuals and periodontitis patients. Additionally, a correlation was found between IL-1α levels and PISA and PESA, highlighting the link between periodontal inflammation indices and a local inflammation [56]. Furthermore, salivary parameters of IL-1β, IL-10, and neutrophil gelatinase-associated lipocalin levels were strongly positively correlated with PISA values [57]. Therefore, these indices are highly relevant for investigating the systemic inflammatory impact of periodontitis. This approach evaluates periodontal inflammation as a continuous variable, which could be very helpful in understanding the relationship between periodontitis and systemic diseases, as will be elaborated on further below in the following sections [9,10,58,59]. The most frequently used index is the PISA, which will be presented first.

2.1. Periodontal inflamed surface area (PISA)

The PISA is a quantitative index by Nesse et al. [10] to assess the extent of inflammatory burden due to periodontal disease. This measure is particularly useful for evaluating the severity and systemic impact of periodontal disease, as the periodontal pocket acts as an access gate to systemic circulation for periodontopathogens and immune system mediators. The index is the multiplication of the sum of PPD and gingival recession (or adding gingival hyperplasia) by the circumference of the tooth at the gingival margin and then by the proportion of the tooth circumference that is bleeding in square millimetre. Periodontal programmes such as ParoStatus® software (ParoStatus.de GmbH, Berlin, Germany) or Excel spreadsheets can assist with calculating PISA values. Nevertheless, PISA lacks to accurately measure the amount of inflamed periodontal tissue in cases of pseudo-pockets or gingival overgrowth, as these conditions cause the amount to appear lower than it actually is. PISA provides a direct estimation of the inflammatory burden in the periodontium, making it a valuable tool for both clinical assessment and epidemiological studies (Table 1).

As Leira et al. [60] indicated, individuals with healthy periodontium have a mean PISA of 34mm^2 (±16mm^2). A PISA of 130mm^2 or higher predicts the presence of periodontitis with 98 % sensitivity and 100 % specificity, while values ranging from 934mm^2 to 3,274mm^2 indicate severe periodontitis. In exceptional cases, for patients with generalised periodontitis and high PPD, however, this can be as high as 6,000mm^2, as shown in Fig. 2. A substantial body of research has indicated that a PISA of approximately 500mm^2 to 600mm^2 is likely to be adequate for inducing systemic inflammation and for serving as the clinical hallmark [61–64].

2.2. Periodontal epithelial surface area (PESA)

PESA is a quantitative metric index to estimate the total root surface area by pocket epithelium in the dentition. Conceptually, PESA represents the anatomical surface through which periodontal pathogens and inflammatory mediators may interact with the host periodontal tissue, vascular supply, and systemic circulation. Because PESA encompasses both inflamed and non-inflamed epithelial surfaces, it is complementary to PISA, which is obtained by weighting PESA by BOP. In this regard, PESA can be utilised as a baseline or denominator in the interpretation of the relative burden of inflammation in pocket epithelium.

Although Nesse et al. [10] are often credited with formalising the PESA/PISA approach, the transformation of linear periodontal measurements to surface areas builds on prior work in dental morphometry and root surface area estimation by Hujoel [9,65].

PESA is calculated in square millimetres and the exact calculation is explained in detail in the publication by Nesse et al. [10]. In practice, many recent publications report PESA values derived through the same spreadsheet algorithm used for PISA, treating PESA as the denominator.

However, there are also some limitations: PESA includes non-inflamed epithelium and thus overestimates the "active" inflammatory surface and therefore, does not reflect biological activity, vascularity, or inflammatory cell infiltration directly [66]. Additionally, in cases of gingival overgrowth or pseudopockets, the use of CAL underestimates PESA. Even using PPD may still produce conservative estimates [10].

In summary, refinements and population adaptations (e.g. ethnic variation in root morphology) have been proposed in the last decade. However, the core approach remains that PESA is first estimated and then modulated by BOP to yield PISA in many studies [66] (Table 1).

2.3. Dentogingival epithelial surface area (DGES)

DGES is a quantitative metric index that is employed to estimate the total surface area of the sulcular, junctional and pocket epithelium of the dentition that is exposed to the microbial biofilm and host-tissue surface. It thereby represents the anatomical epithelial surface through which microbial and inflammatory mediator exchange may occur, offering a structural estimate of the potential "exposed" periodontal epithelial surface in both health and disease.

The concept of DGES was introduced by Hujoel et al. [9]. For calculation, the authors described a detailed process based on meta-analysed root surface area data, root length percentages, and clinical probing measures. The calculation of DGES is expressed in square centimetres, and a comprehensive explanation of the precise calculation can be found in the publication by Hujoel et al. [9]. Readers can also perform the calculation themselves using the Excel spreadsheet provided by the authors. However, DGES does possess certain limitations. Firstly, it does not consider the presence of inflammation. Secondly, it does not measure PESA, as it uses CAL instead of PPD for its calculation. Consequently, both DGES and PESA are ineffective in quantifying the extent of inflamed periodontal tissue. Furthermore, the initial calculations relied on older morphometric data developed in specific populations and mean root-surface area models. However, there may be inaccuracies when applied to diverse ethnic populations or dentitions with altered morphology.

The DGES is recognised as an early and important structural index in periodontal research. However, its limitations, especially in terms of inflammatory activity representation, population specificity, and limited direct systemic disease linkage, have led to its gradual replacement by PESA and PISA in scientific research (Table 1).

2.4. PISA to PESA ratio

The ratio of PISA to PESA quantifies the extent of the exposed epithelial surface that is actively inflamed, thereby providing a relative measure of the inflammatory burden per available epithelial surface. The rationale underpinning this approach is that PESA estimates anatomical surface and PISA estimates the inflamed portion of that surface. The resulting ratio is hypothesised to enhance interpretation by

normalising for inter-individual differences in the epithelial surface area that facilitates the comparison in between individuals or populations.

The PISA/PESA ratio was proposed as a refinement to the evaluation of periodontal inflammatory burden, with the aim of accounting for both the absolute inflamed surface (PISA) and the structural "opportunity" for inflammation represented by PESA. The application of the ratio is intended to facilitate the assessment of the proportion of the epithelial surface that is inflamed, in percentage terms. This approach may offer a more effective reflection of the relative risk of systemic exposure (e.g. microbial translocation, inflammatory mediator release) than PISA alone. For instance, in a study of patients with rheumatoid arthritis, the mean PISA was reported as 291.9mm^2 ±348.7mm^2, and the PISA/PESA ratio was 33.2 % ± 24.2 %. This indicates that approximately one-third of the epithelial surface was inflamed in this sample [58].

The PISA/PESA ratio provides a relative measurement of inflammation that has been normalized to the epithelial surface area, thereby reducing bias from inter-individual variability in the periodontal anatomy (e.g., tooth number, root morphology). The potential benefits of this approach include enhanced comparability across populations with differing dentition sizes or periodontal exposure, and the ability to stratify by the "intensity" of inflammation per unit epithelial surface.

However, it should be noted that the PISA/PESA ratio is not without its limitations. Firstly, PESA represents both, the inflamed and non-inflamed surface area. Consequently, the ratio may mask variations in the absolute magnitude of the burden. For instance, two patients may have identical ratios but very different PISA and PESA absolute values (e.g., 200mm^2/1,000mm^2= 20 % vs. 600mm^2/3,000mm^2= 20 %). The systemic implications may differ significantly despite identical ratios. Secondly, there is a paucity of studies that have explicitly reported the PISA/PESA ratio. The normative data are limited, and interpretation across studies is challenging.

Despite its potential, the ratio remains under-utilised. Its interpretation requires the consideration of both absolute PISA and PESA values, an awareness of measurement assumptions, and the recognition that it does not directly quantify the biological activity of inflammation. It is recommended that studies report the PISA/PESA ratio alongside absolute indices in order to enhance comparability and biological relevance in systemic disease contexts (Table 1).

2.5. Periodontal index for risk of infectiousness (PIRI)

PIRI is a clinical index designed to quantify the risk of systemic bacteraemia or systemic inflammatory load due to periodontal lesions. In this way, PIRI serves as a metric that bridges the gap between periodontal status and systemic health outcomes [59].

In a study investigating patients with coronary artery disease (CAD), the authors described for PIRI a dose-response effect between increased PIRI scores and the presence of CAD, with an adjusted OR of 1.3 per PIRI unit [67]. Thus, PIRI was intended to reflect not only the local burden of periodontal lesions, but also their systemic infectious risk potential.

PIRI comprises two main components: the number and depth of PPDs beyond a certain threshold (scored from 1 to 6), and the number and degree of furcation involvements (scored from 1 to 4). The PIRI score is then used to calculate a patient's risk category. Patients are classified as follows: none or low risk (PIRI= 0), moderate risk (1 ≤PIRI≤ 5), and high risk (6 ≤PIRI≤ 10) [59,68].

The underlying principle is that a greater number and severity of pockets and furcation involvement reflect a larger area of diseased periodontal tissue capable of serving as an inflammatory source. The higher the PIRI score, the greater the assumed risk of systemic dissemination of periodontal biofilms or their locally produced pro-inflammatory mediators.

However, it should be noted that PIRI is not without its limitations. Firstly, the PIRI calculation is relatively simplistic: while it considers the number and severity of pockets and furcations, it does not convert linear measurements into surface area metrics, unlike PESA or PISA. Thus, it may underestimate the actual exposed surface area. Secondly, PIRI does not include BOP or actual measurement of the inflamed surface area. It remains an indirect proxy for infectious risk and does not quantify the active inflammatory interface.

Despite its potential, PIRI is less widely adopted than surface-area metrics and requires further validation. Its strength lies in its focus on infectious risk rather than simply disease extent, but its limitations should be recognised when interpreting results (Table 1).

3. Selection and characteristics of the included studies

To date, there are no comprehensive reviews existing focusing on the relationship between systemic disease and periodontitis over the effect of the usage of periodontal inflammation indices. The selection of periodontal inflammation indices is limited to specific indices that have played a pivotal role in science and clinical practice. Furthermore, the selection of indices was based on the highest biological plausibility in relation to periodontal diseases, the highest evidence and the frequency of citations. The present review included controlled interventional and observational studies, encompassing prospective or retrospective cohort studies and case-control designs. These studies evaluated the treatment of periodontitis or systemic diseases by monitoring the inflammatory status using a periodontal inflammatory index in patients with both periodontitis and a systemic disease. Uncontrolled studies, both interventional and observational, were excluded, in addition to non-original research and animal studies.

A structured electronic search was conducted in May 2025 of the following databases: PubMed/MEDLINE and Web of Science. MeSH and Emtree terms were used. The most recent electronic search was performed on all databases on June 20, 2025.

The search strategy included the terms "inflammation index", "periodontal inflammation index", "periodontal inflamed surface area", "periodontal epithelial surface area", "dentogingival epithelial surface area", "periodontal index for risk of infectiousness", "PISA to PESA ratio", "periodontitis", "periodontal therapy" and "periodontal" as free text words, along with MeSH or Emtree terms (if available), synonyms, singular as well as plural forms and abbreviations (PISA, PESA, PISA/PESA, DGES and PIRI). Furthermore, filters for "humans", "english" and "german" were used. Consequently, 13 studies were included. These studies will be discussed below. An overview with the important characteristics and results is presented in Table 2.

4. Systemic inflammatory diseases and periodontal inflammation indices

4.1. Diabetes mellitus

The global prevalence of T2DM is approximately 11.1 % (around 1 in 9 adults) [69]. This condition arises from a relative or absolute deficiency of insulin, resulting in hyperglycaemia, inflammation and elevated oxidative stress. This condition has the potential to result in systemic complications, including cardiovascular disease, retinopathy and renal diabetes-related complications [70]. A bidirectional relationship has been observed between T2DM and periodontal disease [71–73]. Periodontitis has been shown to affect glycaemic control due to the increased insulin resistance caused by periodontal inflammation [74]. Conversely, periodontitis is likely to worsen in patients with T2DM owing to an impaired immune response to pathogenic/ keystone bacteria [70] and inhibition of connective tissue and alveolar bone metabolism [75]. The onset of T2DM has been shown to increase the incidence and risk of periodontal disease progression as an inflammatory condition [76]. Hyperglycaemia has been demonstrated to reduce immune function and modify systemic inflammatory responses [77,78]. Elevated levels of advanced glycation end-products and oxidative stress have been shown to impede periodontal wound healing by affecting cell migration and proliferation, inducing chronic inflammation and

defective immunity [79], which can ultimately result in an unfavourable periodontal outcome or resolution. Furthermore, raised antibody titers against periodontal microorganisms have been associated with elevated glucose levels, which may provide a further explanation for the relationship between periodontal disease and T2DM [80].

Longitudinal studies have reported that the incidence of new cases of periodontitis among patients with T2DM is two to three times higher than that observed in individuals with normal glucose levels [72]. Furthermore, studies have indicated that patients with poor glycaemic control exhibit a higher prevalence of severe periodontitis, accelerated tooth loss and high PISA when compared to those with optimal glycaemic control [72,81]. Additionally, Nesse et al. [82] observed a dose-response relationship between PISA and HbA1c. A rise in the HbA1c level by 1 % was found to be associated with an increase in PISA of 89mm^2. Conversely, factors associated with poor glycaemic control included severe periodontitis, waist circumference, imbalanced diet, and sedentary lifestyle. A 10mm^2 rise in PISA was found to increase the odds of having HbA1c $\geq$7 % by 2 %. Therefore, a robust bidirectional relationship has been demonstrated between periodontitis and inadequate glycaemic control [83].

A large number of cross-sectional and case-control studies analysed the relationship between T2DM and periodontitis based on PISA, in the absence of treatment or intervention [82–98]. As demonstrated in the studies conducted by Matić-Petrović et al. [89] and Teke et al. [95], the relationship between HbA1c and PESA was examined. Furthermore, positive correlations were found between salivary TNFα levels and PISA and PESA, as well as between adiponectin levels and PISA, in T2DM patients [95]. In addition, a recent cross-sectional study demonstrated a significant association between HbA1c and fasting plasma glucose with PISA and PESA in patients with T2DM under poor glycaemic control [94].

A total of three interventional studies investigated the association between the two diseases based on PISA and systemic parameters (Table 2) [62,99,100]. However, it should be noted that all of the studies involved a small number of patients, with fewer than 50 patients with T2DM and periodontitis. This limits the statistical significance of the analyses. The three studies examined the influence of non-surgical periodontal therapy with and without adjuvant antibiotic administration or professional mechanical plaque removal (PMPR) [101] alone. It is also noteworthy that all subjects had been administered diabetes medication for a considerable duration, thereby ensuring the absence of uncontrolled T2DM within the patient cohort.

Xu et al. [100] investigated patients with long-standing T2DM undergoing non-surgical periodontal therapy with or without adjunctive systemic amoxicillin and metronidazole. Notably, the PISA value exceeded 1,900mm^2 in both groups at baseline. Three months after periodontal therapy, a significant improvement in PISA values was observed. However, these values remained high in both groups at >1,300mm^2, and baseline PISA was not associated with HbA1c reduction (multivariable logistic regression model). Additionally, both groups showed modest reductions in HbA1c (−0.53 % with adjunctive antibiotics and −0.38 % without). Despite these findings, the conclusions are tempered by several limitations: a short follow-up period of three months, unclear blinding of clinicians, and substantial loss to follow-up. These findings suggest that, while adjunctive antibiotics may modestly improve non-surgical periodontal therapy outcomes in severe cases, the inflammatory burden, as measured by PISA persists, which may explain the modest systemic benefits observed.

Ramadhani et al. [99] investigated the adjunctive use of locally delivered minocycline in addition to non-surgical periodontal therapy over a 24 weeks, compared with non-surgical periodontal therapy alone. A limitation of this study was the small cohort of 27 diabetic patients and the significant difference in baseline PISA values between the two groups (293mm^2 vs. 102mm^2), which was likely due to random variation in patient recruitment. This imbalance, combined with the small sample size, introduced potential bias and reduced the ability to detect the true effect of the intervention. In summary, HbA1c levels tended to decrease over time in both groups, with no significant differences observed. However, the absolute HbA1c levels after six months were not fully reported.

Unlike the two studies mentioned above, Komatsu et al. [62] did not perform non-surgical periodontal therapy on the control group. Additionally, the follow-up period was extended to nine months. Combining non-surgical periodontal therapy with the systemic administration of azithromycin led to significant reductions in PISA levels (−818mm^2, $p < 0.0001$) and HbA1c levels (−0.3 %, $p < 0.001$) after nine months. The control group (PMPR only) showed no changes in periodontal or systemic parameters. Significantly, HbA1c showed a strong correlation with PISA in both groups ($r = 0.5963$, $p < 0.0001$) and in the non-surgical periodontal therapy group ($r = 0.4163$, $p = 0.043$). Furthermore, decreases in PISA were found to parallel reductions in HbA1c and inflammatory markers over the nine-month period. Therefore, this study highlights PISA as a powerful parameter linking periodontal therapy to glycaemic control and reflecting local as well as systemic inflammatory status in patients with T2DM. However, it is important to note that the relative impact of non-surgical periodontal therapy or systemic antibiotic administration on reducing PISA and HbA1c levels remains unclear.

Together, these studies illustrate the complex interplay between periodontitis, T2DM, and systemic glycaemic control. Xu et al. [100] and Ramadhani et al. [99] demonstrated that periodontal therapy with adjunctive antimicrobials can yield modest HbA1c improvements. However, their findings are limited by methodological issues and persistent high PISA values post-treatment. In contrast, Komatsu et al. [62] provide compelling evidence that reductions in PISA are directly associated with improved HbA1c, thereby strengthening the case for PISA as a key linking factor between periodontal and systemic health.

However, few studies explored the effect of diabetes treatment, excluding periodontal treatment, on the pathology of periodontal disease parameters like PISA and PESA but without intervention group. Inoue et al. [102] aimed to assess the impact of glycaemic control treatment on periodontal parameters in a cohort of 29 patients with diabetes accompanied by moderate periodontitis. These patients underwent a 2-week intensive glycaemic control regimen in a controlled hospital environment. Periodontal treatment, including oral hygiene instructions, was not provided in this study. After treatment, there were no significant changes in the plaque index. However, HbA1c significantly decreased of 0.5 % and PISA significantly decreased of 10.9mm^2. In a study of a comparable design, Mizutani et al. [103] observed 33 patients with poorly controlled T2DM undergoing intensive diabetes therapy (i.a. lifestyle modifications, caloric restriction, regular exercise and medication administration, e.g. insulin) including 2-weeks of hospitalization and three times PMPR, without non-surgical periodontal therapy. Following a period of six months, a decrease in HbA1c of 9.6 % at the initial baseline measurement, reaching an average of >2 % in the first three months of diabetes care, was observed. This decrease was sustained, maintaining a 2.2 % reduction over six months. The study demonstrated that following diabetes treatment without non-surgical periodontal therapy, there was a statistically significant reduction in PISA and PESA from 318mm^2 to 134mm^2 and 1052mm^2 to 927mm^2, respectively. It was observed that following one month of intensive diabetes care, there was a significant improvement in periodontal parameters under glycaemic control. This finding indicates that enhancements in periodontal parameters and PISA are predominantly attributable to enhanced glycaemic control, rather than changes due to insufficient oral hygiene. It is hypothesised that glycaemic control has the potential to reduce inflammation and periodontal destruction. Furthermore, treatment-induced systemic changes may have influenced the oral microbiome composition and reduced pathogenicity [104]. This notion is supported by recent research, which suggests that glycaemic control can alter the composition of saliva microbiota in patients with T2DM and periodontitis [104]. However, the current evidence on

whether treating T2DM improves PISA without periodontal therapy is inconclusive.

4.2. Cardiovascular disease

Periodontitis and CVD exhibit overlapping risk factors, including but not limited to age, genetic predisposition, smoking, obesity, T2DM, oestrogen deficiency in women, hypertension, socio-economic status and psychological stress [105,106]. The first study to provide positive epidemiological evidence for an association between periodontitis and atherosclerosis was conducted by Mattila et al. in 1989 [107]. In more recent years, remarkable pathological and epidemiological associations between these two diseases have been reported, and an elevated risk of hypertension, endothelial dysfunction and risk of coronary and/or cerebrovascular events, including acute myocardial infarction and stroke [22,106,108–110]. Investigations aimed at elucidating the nexus between periodontitis and CAD have thus far failed to establish a direct causal link. This is largely attributable to the complex, multifactorial ethology underlying both inflammatory diseases [111]. A large cohort study reported that periodontitis could serve as an independent risk marker for atherosclerotic CVD [112]. The most conclusive biological rationale proposed for the connection between periodontitis and CAD implicates the ingress of oral microbiota and/or there toxins into the blood circulatory system [113]. The presence of DNA from periodontal pathogens has been identified in atheromas [114,115] and heart tissue [116]. In an additional study, *Aggregatibacter actinomycetemcomitans* was cultured from specimens obtained from both periodontal pockets and atheromatous plaque of a single patient [117]. This finding indicates that viable bacteria can be transmitted from the oral cavity into the coronary arteries and may directly contribute to the development of atherosclerosis. In experimental studies on animals, it has been demonstrated that *Porphyromonas gingivalis* is capable to penetrate heart tissue that has been compromised by ischemia [118]. This finding suggests a potential link between periodontal bacteria and the development of atherosclerosis, as well as the subsequent CVD following a primary event. In addition, sustained periodontal inflammatory states have been shown to alter the count of circulating neutrophils due to increased bone marrow output or mobilization of the marginal granulocyte pool. These circulating inflammatory mediators are then able to modify endothelial function, leading to impaired vasodilation and causing significant alterations in the vascular structure [22].

Conversely, hypertension has been demonstrated to have an adverse effect on the vascular structures of the periodontal membrane. This, in turn, can result in the dysfunction of the arterioles, which can subsequently lead to gingival bleeding. This process can ultimately result in attachment and alveolar bone loss [119].

A more thorough examination of the prospective long-term cardiovascular benefits of periodontal therapy in patients with CVD it is important to mention recent systematic reviews on the effect of non-surgical periodontal therapy on systemic inflammatory markers. A significant reduction in plasma levels of high-sensitive CRP, TNFα, IL-1β, IL-6, and fibrinogen has been observed in patients with CVD and periodontitis [120,121]. A meta-analysis by Muñoz Aguilera et al. [108] showed that five out of twelve intervention studies confirmed a reduction in blood pressure following non-surgical periodontal therapy, with reductions ranging from 3 to 12.5 mmHg in systolic blood pressure and from 0 to 10 mmHg in diastolic blood pressure. Moreover, Tonetti et al. [122] sought to assess the effect of intensive non-surgical periodontal therapy on endothelial function in a widely acclaimed study, measured by flow-mediated dilatation of the brachial artery. The flow-mediated dilatation exhibited a greater improvement in the periodontal treated group compared to the non-treatment group, both 60 days (difference 0.9 %; $p = 0.02$) and 180 days (difference, 2.0 %; $p < 0.001$) after therapy. The observed degree of improvement was found to be associated with a corresponding improvement in measures of periodontal disease. However, more recent studies have not found clinical evidence for a positive effect on endothelial function after periodontal therapy, and therefore the possibility of a cause-to-effect relationship remains controversial [123,124].

In a recent study by Groenewegen et al. [125], mostly systemically healthy individuals requiring full-mouth tooth extraction due to severe periodontitis exhibited elevated von Willebrand factor (vWF) and CRP levels, and reduced HDL compared with healthy controls. vWF levels correlated positively with PISA, indicating a link between periodontal inflammation and endothelial activation (21 % unit increase in vWF per 1,000mm^2 increase in PISA). However, 12 weeks after complete tooth extraction, no significant improvements were observed in any of the haemostatic or cardiometabolic blood parameters, including vWF, CRP, D-dimer, and lipid fractions. These findings suggest that while periodontitis severity is associated with altered systemic biomarkers, removal of inflamed periodontal tissue does not reverse these systemic alterations in otherwise mostly systemically healthy individuals.

Conversely, Reichert et al. [126] conducted a study on 101 patients diagnosed with moderate to severe periodontitis and CVD, who underwent coronary artery bypass grafting without receiving periodontal therapy. PISA and PESA were determined. After one year, 14 patients experienced a new cardiovascular event. Therefore, the study is of interest in this respect as the cardiovascular endpoint is concerned, as opposed to the utilisation of surrogate parameters. However, periodontitis was only in tendency associated with the incidence of new events (event: PISA= 289mm^2, PESA= 1,393mm^2 vs. no event: PISA= 191mm^2, PESA= 1,165mm^2; $p = 0.453$). One potential explanation for this discrepancy could be the absence of a healthy control group. As demonstrated by Renvert et al. [127], more robust results were obtained, yet PISA was not utilised in the study. The authors investigated 165 consecutive subjects with acute coronary syndrome and 159 healthy controls, matched control subjects regarding periodontal conditions. Following a three-year observation period, a positive association was demonstrated between alveolar bone loss caused by periodontitis and the subsequent occurrence of acute coronary syndrome events.

A large number of observational and cross-sectional studies analysed the relationship between CVD and periodontitis based on PISA without treatment or intervention [128–147]. An additional study examined this relationship using PESA [138] and a further study used PIRI [67,139].

Nevertheless, observational studies are susceptible to residual confounding. In order to establish a more reliable causal relationship, it is essential to conduct periodontal intervention studies that evaluate the efficacy of periodontal therapy and CAD therapy in reducing the risk of cardiovascular disease and periodontitis. The following studies have focused on the effect of an intervention on the underlying cardiometabolic parameters (and PISA), using it as a surrogate for CVD (Table 2). Two out of five studies failed to establish an association between periodontitis and CVD [148,149], whereas three studies demonstrated a link [61,150,151].

Donders et al. [148] conducted a one-year intervention follow-up study assessing whether periodontal therapy could improve endothelial function in otherwise healthy adults with periodontitis. The study included 21 periodontitis patients and 21 healthy controls. Endothelial function was measured using the Reactive Hyperemia Index (RHI). The widely accepted operational definition of endothelial dysfunction is RHI <1.67 [152,153]. The intervention group was treated by non-surgical and surgical (consisted of procedures to reduce or eliminate periodontal pockets and create) periodontal therapy followed by maintenance, whereas the control group obtained one time oral hygiene instructions and one to two times PMPR. PISA value significantly decreased from 1,740mm^2 to 295mm^2 after one year following the intervention ($p < 0.001$). In the control group PISA value decreased slightly from 319mm^2 to 284mm^2 after one year. However, despite this marked reduction in inflammatory burden in the intervention group, no significant improvement was observed in both groups in endothelial function (baseline RHI= 2.5; 1-year RHI= 2.4; $p = 0.52$) or in secondary cardiovascular parameters, including high sensitive CRP, lipid profiles,

HbA1c, and systolic blood pressure. The authors attributed the lack of improvement to the physiological baseline RHI values, suggesting that endothelial dysfunction must be present to detect an effect. Importantly, no correlation was found between PISA reduction and endothelial improvement, indicating that lowering periodontal inflammation may not enhance the endothelial function in systemically healthy individuals without CVD.

Seinost et al. [149] conducted a three-arm randomized clinical trial including 89 patients with peripheral arterial disease and severe periodontitis. Patients in group 1 received non-surgical periodontal therapy plus systemic antibiotics (500 mg amoxicillin, 125 mg clavulanic acid and 500 mg metronidazole). Patients in group 2 received non-surgical therapy without antibiotics, whereas patients in group 3 obtained oral hygiene instructions only. Vascular inflammation was quantified using ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography (PET/CT) as a non-invasive tool, targeting arterial inflammation in the aorta and other major vessels [154]. By tracking changes in inflammation over time, ^{18}F-FDG PET/CT measurements can be used as surrogate markers of anti-atheroma intervention [155]. Despite successful periodontal therapy, no significant differences in vascular inflammation were observed between the groups after three months. A major limitation was the high rate (76 %) of statin therapy, potentially masking any periodontal therapy effects on vascular inflammation. The findings suggest that periodontal therapy alone may not significantly modulate systemic vascular inflammation in patients with advanced atherosclerosis or strong pharmacological control of inflammation. However, the study confirmed the utility of imaging-based inflammation markers in evaluating systemic impacts of periodontal therapy.

Jockel-Schneider et al. [151] assessed whether intensive periodontal therapy, with or without systemic antibiotics, could influence arterial stiffness in 55 patients with severe periodontitis. After non-surgical periodontal therapy, patients were monitored for 12 months, with maintenance treatments scheduled at three-month intervals. PISA significantly decreased from 865mm^2 at baseline to 95mm^2 at 12 months ($p < 0.001$). Arterial stiffness measured by pulse wave velocity [156] remained stable (8.92m/s vs. 8.85m/s, $p = n.s.$), other vascular parameters like augmentation index (23.8 vs. 30.6, $p = 0.04$) and aortic pulse pressure (39.5 mmHg vs. 45.8 mmHg, $p = 0.011$) increased modestly but significantly. Interestingly, changes in PISA after therapy were significantly correlated with all vascular parameters (Kendall's tau= 0.208 - 0.287, $p < 0.025$), indicating a measurable link between periodontal inflammation and vascular function. The authors proposed the existence of a threshold level of periodontal inflammation, that limits further improvement of the vascular status. The study also suggested that adjunctive antibiotics could improve vascular outcomes. However, the subgroup sizes were too small for statistical verification. Recent studies indicated, that dietary behaviour is considered one of the most effective modifying risk factors for CVD and possibly also for periodontitis [157,158]. Dietary behaviour can exhibit pro- and anti-inflammatory properties [159]. Current guidelines for the treatment of CVD advocate the consumption of plant-based foods, the replacement of saturated fats, and the reduction of processed and red meat [160–162]. Consequently, Pappe et al. [150] investigated the potential of a whole-food plant-based diet (WPBD) to modulate periodontal inflammation in patients with elevated CVD risk. Over 16 weeks, 36 participants were divided into two groups: one group followed a WPBD, while the other group maintained their usual dietary habits. The WPBD group exhibited a modest yet non-significant reduction in PISA (−33mm^2), while PISA increased (+23mm^2) in the control group. The difference in PISA change between groups was highly significant ($p = 0.001$). No changes were found in metabolic markers (HbA1c, HDL, LDL or CRP). The findings suggest that anti-inflammatory dietary patterns may stabilize or reduce periodontal inflammation in individuals with CVD risk. However, due to the small sample size and heterogeneity in periodontal status, further long-term studies are required to confirm whether dietary modulation of PISA leads to a reduction in cardiovascular risk.

Atrial fibrillation (AF) is the most prevalent arrhythmia that increases the risks of stroke, heart failure, and mortality. Miyauchi et al. [61] investigated the role of PISA as a predictor of AF recurrence following radiofrequency catheter ablation (RFCA). RFCA has been demonstrated to exhibit a higher AF recurrence-free survival rate in comparison with antiarrhythmic drugs [163]. In a study including 288 periodontitis patients (97 receiving non-surgical periodontal therapy and 191 controls), baseline PISA was found to be higher in the treatment group (614mm^2) compared to the non-treatment group (311mm^2). After 1.4 years of follow-up, patients with higher PISA showed significantly more AF recurrences, with a cut-off value of 615mm^2 predicting recurrence with high specificity of 89 %. Patients who underwent non-surgical periodontal therapy during the RFCA blanking period demonstrated significantly fewer AF recurrences, particularly among those with high baseline PISA. Multivariable model confirmed that periodontal therapy is an independent predictor of reduced AF recurrence. This study highlights that high PISA values are strongly associated with AF recurrence after RFCA. Moreover, the investigators suggest that a reduction in PISA, achieved through non-surgical periodontal therapy, may enhance cardiac rhythm stability. This finding indicates a direct inflammatory link between periodontal and arrhythmia.

In summary, these five studies underscore the multifactorial association between periodontal inflammation, quantified by PISA, and cardiovascular health. While Donders et al. [148] and Seinost et al. [149] found no vascular improvements in relatively healthy or pharmacologically treated patients, Pappe et al. [150] and Miyauchi et al. [61] in contrast demonstrated that both dietary and periodontal therapy can modulate PISA and influence cardiovascular outcomes, particularly in patients considered to be at risk for CVD. Jockel-Schneider et al. [151] further provided direct evidence of quantitative correlations between PISA reduction and vascular parameters. Together, these findings indicate that PISA serves as a quantifiable tool linking local periodontal inflammation to systemic vascular diseases. Treatment of both diseases appears to be significant in terms of reducing vascular risk and periodontal breakdown, in addition to preventing associated CVD. However, the degree to which PISA reduction translates into measurable cardiovascular improvement remains inconclusive and is likely dependent on baseline vascular health, systemic inflammatory burden, and systemic medical therapy.

4.3. Rheumatoid arthritis (RA)

RA occurs in about 0.5–1 % of the world's population, making it the most common autoimmune disease worldwide [164]. Around two-thirds of RA patients suffer from moderate or severe periodontitis [165,166]. RA is a prevalent chronic immune-mediated inflammatory disease characterised by joint inflammation, which causes progressive joint destruction, resulting in functional impairment and disability [167]. Beyond joint involvement, RA increases the risk of cardiovascular disease and premature death. There is evidence that RA is associated with periodontitis. Overlapping molecular pathways of inflammation underlie periodontitis and RA [168]. In both diseases, local tissue destruction involves the overproduction of inflammatory cytokines and proteolytic proteins, such as matrix metalloproteinases, TNFα and IL-6 [169,170]. Studies have demonstrated the beneficial therapeutic effects of TNFα and IL-6 receptor inhibitors on rheumatological and periodontal inflammatory conditions in RA patients [169,171,172]. Traditional RA treatment relies on conventional synthetic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate. Methotrexate is a folate analogue that inhibits the IL-1 and TNFα production. However, advances in understanding key events in the pathogenesis of RA have led to the development of biological DMARDs [164]. The most validated and effective therapy blocks or antagonises the effects of TNFα, a cytokine considered to orchestrate the

inflammatory response in RA [173]. Nevertheless, apart from its well-documented therapeutic value, TNFα inhibition is associated with an increased risk of infectious adverse events [174].

While synthetic and biological DMARDs have demonstrated efficacy in the treatment of RA, there is currently insufficient evidence to demonstrate the impact of these anti-rheumatic treatments on the periodontal condition of RA patients [175,176].

Several cross-sectional and case-control studies using PISA, without treatment or intervention, confirmed an association between increased periodontal severity and RA [58,177–185]. However, PESA was used less frequently [58,183].

These findings led to the hypothesis that the severity of periodontitis and its therapy may have an impact on rheumatological severity and the effectiveness of rheumatological drugs, and vice versa. However, the effects of different periodontal therapies based on PISA was investigated by de Pablo et al. [63], and the efficacy of different rheumatological drugs on PISA was analysed by de Smit et al. [186]. Furthermore, the effects of biological DMARDs medication in patients with high and low PISA was demonstrated by Kobayashi et al. [187] and Yamashita et al. [188] (Table 2). de Pablo et al. [63] assessed the impact of non-surgical periodontal therapy including oral hygiene instructions (OHI) on rheumatologic parameters in patients suffering from RA and generalized periodontitis. The control group received only OHI. All patients received a treatment with biological DMARDs. It was not possible to achieve complete resolution of periodontal inflammation in any patient. However, there was a distinct improvement in periodontal parameters in the intervention group. Conversely, PISA improvements diminished after 6 months. Furthermore, it was observed that measurement of RA disease activity, including tender joint count, swollen joint count, patient global visual analogue scale, and musculoskeletal ultrasound scores, exhibited a tendency to improve as a result of non-surgical periodontal therapy. Conversely, the RA disease activity measurement exhibited a notably lesser decrease in the control group. Moreover, periodontal therapy resulted in an improvement in RA disease activity and ultrasound measures in patients receiving biological DMARD medication.

In a small longitudinal study, de Smit et al. [186] included patients suffering from gingivitis, moderate and severe periodontitis, and RA. The authors analysed the effect of methotrexate or methotrexate combined with anti-TNFα (etanercept) treatment on PISA. No periodontal therapy was permitted. Subsequent follow-up periods of up to six months have demonstrated a negligible enhancement in PISA and other periodontal parameters, despite a significant improvement in RA disease activity scores. This finding indicates that systemic treatment alone does not influence PISA and therefore may be inadequate for treating periodontal inflammation. In addition, Mayer et al. [189] and Üstün et al. [190] demonstrated the impact of anti-TNFα treatment on the periodontium of RA patients at the local level. Anti-TNFα can modify the host response in the inflammatory exudate of the periodontium. This local effect may be too small to be reflected in clinically measurable and/or relevant changes, even using the currently most sensitive method PISA for assessing the inflammatory burden of periodontal disease [174].

In two studies, the same working group analysed patients suffering from RA who were undergoing biological DMARD therapy, with and without periodontitis. Patients were divided into two groups, low and high PISA, based on the median PISA value (79mm^2 and 75mm^2). The parameters of RA activity were then analysed (i.a. clinical disease activity index, tender joint count and swollen joint count). No periodontal therapy was performed, nor was there a change to the oral hygiene regime. Six months after the initial administration of biological DMARDs, certain univariate RA activity scores and the multivariate analyses indicated a significantly positive association between baseline PISA and RA activity. The authors concluded, that rheumatologic therapy is less effective in patients with periodontitis. Furthermore, they found that baseline PISA is associated with the clinical response to biological DMARDs in patients with RA [188]. Subsequently, the aforementioned working group disseminated a 1-year follow-up study, employing the same study design. RA activity scores demonstrated superior outcomes in patients with no or mild periodontitis following the CDC/AAP case definition [191], while baseline PISA exhibited no statistically significant association with RA activity scores. The observed discrepancy may be attributable to reduced bleeding on probing and, consequently, potential underestimation of true periodontal disease severity in patients undergoing immunosuppressive therapy [187]. However, a notable limitation of the two studies is the absence of any reporting of PISA following 6 and 12 months of biological DMARD therapy.

A recent published meta-analysis by Sun et al. [192] analysed nine clinical studies in patients with RA, without including the aforementioned studies or PISA. The conclusion drawn from this study was that non-surgical periodontal therapy could improve RA activity scores.

The inconsistent results obtained in the studies under review are attributable to the relatively small size of the patient cohort in each study. In addition to the drug under investigation, patients are often administered various other pharmaceuticals, which has the potential to distort the results of a small sample size. For instance, it was challenging to evaluate the respective responses to a beneficial effect of treatment with inhibitors of TNFα or IL-6 receptors.

In summary, immunosuppressive medication may dampen local periodontal immune responses, reducing BOP and PISA, which complicates periodontal disease classification in RA patients [187]. However, the reviewed studies support an association between RA and periodontitis, with PISA emerging as a useful quantitative marker for systemic inflammatory burden. While PISA appears to correlate with treatment outcomes in RA, immunosuppressive therapy may blunt its sensitivity. Future trials should account for medication effects and consider combining periodontal and rheumatologic interventions for optimal patient outcomes.

4.4. Chronic kidney disease (CKD)

CKD remains a prevalent public health problem. In 2017, the global prevalence of CKD was estimated at 9.1 % (697.5 million cases) and 1.2 million people died from CKD [193]. The increasing incidence of CKD, which is a direct cause of global morbidity and mortality and an important risk factor for CVD, poses major challenges for healthcare and the economy in the near future.

CKD is characterised by a decline in kidney function or the presence of kidney damage. There are a number of methodologies employed in the diagnosis and staging of CKD. The estimated glomerular filtration rate (eGFR) and the urine-albumin-to-creatinine-ratio (UACR) have frequently been utilised as renal biomarkers. The eGFR is utilised in the diagnosis, staging and prognosis of renal diseases. Furthermore, it plays a pivotal role in the determination of optimal drug dosages and the subsequent risk stratification for a range of clinical procedures and future outcomes. The eGFR is typically calculated using plasma creatinine values. An eGFR of <60 mL/min/1.73m2 for a period of three months or more being considered indicative of renal dysfunction [194].

Albuminuria is the most frequently used marker of kidney damage in clinical practice and research. It is estimated that over 50 % of cases of CKD may be overlooked if UACR is not taken into consideration. The estimation of UACR has been shown to have certain advantages over other tests in terms of sensitivity and the level quantification. It is recommended that the result of a spot sample should be <30 mg/gCr and that a minimum of two to three measurements are taken over a period of two to three months. Furthermore, the assessment of UACR in CKD screening appears to enable a more accurate prediction of poor quality of life [195,196].

It has been hypothesised that a variety of inflammatory processes may act as stimulators of the renal inflammatory response, thereby triggering CKD [197–199]. The association between periodontitis and CKD has been the focus of considerable research since the 2000s, leading to the recognition of periodontitis as a novel, non-traditional risk factor

for CKD [199,200].

It is suspected that the bacteria present in subgingival biofilm have the capacity to enter the circulation system and promote an inflammatory response in the renal endothelium [201–203]. Furthermore, proinflammatory cytokines, which are locally produced in periodontal lesions, have the capacity to enter the bloodstream, resulting in systemic inflammation. This is characterised by increased levels of inflammatory biomarkers, such as CRP [204]. In contrast, systemic inflammation has been demonstrated to lead to progression of CKD [205], and a high CRP level has been shown to be a predictor of mortality in these patients [206].

Periodontal therapy has been demonstrated to play an important role in reducing inflammatory mediators. A number of studies have indicated that the kidneys play a significant role in the clearance of cytokines [207]. High levels of inflammatory markers have been demonstrated to exert a detrimental effect on the renal system, given that an increased nephron filtration of plasma proteins results in further release of cytokines in the renal interstitium, with subsequent fibroblast proliferation, fibrogenesis, and ultimately renal scarring, contributing to progressive deterioration in function. Consequently, it can be hypothesised that periodontal therapy could exert a positive effect on both systemic inflammatory markers and renal endothelial function via enhanced filtration [208].

A substantial number of cross-sectional studies [209–213], in addition to a number of longitudinal studies [205] based on PISA, lend support to the potential relationship between periodontitis and CKD. However, only one prospective interventional study is investigated the association between the two diseases based on PISA, eGFR and UACR (Table 2). Vachhani & Bhavsar [64] analysed 80 Indian CKD patients with generalized moderate to severe periodontitis over 6 months. The intervention group received non-surgical periodontal therapy including oral hygiene instructions, while the control group received only oral hygiene instructions. The intervention group showed significant improvements in a reduced PISA, increased eGFR and reduced UACR at both three and six months post-treatment. In contrast, the control group exhibited a deterioration in all parameters. The study demonstrates that periodontal therapy can mitigate systemic inflammation and improve renal outcomes in CKD patients, suggesting a potential therapeutic benefit of both diseases.

The results are similar to those obtained by Almeida et al. [214] The study reported significant improvement after non-surgical periodontal therapy in eGFR values up to 6 months. But the authors did not include PISA and an interventional group. Conversely, the outcomes diverge from those reported in a study by Grubbs et al. [215] No significant alteration in the magnitude of the biomarkers measured in response to intensive non-surgical periodontal therapy was observed. The reasons for this discrepancy are multifaceted, including the presence of more severe periodontitis in the interventional group, the absence of a true control group, and the control group got beside oral hygiene instructions additionally a professional mechanical tooth cleaning and had hopeless teeth extracted. This could have led to a reduced periodontal burden with reduced differences in periodontal and systemic biomarkers.

A recent systematic review reported that patients with periodontitis were 1.54 times more likely to develop CKD than those without periodontitis (relative risk: 1.54, 95 %CI: 1.40–1.70). The incidence of periodontitis in CKD patients was found to be 1.98 times higher than that observed in healthy individuals with an odds ratio of 1.98 (95 %CI: 1.53–2.57). The review established a bidirectional association between periodontitis and CKD through a meta-analysis of observational studies [216]. Nevertheless, Nanayakkara and Zhou [217] demonstrated that the findings were inconclusive with regard to the directional association: the random-effects model showed an incidence rate ratio (IRR) of 2.1 (95 %CI: 0.72–6.15,$p = 0.177$), while the fixed-effect model yielded an IRR of 1.76 (95 %CI: 1.11–2.77, $p = 0.016$), indicating significant heterogeneity ($I^2 = 78.3$ %, $p = 0.031$). Therefore, the results indicated that there was a non-directional association between periodontitis and CKD, based on the extant studies, owing to significant variability in study design, for example, clinical parameters. It is recommended that future studies consider the standardisation of methods and the employment of more robust clinical inflammatory parameters, such as PISA.

5. Limitations of studies related to periodontal inflammation indices

The interpretation of evidence on the association between periodontitis and systemic inflammatory diseases requires careful consideration of several methodological and conceptual limitations in the studies discussed. Although considerable progress has been made in recent years, the current literature remains heterogeneous in design and reporting quality, limiting the strength of the available conclusions.

Only a small number of studies used periodontal inflammation indices, such as PISA, PESA, ratio of PISA to PESA, DGES or PIRI, to assess the association between systemic diseases and periodontitis. Most available data are based on study designs, which do not include a periodontal or systemic intervention. The evidence for PESA, ratio of PISA to PESA, DGES or PIRI, and related indices therefore remains extremely limited. To date, only interventional studies have been published using PISA (Table 2). Using only PISA could be problematic because calculations based on the mean values of the tooth root surface area and root lengths in patients with inflammatory gingival overgrowth, e.g. in response to anti-rheumatic drugs, results in an underestimation of the real value.

A major limitation concerns study design and analytical scope. Five studies were substudies of larger clinical trials without a true primary outcome, resulting in exploratory analyses [99,150,151,187,188]. Furthermore, most studies were single-center investigations conducted in specialized periodontal clinics. Patients attending such clinics typically present with more advanced disease and may not represent the general population, which leads to selection bias and limiting generalizability. Consequently, the external validity of these findings is limited.

The majority of the studies in this review included small sample sizes, typically fewer than 90 participants, only one study involved 288 individuals [61]. Small cohorts reduce statistical power and yield wide confidence intervals, indicating substantial uncertainty about true effect estimates (Xu et al., 2024). Approximately half of the studies matched participants for age and sex. However, other potential confounders such as smoking status, socio-economic factors, comorbidities such as CVD and T2DM, which were not the primary focus of the study, and medication use were inadequately controlled. In particular, the impact of additional drugs, such as anti-rheumatic medications, on PISA values and systemic biomarkers was rarely assessed. Furthermore, differences in inclusion and exclusion criteria, recruitment sources, and disease classification introduced substantial heterogeneity. In several studies, exclusion of participants with severe CVD or severe diabetic complications resulted in the exclusion of clinically relevant subgroups [100]. The classification of periodontitis varied considerably across studies, with different diagnostic systems [11,191,218,219]. Inconsistencies also existed in the criteria for defining periodontal health and disease severity. Moreover, many studies did not control for plaque accumulation, despite the influence of plaque on bacteraemia and systemic inflammatory responses [40,41]. Therefore, poor oral hygiene and high plaque indices may influence periodontal and systemic inflammation indices.

The presence of multimorbidity is more prevalent among older adult individuals. 50 % of periodontitis patients had at least one comorbidity [27,28]. These concurrent inflammatory conditions and additional influential factors are more likely to be present in adult patients than in adolescents. Consequently, comparisons between young patients with periodontitis or systemic diseases and healthy controls are likely to be less influenced by confounding factors. It is reasonable to hypothesise that differences in blood parameters, which can serve as a surrogate for

systemic diseases and periodontal inflammation indices, between individuals with and without periodontitis would be more apparent among younger patients. In none of the studies discussed was the average age of the patients below 50 years.

Short follow-up duration represents another major constraint. Most intervention studies assessed outcomes three months after periodontal therapy, a period during which local and systemic inflammatory markers typically show high improvement. However, given the chronic nature of periodontitis and systemic inflammatory diseases such as T2DM and RA, longer follow-up is necessary to determine the durability of systemic or periodontal therapeutic effects. The discussed studies disregarded systemic events as hard clinical endpoints remain scarce due to methodological, financial, and ethical challenges [220,221]. It is ethically challenging to maintain control groups with untreated periodontitis over extended periods, like some studies did, particularly in patients with systemic comorbidities [186–188,222].

Achieving satisfactory periodontal therapy outcomes in the discussed studies is challenging, and full resolution of periodontal inflammation may not be attainable for some patients. For instance, Xu et al. [100] observed a mean PISA of $>1{,}300mm^2$ in both groups three months following periodontal therapy. However, inadequate periodontal therapy worsens the results and interpretability of the discussed studies. The logistical challenges require careful consideration. In certain instances, additional appointments may be required in order to maintain patient motivation.

The discussed studies also demonstrate limited geographic representation. Nearly all were conducted in Asia or Europe, while no data are available from America or Africa. This imbalance may mask ethnic, genetic, or environmental differences that could influence both periodontal and systemic inflammatory responses. Broader, multi-center investigations across diverse populations are therefore warranted.

In summary, current evidence linking periodontitis and systemic diseases only through PISA and studies are limited by small sample sizes, short follow-up periods, heterogeneous disease definitions, lack of hard endpoints, and incomplete control for confounding variables. The majority of single-center, exploratory analyses further constrains generalizability. In the absence of further data, it is not possible to confirm or refute that there is a causal relationship between periodontitis and the systemic inflammatory diseases presented.

6. Conclusions and outlook

The potential association between systemic inflammatory diseases and periodontitis is of great public health importance due to the high prevalence of these diseases and their potential impact on public health if risk factors could not be identified or therapeutic opportunities are explored. Periodontitis is primarily quantified based on the severity and extent of CAL and/or PPD, in addition with BOP. This includes signs of past disease manifestations and progression, such as attachment and bone loss, which offer limited insight into the current activity of the disease. Periodontal and systemic inflammation indices are ideal tools for assessing present and future disease activity, as well as for the precise detection and quantification of periodontitis and monitoring the risk of its future development. Furthermore, inflammation indices could be used to evaluate the impact of periodontitis on systemic health, providing a means of quantifying its influence on systemic diseases and vice versa.

This is the first review to provide a comprehensive summary of the current scientific evidence on the possible association between periodontitis and systemic inflammatory disease, as measured by the periodontal inflammatory load. A major advantage of the periodontal inflammation indices discussed here is that they are based on parameters frequently used in daily clinical practice worldwide. They are quick and reliable to measure, and easy to enter into periodontal programmes (like ParoStatus® software) or Excel spreadsheets. PISA, for example, is an extremely useful tool for assessing the total burden of periodontal inflammation, which forms the biological basis for the plausibility of any potential association between periodontitis and systemic diseases [82]. Unfortunately, no intervention studies relating to PESA, the PISA-to-PESA ratio, DGES or PIRI could be identified for this review.

We were able to identify four systemic diseases for which intervention studies based on PISA were available. Of these, half indicated that there is evidence of a causal association between PISA/periodontal therapy and CVD [61,150,151], T2DM [62,100] and RA [63,188] inflammatory status. Only one study was published relating to CKD [64], indicating an association between periodontal therapy and CKD inflammatory status. However, the methodological quality of the presented and discussed studies was weak. Nevertheless, the evidence described in this review indicates that periodontitis could be defined as a systemic inflammatory disease because therapy for this disease affects PISA, and vice versa.

Despite the limited results of the studies presented, it could be concluded that **periodontal therapy may represent a non-pharmacological intervention** for preventing and reducing disease activity in the four conditions [63]. Additionally, healthcare professionals need to raise their awareness of periodontal disease and its effect on their patients' overall health. Consequently, it may be worthwhile for various medical disciplines, researchers, and professional organisations to engage in comprehensive discourse and issue official statements concerning **periodontal therapy as a primary and secondary prevention** for systemic diseases. Despite this, our review could not find strong evidence of a causal relationship between the four discussed diseases. However, there is a wealth of evidence, particularly for T2DM and CVD, which suggests a causal link. Therefore, to raise awareness of periodontitis in general medicine, it can be considered a "chronic oral inflammatory disease with systemic implications" [23].

The following recommendations should be considered for future studies [29,63,223]:

Firstly, larger populations from different continents, such as America and Africa, should be included in order to evaluate their global validity. The 2017 classification of periodontitis should be used more consistently in these studies [3,11]. Furthermore, confounders such as age (with participants as young as possible to minimise inflammaging), gender, smoking status, and racially matched cohorts should be taken into account. Studies including more periodontal inflammation indices, such as PESA, DGES and PIRI, would be useful for better evaluation. In addition, evaluating the combination of different indices may more precisely reflect the balance between host immune and inflammatory conditions, since it would integrate more components of the immune response.

Secondly, the relationship between periodontal inflammation indices and inflammatory cytokine levels in oral fluids (such as saliva and gingival crevicular fluid) should be explored. Exploring these correlations could help integrate clinical periodontal indices more effectively with local biochemical markers of inflammation, potentially contributing to the development of more comprehensive, biologically grounded assessment tools. Thirdly, a comprehensive investigation of the underlying biological mechanisms of the link between periodontitis and systemic inflammatory disease is essential. In patients with both periodontitis and comorbidities, periodontal inflammation indices may reflect the combined effects of the two conditions. Additionally, an artificial intelligence-based network analysis could be established to identify systemic multimorbidity clusters in patients with periodontitis, as well as internal and external factors that affect the severity of these clusters [27], which may influence inflammation values. Therefore, this review suggests that periodontal and systemic inflammation indices could be a useful tool to demonstrate the link between periodontal and systemic inflammatory diseases.

Fourthly, periodontal screening should be performed in general medical clinics or a clinical research facility to maximise the number of potentially eligible patients captured. A dedicated line of communication should be provided for all clinical and trial-related concerns, and regular reminders should be sent to patients/study participants about

their upcoming dental/medical appointments. Patients with multiple morbidities often require multiple hospital appointments, so it is important to send timely reminders to reduce the risk of missed appointments or high numbers of study dropouts. The World Health Organization [224] suggests considering ways of strengthening the link between dental and medical care services. Horizontal service integration, delivered by multidisciplinary teams including medical, dental, and wider healthcare professionals, should be established. This enables them to deliver more person-centred services [225].

Fifthly, carefully designed prospective multicentre interventional studies and longer follow-up periods are required to substantiate possible associations. These will help elucidate possible causal, bidirectional relations between periodontitis and local and systemic inflammation indices. Understanding the biological mechanisms and principles determining this complex interplay could substantially advance personalised diagnostics, prognostics, and therapeutic management. Periodontal inflammation indices could be used as prognostic markers to predict future destructive events and assess the efficacy of treatments at a systemic level. Developing and applying biological tools for diagnostics and assessing treatment outcomes is a key step in the growing medicalisation of periodontology.

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