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Periodontal Inflamed Surface Area (PISA): A Measuring Factor for Local Periodontal Inflamed Burden Connecting to Systemic Inflammation: A Comprehensive Review

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1. Introduction

Interrelationship with general health

Periodontitis is a type of systemic immune inflammation that is caused by the complex infection of a variety of microorganisms in the subgingival plaque and the imbalance of the microbial ecological environment in the mouth. It is a chronic inflammatory disease resulting in tissue destruction and periodontal pockets formation in periodontitis-affected tissues. An ulcer surface is formed on the inner surface of the periodontal pocket by disrupting the continuity of epithelial cells, which results in easy bleeding. This indicates that a mild chronic inflammatory condition persists throughout the body, not just in the periodontal tissue. Approximately 10% of the world's population has severe periodontitis (Frencken et al., 2017) (1) . In addition, periodontitis may have a negative impact on body balance control and the development of persistent disease (Brito et al., 2012) (2) . Therefore, periodontitis is a highly prevalent chronic inflammatory disease with negative and far-reaching effects on many aspects of daily life (3) . Since the 1999 workshop considerable evidence has emerged concerning potential effects of periodontitis on systemic diseases (4) . Various mechanisms linking periodontitis to multiple non oral and non-communicable diseases have been proposed (5) . Specific oral bacteria in the periodontal pocket may gain bloodstream access through ulcerated pocket epithelium. Inflammatory mediators from the periodontium may enter the bloodstream and activate liver acute phase proteins, such as C-reactive protein (CRP) (6) , which further amplify systemic inflammation levels. Hence the active bacterial subversion of the host immune response in ways enable the persistence of pathogens in the local inflammatory environment of periodontitis and the induction of pathology or complications at systemic sites (7) . Case-control (8) and pilot intervention studies (9) show that periodontitis contributes to the overall inflammatory burden of the individual which is strongly implicated in atherosclerosis (10) , diabetes (11) , stroke and coronary heart disease (12) , chronic kidney disease (13) and adverse pregnancy outcomes (14) .

Effect of periodontal treatment in controlling systemic diseases:

Periodontal therapy (PT) is a standard therapeutic modality used to control infection and inflammation in periodontal diseases. PT includes surgery and non-surgical periodontal therapy (NSPT), and the latter is feasible and easily been performed by periodontal practitioners, mainly including professional oral hygiene instructions (OHI), full-mouth scaling and root planning (SRP) to remove supra/subgingival biofilm and calculus (15) . Recently, many scholars have begun to investigate and study the effects of NSPT on systemic inflammation and various systemic diseases as mentioned earlier like diabetes, stroke, and coronary heart disease chronic kidney disease, adverse pregnancy outcomes (16) (17) (18)

Modestly sized studies of periodontitis treatment in uncontrolled Type II diabetes subjects have shown value in reducing hyperglycaemia, although reductions achieved have not been supported in some larger studies where the periodontal treatment outcomes were less clear (19) . Although intriguing health economics analyses have shown a reduction in cost of care for multiple medical conditions following treatment for periodontitis, little direct periodontitis intervention evidence, beyond the diabetes experience, has convincingly demonstrated the potential value of effectively treating periodontitis relative to overall health benefits. (18) Current evidence that effective treatment of certain cases of periodontitis can favourably influence systemic diseases or their surrogates, although limited, is intriguing and should definitively be assessed.

Hence, factors that are needed to be considered in formulating a diagnostic classification of periodontal disease must include the medical status of the patient and the level of expertise needed to provide appropriate care. If the patient has severe systemic disease, as indicated by their American Society of Anesthesiologists (ASA) status (20) , this can seriously affect the clinician's ability to control disease progression due to the patient's inability to withstand proper treatment or their inability to attend necessary maintenance care. Periodontitis is a type of systemic immune inflammation that is caused by the complex infection of a variety of microorganisms in the subgingival plaque and the imbalance of the microbial ecological environment in the mouthVarious mechanisms linking periodontitis to multiple non oral and non-communicable diseases have been proposed (5) . Specific oral bacteria in the periodontal pocket may gain bloodstream access through ulcerated pocket epithelium. Inflammatory mediators from the periodontium may enter the bloodstream and activate liver acute phase proteins, such as C-reactive protein (CRP) (6) , which further amplify systemic inflammation levels. Periodontal therapy (PT) is a standard therapeutic modality used to control infection and inflammation in periodontal diseases. PT includes surgery and non-surgical periodontal therapy (NSPT) Currently, a large variety of classifications are used for periodontitis as a risk factor for other diseases. The only classification that quantifies the amount of inflamed periodontal tissue, to assess the inflammatory burden posed by periodontitis on systemic burden is **PERIODONTAL INFLAMMED SURFACE AREA (PISA) SCORE** Chronic Periodontitis, PISA, Local and Systemic Inflammation**.**

Existing Classification and Need for such a classification and index:

The lack of a universal periodontal case definition has led both European and American experts in this field to publish consensus paper in which they suggest that the case definition developed by the CDC-AAP is the one that has to be used in periodontal epidemiological studies (21) .

The estimation of the prevalence of chronic periodontitis is influenced by case definitions of this disease as well asrecording protocols. Diagnosis of periodontitis is based on severity and extent of clinical attachment level (CAL) andprobing pocket depth (PPD), bleeding on probing (BOP) and radiographically by assessing the bone loss. In 2007, the Centres for Disease Control and Prevention (CDC) in collaboration with the American Academy of Periodontology (AAP) developed case definitions for moderate and severe periodontitis for use in epidemiological research (22) . In addition, the same working group published in 2012 an updated paper (23) , where they introduced the definition of mild periodontitis cases. Therefore, mild periodontitis was defined as2 interproximal sites with CAL3 mm and2 interproximal sites with PPD4 mm (not on the same tooth) or 1 site withPPD5 mm. Moderate periodontitis was defined as2 inter-proximal sites with CAL4 mm (not on the same tooth) or2 interproximal sites with PPD5 mm, also not on the same tooth. Severe periodontitis was defined as the presenceof2 interproximal sites with CAL6 mm (not on the same tooth) and1 interproximal site with PPD5 mm.

However, this classification is based on linear measures (PPD and CAL) and may not quantify the amount of inflamed periodontal tissue as values are specific for each tooth and nocumulative value exists, which assesses the total inflammatory status of the periodontium. Moreover, various Indices used to assess the severity of gingivitis like Gingival Index, Modified Gingival Index, to assess periodontitis like Russell Periodontal index (RPI) (24) or bleeding index and forepidemiological studies and surveys like Community Periodontal Index (CPI) (25) are not familiar to most medical personnel and are not quantitatively evaluated. Although no gold standard for periodontitis as a risk factor for other diseases exists, a list of demands was assembled for the construction of a new classification of periodontitis. The first and foremost demand was that the new classification should adequately quantify the amount of inflamed periodontal tissue. Second, the classification should be easy to use and broadly applicable. This means that the classification should make use of clinical measurements commonly used to establish periodontitis, CAL, gingival recession (GR) and BOP measurements.

A classification that quantified the total surface area of attachment loss Attachment Loss Surface Area (ALSA) was found by Hujoel et al.2001. To calculate the ALSA, formulas were generated whereby linear probing measurements, from the cemento–enamel junction (CEJ) to the bottom of the pocket (i. e. CAL), around a particular tooth are transformed into the ALSA for that particular tooth (26) . The ALSA quantifies the root surface area that has become exposed due to attachment loss. However, the ALSA cannot be used to quantify the amount of inflamed periodontal tissue. ALSA does not quantify the to calculate periodontal epithelial surface area (PESA), PPD measurements are used. However, PESA does still not quantify the surface area of inflamed pocket epithelium. After all, the PESA also includes healthy pocket

To calculate the inflamed part of the PESA, part of the PESA that is affected by BOP is calculated. Thus, the bleeding surface area, the periodontal inflamed surface area (PISA), may be thought of as the main contributor to any systemic inflammatory burden posed by periodontitis. Therefore, an objective index was made that provide information accessible to the medical department.

Thus, BOP values calculated at six sites per tooth were utilized for calculation of periodontal inflamed surface area (PISA). PISA is calculated by multiplying the BOP positive sites and PESA values.

Microsoft excel Spreadsheets are freely available from website: www.parsprototo.info. PISA can be calculated with the help of spreadsheets by entering the values of CAL, LGM by entering PPD measurements as measured on six sites per tooth. In addition to research purposes, the spreadsheet might also be used to show patients their surface area of bleeding pocket epithelium in milli-metres square, illustrating the inflammatory burden periodontitis potentially poses to their body.

2. Literature Review

PISA and Severity of Periodontal diseases:
With varying degrees of periodontal disease progression, a steady increase in PISA scores was seen. PISA values for disease severity vary depending on the population studied, and different upper and lower limits were found in studies on several populations. PISA results rise as disease severity rises. Mean PISA values for mild, moderate, and severe periodontitis are, respectively, 116 mm2, 259 mm2, and 406 mm2 (27) . The cut-off points for PISA values when considering the periodontitis case defining classification used by the American Academy of Periodontology and the Centers for Disease Control and Prevention, values for the severe periodontitis group ranged from 934.71 mm2 to 3274.96 mm2, those for the moderate periodontitis group from 521.58 to 790.30 mm2, and those for the mild periodontitis group ranged from 110.16 to 447.01 mm2, the group without periodontitis showed PISA values between 10.22 and 62.78 mm2 (28)

PISA and Smoking:
Smokers and tobacco chewers had lower PISA scores than people without a history of tobacco use. Smokers and tobacco chewers had mean PISA scores of 215 mm2 and 217 mm2, respectively, while individuals who did not have either of these habits scored between 277 mm2 and 283 mm2 The lower values in patients with tobacco use are compatible with the decreased bleeding on probing that is observed in such patients13, as bleeding on probing is a crucial parameter in the computation of PISA. With PI and the amount of present smoking, PISA results rise (29) .

PISA and Systemic Diseases

1) Diabetes
It is now well accepted that type 2 diabetes and periodontitis have a reciprocal causal relationship in which one influences the other and vice versa. To evaluate the dose-response correlations between the amount of inflammatory periodontal tissue and a widely determined disease activity parameter for diabetes, such as HbA1c, PISA indeed appears to be an important tool. In a study by Nesse et al (30) , for type2 diabetics, revealed a dose-response association between HbA1c levels and PISA. Patients with diabetes had a higher PISA value (316 mm2) than patients without diabetes (273 mm2). In other words, a 1.0% increase in HbA1c is correlated with a 333 mm2 increase in PISA on a group basis. Likewise, a 1.0% drop in HBA1c is linked to a drop in PISA of 333 cm2. This dose-response association may point to a connection between PISA and HbA1c at the causal level. The results of this study also imply that PISA is a valuable method for measuring the dose-response correlations between the amount of inflammatory periodontal tissue and HbA1c. In anoriginal research conducted by Saktehi Devi et al in 2015 to evaluate PISA and its relationship with glycemic control in type 2 diabetes with and without periodontitis, concluded that when HbA1c increased, the PISA values also increased in type 2 diabetic patients with and without periodontitis (31) .

2) Cardio-Vascular Diseases
PISA scores were found to be higher in hypertensive patients (318 mm2) as compared to healthy individuals (273 mm2) (29). The association of PISA and BoP with blood pressure (BP) in NHANES III was evaluated in a study by Davide Pietropaoli et al. they concluded that PISA and BoP describe the association of periodontal inflammation and BP with subtle differences that might in part be explained by the systemic impact of the disease activity-related fluctuations in low-grade inflammation. Patients with severe PISA and BoP appear at higher risk of high/ uncontrolled BP, and monitoring for disease relapse might help controlling for systemic inflammatory burden, with potential benefits on BP profile (32).

The study aimed to test the hypothesis that higher periodontal inflamed surface area (PISA) values have positive correlations with increased complete blood parameters in CAD patients, demonstrated, blood parameters (PDW, RDW and MPV) in CAD patients with/without periodontitis can be used to assess the relationship between these chronic inflammatory diseases using PISA values for the assessment periodontitis. The study also provide scientific background (in addition to the abovementioned studies in the literature) for using PISA in the assessment of periodontitis and in clarifying the relationship between systemic diseases and periodontitis in further studies (33) .

3) Chronic Kidney Diseases
A Japanese study has used this index in patients with CKD and CP.31 The study investigated the effect of PD on kidney function in community-dwelling elderly patients. Participants were classified into quartile groups according to their PISA score, and then divided into 2 groups: the highest quartile vs. the other 3 groups combined. The results showed that patients in the highest PISA quartile had a 2.6-fold greater risk of a decreased kidney function after 2 years of follow-up (OR: 2.58; 95% confidence interval (CI): 1.34–4.98) (34).

In one of our study to evaluate the effects of non-surgical periodontal therapy (NSPT) on periodontal clinical parameters (PISA), serum inflammatory factor high-sensitivity C-reactive protein (hs-CRP) and renal biomarkers in patients with CKD and chronic periodontitis (CP), PISA scores as well as the serum levels of hs-CRP and UACR significantly de-creased while eGFR significantly increased ingroup 1 receiving NSPT, including scaling and root planing (SRP) and oral hygiene instructions as compare to group 2 receiving only oral hygiene instructions without NSPT six months after treatment as compared to baseline ($p < 0.001$) (13) .

PISA and Microbiological Analysis
Complex periodontal pathogens, like P. gingivalis, are the cause of periodontal diseases. There were no statistically significant findings in the study done to determine an association between P. gingivalis and PISA. Thus, it was determined that the total amount of plaque is what causes and is thought to be a key influence in periodontal inflammation11.

In the study, conducted by Hideo Shigeishi et al, to determine the relationship between oral EBV and P gingivalis prevalence and the periodontal inflamed surface area (PISA) in middle-aged and older adults, concluded that oral EBV was significantly associated with higher PISA values. This result highlights the key role of oral EBV in periodontitis severity in middle-aged and older people (35).

Akito Sakanaka et al performed a study to identify robust biomarkers for periodontal inflammation severity using PISA as an indicator of periodontal inflammatory status. Based on multivariate analyses using pre-debridement salivary metabolomics data, they found that metabolites associated with higher PISA included cadaverine and hydrocinnamate, while uric acid and ethanolamine were associated with lower PISA (36).

Periodontitis progression and IL-1 have a well-established association. A study by Kalaichelvi Govindarajan et al assessed the correlation of PISAindex with the gingival crevicular fluid (GCF) levels of IL-1α, which would be helpful in evaluating the validity of PISA index in terms of reflection of the diseaseThere was a positive correlation between IL-1α and PISA in periodontitis groups compared to healthy. Similarly, cytokine levels in GCF were closely associated with the severity of gingival inflammation and/or periodontal tissue destruction. (37).

Simplified PISA:
Periodontal disease is a risk factor for non-communicable diseases through the localized inflammation and periodontal pathogens (38) . Recent studies have reported that PISA is effectively associated with systemic markers of low-grade inflammation, such as C-reactive protein (13) . However, calculation of the PISA is difficult, requiring six-point probing depth measurements with or without bleeding on probing on 28 teeth, followed by data input in a calculation program. Moresimple methods are essential for screening periodontal disease in epidemiological studies. In the study, a convenient partial examination method was used to estimate PISA (39) . Cross-sectional data of 254 subjects who completed active periodontal therapy were analyzed. Teeth that represent the PISA value were selected by an item response theory approach. The maxillary second molar, first premolar, and lateral incisor and the mandibular second molar and lateral incisor were selected. The sum of the PISAs of these teeth was significantly correlated with the patient's PISA (R2 = 0.938). More simply, the sum of the maximum values of probing pocket depth with bleeding for these teeth were also significantly correlated with the patient's PISA (R2 = 0.6457). Thus, the study provided estimates of PISA values in relation to each CDC-AAP category in order to facilitate researchers an approximated range.

3. Conclusion

PISA, a very practical and convient index that measures the surface area of bleeding pocket epithelium in square millimetres, is computed using traditional clinical indices of periodontal health, specifically BOP paired with either PD or CAL and gingival recession. Because there is no need to calculate the mean or maximum value for this variable, PISA can display the patients' inflammatory state as one contentious variable.

A patient with CDC-AAP categorization may be located using a PISA value of 130.33mm2. When investigating periodontitis as a potential risk factor for systemic diseases, it appears that PISA is a periodontal parameter that may be used in conjunction with the CDC-AAP case definition classification.

Well-designed RCTs need to be conducted to rule out the correlation of inflammatory burden posed by PISA in periodontal disease with various non-communicable systemic diseases and henceforth, to evaluatea causal relationship between them.

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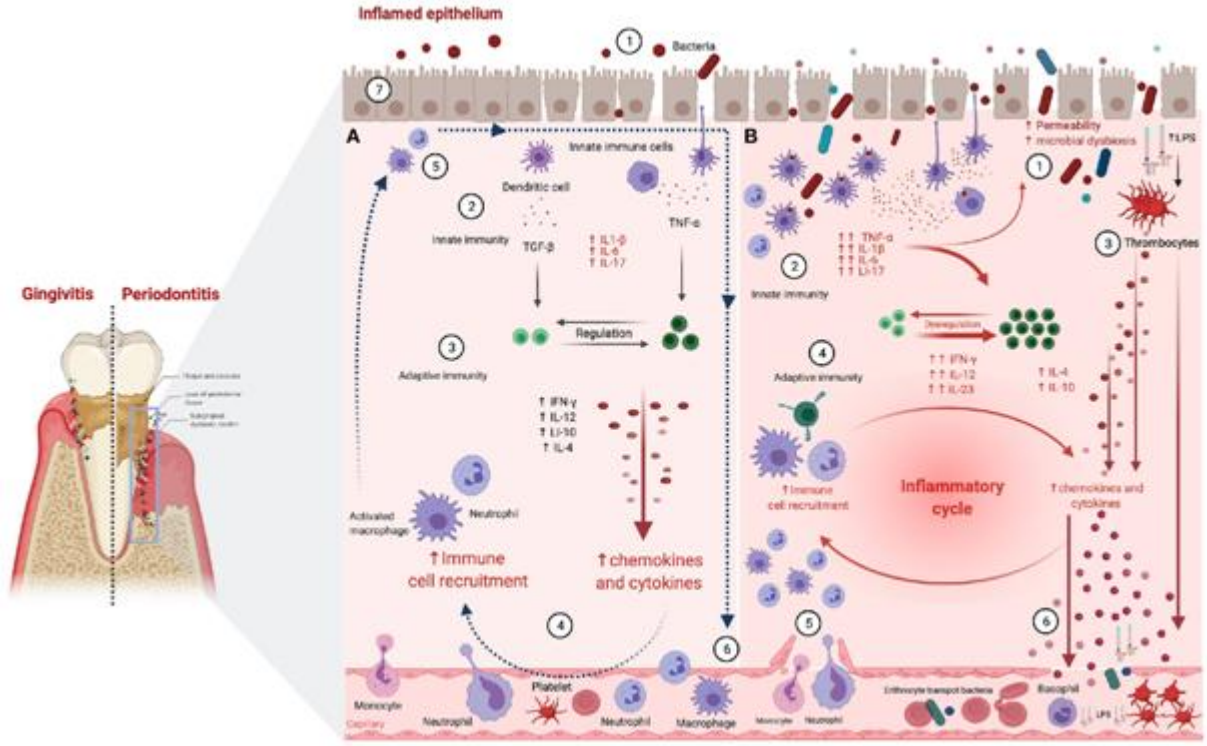

Figure 1: Periodontitis-associated immune and inflammatory processes. (A) Resolved inflammation and infection clearance scenario: 1 Epithelial permeability and periodontopathogens entry.2 Innate immune cells detect LPS leading to pro-inflammatory cytokine production.3 T cells are activated enhancing innate response via macrophage and neutrophil activation.4 Macrophages and neutrophils release pro-inflammatory cytokines increasing vascular permeability.5 Neutrophils clear periodontopathogens via infiltrating monocytes/macrophages, releasing tissue healing factors.6 Neutrophils and macrophages exit the inflammation site and move back into the bloodstream. Pro-resolution mediators restrain immune cell influx, reversing vascular permeability, and coordinating the clearance of inflammatory debris.7 The progression of acute into chronic inflammation is limited. (B) Unresolved periodontal inflammation and infection remaining scenario: 1 Greater epithelial permeability and massive entry of periodontopathogens.2 Innate immune cells detect LPS, leading to pro-inflammatory cytokine production and phagocyte activation.3 LPS activates thrombocytes, enhancing antimicrobial peptides and cytokine production.4 Adaptive immune cells activate macrophages and neutrophils releasing pro-inflammatory cytokines.5 Vascular permeability increases and leukocyte influx persist in inflamed periodontal tissues, due to failure of infection clearance, followed by the establishment of chronic inflammatory lesions.6 Pro-inflammatory mediators and antimicrobial peptides are dumped into the circulation and may trigger inflammation in remote sites [Figure generated with BioRender (Biorender. com)].