The Roles of Neutrophils Linking Periodontitis and Atherosclerotic Cardiovascular Diseases

Rizky A. Irwandi¹, Scott T. Chiesa², George Hajishengallis³, Venizelos Papayannopoulos⁴, John E. Deanfield² and Francesco D’Aiuto¹*

¹ Periodontology Unit, UCL Eastman Dental Institute, University College London, London, United Kingdom, ² UCL Institute of Cardiovascular Science, University College London, London, United Kingdom, ³ Department of Basic & Translational Sciences, Laboratory of Innate Immunity & Inflammation, Penn Dental Medicine, University of Pennsylvania, Philadelphia, PA, United States, ⁴ Antimicrobial Defense Laboratory, The Francis Crick Institute, London, United Kingdom

Inflammation plays a crucial role in the onset and development of atherosclerosis. Periodontitis is a common chronic disease linked to other chronic inflammatory diseases such as atherosclerotic cardiovascular disease (ASCVD). The mechanistic pathways underlying this association are yet to be fully understood. This critical review aims at discuss the role of neutrophils in mediating the relationship between periodontitis and ASCVD. Systemic inflammation triggered by periodontitis could lead to adaptations in hematopoietic stem and progenitor cells (HSPCs) resulting in trained granulopoiesis in the bone marrow, thereby increasing the production of neutrophils and driving the hyper-responsiveness of these abundant innate-immune cells. These alterations may contribute to the onset, progression, and complications of atherosclerosis. Despite the emerging evidence suggesting that the treatment of periodontitis improves surrogate markers of cardiovascular disease, the resolution of periodontitis may not necessarily reverse neutrophil hyper-responsiveness since the hyper-inflammatory re-programming of granulopoiesis can persist long after the inflammatory inducers are removed. Novel and targeted approaches to manipulate neutrophil numbers and functions are warranted within the context of the treatment of periodontitis and also to mitigate its potential impact on ASCVD.

Keywords: neutrophils, systemic inflammation, trained immunity, innate immune memory, periodontitis, periodontal disease, atherosclerosis, atherosclerotic cardiovascular disease

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) consists of a group of disorders that affect the heart and blood vessels (1) and include coronary heart disease, cerebrovascular disease, and peripheral vascular disease (2). ASCVD is a major cause of global mortality and a leading contributor to disability as it causes 18.6 million deaths and contributes to 34.4 million people living with disability in 2019 (3). Although its pathogenesis, progression, and complications comprise multiple complex processes, inflammation plays a key role in each stage of the disease (4).
Periodontitis is a common chronic inflammatory disease caused by oral microbial dysbiosis. The onset and progression of the disease could span over decades and is influenced by genetic and environmental factors. This prevalent oral disease is characterized by progressive destruction of hard and soft tissues supporting the tooth, including the periodontal ligament and alveolar bone (5). Untreated periodontitis leads inevitably not only to tooth loss but also to masticatory impairment and negative influences on the quality of life of a patient (6). Like ASCVD, periodontitis is a major public health concern as it affects over half of the population of the world (7) and 5–15% of the global population presents a severe form of the disease (8), causing increased costs of oral healthcare (9).

The evidence linking periodontitis to systemic diseases has previously focused on the findings that periodontal bacteria and their endotoxins disseminate physically through the blood circulation (10, 11). However, periodontitis also triggers systemic inflammation, indicated by an increased level of C-reactive protein (CRP), TNFα, IL-1β, and IL-6 in the serum of patients (2). Because of chronic inflammation occurring at the periodontium, endotoxemia, bacteremia, and systemic inflammation are collectively implicated in numerous systemic diseases, including atherosclerotic cardiovascular disease (ASCVD) (12–14).

Neutrophils are the most abundant inflammatory cells in humans and the first-line defense against infection in the innate arm of the immune system. They are derived from the myeloid differentiation lineage of hematopoietic stem cells (HSCs) in the bone marrow. Upon detection of pathogens, neutrophils capture and destroy invading pathogens via phagocytosis and intracellular degradation, degranulation, and the formation of neutrophil extracellular traps (NETs) (15). Moreover, the emerging evidence over the past decade reveals that neutrophils are involved in chronic inflammation and are implicated in chronic inflammatory disorders, including periodontitis and ASCVD (16–20). Periodontitis appears to be associated with hyper-responsive neutrophils (21–23), which might, at least in part, be attributed to the notion that oral disease could influence hematopoietic tissue activity and trained immunity (12). Trained immunity represents a non-specific memory in innate immune cells that is induced by earlier encounters with infectious or inflammatory stimuli and which promotes increased immune responses to future challenges with the same or different stimuli (24, 25). Meanwhile, in ASCVD, neutrophils contribute to different stages and clinical manifestations of atherosclerosis (26) and literature also suggests that inflammation-adapted hematopoietic stem and progenitor cells (HSPCs) may contribute to the disease pathogenesis (27–29). As such, recent consensus between the European Federation of Periodontology and the World Heart Federation includes neutrophil hyper-responsiveness as one of the mechanisms to explain the epidemiological association between periodontitis and ASCVD (2).

Mechanisms linking periodontitis to ASCVD and the effect of periodontitis treatment in improving the surrogate markers of ASCVD in an attempt to show causal interactions between the two diseases have been extensively explored (2, 14). However, the causal mechanistic pathways between these two common non-communicable diseases are yet to be fully understood. In this review, we aim to critically address the role of neutrophils in linking periodontitis to ASCVD. Systemic inflammation triggered by different causes, including periodontitis, may drive inflammatory adaptation of HSPCs and trained granulopoiesis in the bone marrow, resulting in increased production of neutrophils with a hyper-responsive phenotype (12, 30). This systemic inflammation-driven modification of granulopoiesis can contribute to atherosclerosis in a stage-dependent manner. However, although the periodontitis treatment successfully achieves the resolution of the periodontal tissue site and improves surrogate markers of ASCVD, studies reveal that the hyper-responsive function in neutrophils may persist (23, 31). Therefore, novel approaches to target neutrophils by manipulating their numbers and functions are warranted in periodontitis treatment and to mitigate its impact on ASCVD.

THE LINK BETWEEN PERIODONTITIS AND ASCVD

The impact of the treatment of periodontitis on cardiovascular outcomes and surrogate markers of ASCVD has been extensively explored. Patients with periodontitis exhibit an increased risk of coronary and cerebrovascular events compared with periodontally healthy individuals. These findings may not apply to the whole population as influenced by the demographic characteristics, individuals, studies, and case definition of periodontitis (2, 32). In the ARIC study on 6736 dentate participants with 299 incidents of ischemic stroke, it was revealed that seven periodontal profile classes, that were used to assess the participants were associated with an increased risk of cardioembolic and thrombotic stroke subtypes compared with periodontally healthy participants. The assessment in this study was based on seven tooth-clinical parameters, resulting in seven different periodontal profile classes, and the greater class indicates a more severe form of periodontitis (33). Lastly, based on the 1999–2010 Taiwanese National Health Insurance Research Database involving 393,745 patients with periodontitis and 393,745 non-periodontitis individuals, there was a significantly increased incidence of arterial fibrillation in patients with periodontitis compared with controls (34). The findings from all studies had been adjusted for a wide range of potential confounders, indicating that periodontitis is an independent risk factor for an increased risk of ASCVD events.

Treatment of periodontitis may influence the progression of ASCVD. The study involving 511,630 periodontitis patients and 208,713 individuals without periodontitis from The Longitudinal Database of Taiwan’s National Health Insurance demonstrated that patients receiving dental prophylaxis had a lower hazard ratio of acute myocardial infarction compared to periodontally healthy controls, suggesting an almost 10% reduction in the risk of a new ASCVD event (35). These improvements were not observed across all types of periodontitis and controls, suggesting
a difference in host susceptibility and response even after the treatment of periodontitis when looking at future incidence of ASCVD events (36).

Consistent evidence suggests that periodontitis is associated with higher blood pressure and endothelial dysfunction (2, 37–39). A recent review and subsequent meta-analysis of intervention studies confirmed that the management of periodontitis can be a novel non-drug approach for the treatment of hypertension. The evidence is still inconclusive as to whether the treatment of periodontitis influences blood pressure even in the absence of hypertension (40). The basis of this improvement in vascular function could be linked to the effect of the treatment of periodontitis in improving endothelial function as assessed by flow-mediated dilation (FMD) (41–44). A possible mechanism by which local periodontal treatment improves endothelial function in periodontitis patients is endothelial nitric oxide synthase/nitric oxide (eNOS/NO) activation. NO is mainly produced by eNOS in endothelial cells and induces the relaxation of smooth muscle cells (45, 46). Meanwhile, IL-6, TNFα, IL-1β, and CRP directly reduced eNOS at both mRNA and protein levels in human endothelial cells (47–49). As a result, NO bioavailability in the serum is reduced, leading to endothelial dysfunction and periodontitis is associated with this surrogate marker of ASCVD (50, 51). Hepatocytes are the major producers of CRP triggered by IL-6 and IL-1β stimulation, while TNFα also upregulates CRP production in human coronary artery smooth muscle cells (52–55). A recent meta-analysis reveals a progressive CRP level reduction up to 6 months in patients with periodontitis following effective treatment (37). This was also associated with a reduction of reduced serum IL-6, TNFα, and IL-1β in patients with periodontitis compared to baseline (56–59). Collectively, these findings suggest that reduced levels of CRP, IL-6, TNFα, and IL-1β after treatment of periodontitis could restore eNOS activity and NO bioavailability, resulting in improved endothelial dysfunction.

**PERIODONTITIS AS A TRIGGER OF SYSTEMIC INFLAMMATION**

Periodontitis and ASCVD share similar hallmarks of inflammatory mechanisms (60), genetic (2, 61), and common risk factors (62). However, a significant body of evidence supports an independent association between periodontitis and ASCVD following adjustment for confounders and shared risk factors (63, 64). This independent association can be explained by the capability of periodontitis to trigger a low-grade but consistent systemic inflammation, which may contribute to the development of ASCVD (65). Patients with periodontitis exhibit an elevated level of systemic pro-inflammatory mediators, which include CRP, TNFα, IL-1β, IL-6, as well as increased neutrophil numbers in the blood (2, 14, 66–69). A retrospective study involving 60,174 participants revealed that even after the adjustment of confounders, participants with periodontitis were 1.59 times more likely to have ASCVD (63). Previously, an 8-year prospective cohort study involving 11,869 participants also showed that those reporting poor oral hygiene had an enhanced risk of CVD events as well as an elevated level of CRP and fibrinogen in the serum (70).

Systemic inflammation triggered by periodontitis potentially occurs because of bacterial dissemination or periodontal tissue-derived inflammatory mediator leakage into the blood circulation. The ulceration of the epithelium owing to local periodontal inflammation along with the support of its rich vascularization may provide greater access for bacteria and their endotoxins such as lipopolysaccharides (LPS) to the circulation, leading to bacteremia (13). This event has been reported in patients with periodontitis during mastication, toothbrushing, and dental scaling (10, 11). Bacteremia would induce inflammatory alterations in the endothelium, which include enhanced expression of adhesion molecules and the production of pro-inflammatory cytokines. With regard to the spillover of inflammatory mediators into the bloodstream, this can affect vascular tissues as well as other distant organs, including the liver, which then may initiate an acute-phase response (14).

**INFLAMMATION AND NEUTROPHILS: IMPLICATIONS FOR ATHEROSCLEROSIS**

Atherosclerosis is a cause of myocardial infarction, ischemic cardiomyopathy, and ischemic stroke that contribute to most deaths in the population worldwide (4). Arterial wall damage due to blood lipid profile imbalance, oscillating shear stress, and pro-inflammatory mediators initiates this underlying ASCVD pathology. The subsequent processes are endothelial cell activation in arterial tissue, myeloid cell adhesion to the endothelium, and infiltration into the arterial intima (26). At the late stage of atherosclerosis, inflammatory cell accumulation, lipoprotein deposition, and cellular debris buildup are responsible for the arterial plaque formation followed by the plaque instability leading to atherosclerotic plaque rupture. Atherosclerosis is a decades-long process with many stages of evolution, and evidence suggests that neutrophils are involved in different stages of atherosclerosis (Figure 1) (26).

The onset of atherosclerosis is characterized by endothelial dysfunction, which induces neutrophil recruitment to the endothelium. Specifically, the dysfunction up-regulates the expression of various endothelial cell adhesion molecules, including E-selectin, P-selectin, and intracellular adhesion molecule-1 (ICAM-1) (71). Platelets then deliver CCL5, the primary ligand of CCR5 on the endothelium and promote cathepsin G secretion by neutrophils, resulting in the firm adhesion to and accumulation of the cells in the endothelium (72, 73). Furthermore, neutrophils aggravate endothelial dysfunction by secreting reactive oxygen species (ROS), azurocidin, proteinase 3, Cathelicidin, and cathepsin G in the arterial lumen (26, 74). ROS and proteases activate and dysregulate the endothelial cell layer and degrade the underlying extracellular matrix, enabling leukocyte infiltration and low-density lipoprotein (LDL) extravasation (26). Azurocidin also contributes to increasing endothelial
permeability (26, 74–76), whereas azurocidin, proteinase 3, cathelicidin, α-defensin, and cathepsin G all promote myeloid cell recruitment and facilitate monocyte entry into the atherosclerotic lesions (74, 77–82).

The progression of the lesion continues following the aggravation of endothelial dysfunction by neutrophils, where macrophage activation and foam cell formation occur in the arterial intima. Neutrophil-derived granule proteins, cathelicidin, and α-defensin activate macrophages toward a pro-inflammatory state (M1 macrophage phenotype). Neutrophils also secrete myeloperoxidase (MPO) to generate oxygen radicals that oxidize apolipoprotein B, a protein structure in LDL (82). Subsequently, macrophages take up this oxidized LDL (oxLDL), resulting in foam cell formation (83).

Moreover, NETs stimulate macrophages by turning on transcription factors encoding IL-6 and IL-1β. These cytokines promote the differentiation of Th17 cells, which in turn amplify neutrophil recruitment in the lesion (84). At this stage, because of sustained myeloid cell recruitment and foam cell generation, the atheroma becomes pronounced.

In the late stage of atherosclerosis, neutrophils destabilize the atherosclerotic plaque. Mechanistically, activated vascular smooth muscle cells (VSMCs) in advanced atherosclerotic lesions induce neutrophil chemotaxis and secrete CCL7, which stimulates NET release. One of the NET cytotoxic components, histone H4, disrupts the integrity of the VSMC plasma membrane, leading to cell lysis (85). Moreover, endotoxemia in a mouse model of atherosclerosis revealed that leukotriene B4-induced neutrophil recruitment to atherosclerotic plaques induces collagen degradation and VSMC lysis, leading to the feature of plaque instability (86). In eroded human plaques, neutrophils colocalized with toll-like receptor 2 of endothelial cells, and an in vitro experiments showed that co-culture of neutrophils with endothelial cells potentiates endothelial stress and apoptosis, resulting in endothelial cell detachment followed by luminal endothelial cell desquamation (plaque erosion) (19).

Lastly, NETs are also involved during endothelial erosion as the disruption of NETs by either peptidyl arginine deiminase 4 (PAD4) gene knockout or DNase I treatment in atherosclerotic mice attenuates endothelial disintegration and endothelial cell apoptosis (87).

Neutrophils play dual roles, which are both adverse and favorable for cardiac tissue repair following myocardial infarction (Figure 2A). Tissue necrosis/ischemia post-acute myocardial infarction releases alarmins and inflammatory signals that attract neutrophils to the site of infarction (88). Activated neutrophils secrete ROS, proteases, NETs, and IL-1β. Granulopoiesis stimulated by IL-1β leads to neutrophil accumulation in the injured site, which is harmful to the remodeling of the ischemic area, resulting in eventual heart failure (89, 90). Following neutrophil accumulation, monocytes and monocyte-derived macrophages infiltrate the infarcted site to phagocytose cell debris and apoptotic neutrophils, activating cardiac repair (88). Intriguingly, neutrophils also contribute to this cardiac healing as their damage-associated molecular patterns (DAMPs), such as neutrophil gelatinase-associated lipocalin (NGAL) and S100A8/A9, stimulate macrophages to shift toward reparative phenotypes (91, 92). These anti-inflammatory macrophages aid in the resolution of inflammation (88). Neutrophils also secrete annexin A1, which stimulates pro-angiogenic macrophage polarization. These macrophage phenotypes release vascular endothelial growth factor A (VEGFA) to support angiogenesis in the ischemic site of...
the myocardium (93). Besides cardiac tissue repair, neutrophils aggravate other atherosclerosis complications, namely, ischemic stroke (Figure 2B). Following an episode of ischemic stroke, dying neurons attract neutrophils to the area to release ROS and elastase to enhance endothelial cell dysfunction and permeability. NETs contribute to thrombus growth, thereby increasing stroke volume. Neutrophils also promote neuronal cell death in a process that is likely to involve NETs (26, 94).

**IMPACT OF PERIODONTITIS-INDUCED SYSTEMIC INFLAMMATION ON BONE MARROW ACTIVITY AND SUBSEQUENT CIRCULATING NEUTROPHIL ALTERATIONS: PLAUSIBLE MECHANISMS**

Modulation of HSPCs in the Bone Marrow: A Key Role for Periodontitis-Induced Systemic Inflammation

Trained immunity can be initiated in the bone marrow via sustained epigenetic, metabolic, and transcriptional adaptations in HSPCs, leading to enhanced myeloid-biased differentiation and production of increased numbers of trained myeloid cells, including neutrophils (trained myelopoiesis/granulopoiesis) (95, 96). This training is based on the ability of HSPCs to sense numerous inflammatory cues in response to hematopoietic stress such as systemic inflammation (12, 96). HSPCs can directly sense pathogen-associated molecular patterns (PAMPs), such as LPS, via their pattern recognition receptors (PRRs), such as toll-like receptors (for example, TLR-4 for sensing LPS). Regarding the direct mechanism, in the context of periodontitis-induced bacteremia, it could be envisioned that systemically disseminated periodontal pathogens or their products (for example, LPS or lipopeptides) may also reach the bone marrow, resulting in innate immune training of HSPCs. However, indirect activation relies on specialized cells residing in either the peripheral tissue or bone marrow to affect the hematopoietic system through the release of cytokines (97, 98).

In addition to direct sensing of pathogens, cytokines and growth factors derived from both the bone marrow niche and peripheral tissue can mediate indirect adaptation of HSPCs (97, 98). IL-1β promotes myeloid differentiation and self-renewal of HSPCs as chronic administration of this cytokine elevates the number of myeloid-bias HSPCs. This is also consistent with the recent finding that enhanced myelopoiesis of HSPCs in a mouse model of β-glucan or experimental periodontitis-induced trained
monocyte progenitors (GMPs) (105). Moreover, in emergency granulopoiesis, G-CSF promotes the mobilization from the bone marrow to the circulation (104). Protein release by monocytes in the bone marrow niche is responsible for HSPC adaptation of HSPCs toward trained granulopoiesis (99). This notion was recently confirmed in a preclinical model. Specifically, it was shown that ligature-induced periodontitis (LIP)-associated systemic inflammation leads to maladaptive innate immune training in the bone marrow (i.e., generating inflammatory memory) and the generation of increased numbers of hyper-reactive neutrophils; these populate oral and non-oral tissues and promote the emergence of inflammatory comorbidities, as exemplified by the periodontitis-arthritis axis (99). This is consistent with available clinical observations as outlined below. Intriguingly, the transplantation of bone marrow from LIP-subjected mice to healthy recipient mice resulted in increased severity of arthritis in the latter, as compared with the transplantation of bone marrow from periodontally healthy mice (99). The implication of this finding (if a similar phenomenon is confirmed in humans) is that clinicians should take inflammatory memory in the bone marrow into consideration when selecting appropriate donors for hematopoietic transplantation (99).

Indeed, the notion that periodontitis might trigger an adaptation of HSPCs is supported by clinical imaging studies using 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG-PET/CT). One study revealed that periodontal inflammation was associated with hematopoietic activity in the bone marrow and arterial inflammation. Furthermore, the authors used mediation path analysis to show that the relationship between periodontal and arterial inflammation was significantly mediated by bone marrow activity (109). More recently, another study using the same cohort of 304 participants as the aforementioned study showed that periodontal inflammation (as determined by 18F-FDG-PET/CT) is independently correlated with not only increased arterial inflammation but also increased risk of future cardiovascular events (64). Additionally, another study harnessing the same imaging technique also reported a trend for increased periodontal inflammation and femur bone marrow activity in patients with periodontitis (relative to controls), albeit no differences were observed in vascular inflammation between the two groups (110). The lack of clear differences in this study is likely attributed (a) to the small sample size (14 participants as opposed to >300 participants in the above-discussed studies) and (b) to the fact that participants with severe periodontal disease were under supportive periodontal therapy, which could have mitigated inflammation and associated parameters, including surrogate markers of ASCVD (discussed below) (110). Moreover, the control group also included individuals with mild periodontitis, which could also impact systemic inflammation and hematopoietic tissue activity, thus reducing potential differences compared with the experimental group.

**Alteration of Circulating Neutrophils in Periodontitis and its Putative Effect on Atherosclerosis**

Patients with periodontitis exhibit elevated numbers of neutrophils and altered phenotypes presenting hyper-reactive features in cellular functions (discussed below) (21–23, 68, 69, 89). We recently demonstrated that serum levels of the neutrophil specific cytokines TNFα and IL-1β are elevated in periodontitis patients (66, 67). Plasma IFNγ, a type 1 IFN, is also higher in periodontitis patients compared to healthy controls (106). However, the role of type 1 IFN-mediated trained granulopoiesis in inducing hyper-responsive neutrophils in periodontitis patients needs to be addressed experimentally. Recent evidence indicates an increased level of serum G-CSF in ligature-induced periodontitis mice (107). Fibroblasts in the periodontal tissue contribute to the release of G-CSF during periodontal inflammation, resulting in the promotion of granulopoiesis (108). Based on the cumulative evidence of the effect of cytokines and growth factors on HSPCs and the abovementioned clinical studies, it could be shown that periodontitis-associated systemic inflammation may modulate HSPCs toward trained granulopoiesis (Table 1). This notion was recently confirmed in a preclinical model. Specifically, it was shown that ligature-induced periodontitis (LIP)-associated systemic inflammation leads to maladaptive innate immune training in the bone marrow (i.e., generating inflammatory memory) and the generation of increased numbers of hyper-reactive neutrophils; these populate oral and non-oral tissues and promote the generation of hematopoietic transplantation (99).
periodontitis (119). These include increased levels of ROS production in response to fMLP, PMA, or periodontal pathogens (21–23, 102, 111–115), elevated TNFα production following stimulation with the periodontal pathogen, Fusobacterium nucleatum, in vitro (116), and elevated neutrophil elastase levels linked to periodontal tissue destruction (117, 118). The systemic effect of this alteration has been recently confirmed in an experimental study with mice and experimental periodontitis that exhibited hyper-inflammatory neutrophil response following the exposure to secondary peritonitis compared with mice without periodontitis (119).

These altered features in neutrophils present a hallmark of trained myelopoiesis, which includes increased numbers of myeloid cells with enhanced inflammatory responsiveness (24, 95). As such, these changes may implicate the response of future inflammatory stimuli that drive certain pathological processes such as atherosclerosis.

Neutrophils that are increased in number and hyper-responsiveness due to periodontitis can contribute to any stage of this ASCVD pathology. Further research should address this hypothesis experimentally. However, it is still interesting to speculate that periodontitis-induced neutrophil alteration contributes to the association between periodontitis and ASCVD because of several clinical studies that support this notion. An elevated number of neutrophils in peripheral blood may increase the risk of ASCVD in periodontitis patients because neutrophil counts from peripheral blood are positively correlated with ASCVD risk (120, 121). Moreover, periodontitis patients consistently present with endothelial dysfunction, which is a key feature of ASCVD (2). This disturbed vascular function and elevated neutrophil ROS production triggered by periodontitis can aggravate the initiation of atherosclerosis. The latter may also potentiate the progression of atherosclerosis, particularly in oxidizing LDL. Hyper-responsiveness of neutrophils characterized by excessive production of neutrophil elastase and ROS in periodontitis patients could also contribute to the late stage of atherosclerosis as both hyper-reactive features induce endothelial apoptosis, resulting in endothelial desquamation (plaque erosion), fibrous cap thinning and plaque ruptures. Finally, whereas the production of NETs by circulating neutrophils has been shown to be comparable between patients with periodontitis and healthy controls, plasma NET degradation was lower in patients with periodontitis than in controls, suggesting an impaired NET degradation process in the plasma of periodontitis patients (122). This impairment might favor atherosclerosis complications, especially in post-ischemic stroke where NET accumulation promotes thrombus formation and expands stroke volume. In this context, a case-control study revealed that periodontitis was an independent predictor of poor outcome in post-ischemic stroke patients (123).

**IMPACT OF PERIODONTITIS TREATMENT ON NEUTROPHILS**

Whereas the treatment of periodontitis improves the surrogate markers of ASCVD, its long-term cardiovascular-protective effect is uncertain. A reduction of several serum inflammatory markers that is expected to reduce the risk of ASCVD is not observed in serum IFNγ and IL-10 because both markers remain unchanged following periodontitis treatment (40). As these markers are predominantly generated and released into blood circulation by inflammatory cells, it is interesting to speculate that while successful treatment indeed achieves the resolution of periodontal inflammation, circulating inflammatory cells still retain their periodontitis-induced altered phenotypes. The latter is supported by clinical studies that investigated the functions of peripheral blood-derived neutrophils and monocytes in periodontitis patients after the treatment. The hyper-responsiveness of these myeloid cells persisted as the levels of cytokines produced by the cells in response to pathogen or LPS stimulation were comparable between neutrophils from patients before and after periodontal treatment (31, 116). Similarly, a longitudinal study on the circulating neutrophil profiles of patients with periodontitis showed that neutrophils (as a proportion of total cells isolated from peripheral blood of periodontitis patients) did not change between baseline (before treatment) and after 3-, 6-, and 12-month post-periodontitis treatment (124). The retained neutrophil phenotypes might be because of the trained myelopoiesis induced by periodontitis-triggered systemic inflammation. In murine experiments, long-lasting changes in myelopoiesis were observed following either microbial- or sterile-induced inflammation (29, 95). Similarly, a recent report shows that upon the LIP resolution, HSPCs in the bone marrow retain a myeloid differentiation bias (99).

**TARGETING NEUTROPHILS AS A NOVEL THERAPEUTIC APPROACH: DUAL BENEFIT ON PERIODONTITIS AND ASCVD**

The targeted therapeutic approach for ASCVD has been established by focusing on the reduction of inflammation (Table 2). The first clinical trial, CANTOS, in an attempt to close the gap between pre-clinical studies and clinical practice, provided evidence that reducing inflammation could be relevant to treating atherosclerosis in humans. In this trial, the anti-IL-1β antibody, Canakinumab, was administered subcutaneously to individuals with a sustained acute myocardial infarction. The trial revealed a significant reduction in the rates of recurrent cardiovascular events, hospitalization for heart failure, and heart failure-associated death (125, 126). However, the adverse event in the group receiving Canakinumab was more significant death due to infection or sepsis compared to the placebo group (125). Moreover, oral administration of colchicine in patients with a recent myocardial infarction significantly reduces the risk of ischemic cardiovascular events (127). The benefits of colchicine were also observed in patients with chronic coronary disease (128). Unfortunately, patients in the colchicine group showed higher incidents of pneumonia and non-cardiovascular-caused death than those in the placebo group (127, 128). Other clinical studies on targeting inflammation in ASVD treatment have been...
TABLE 2 | Summary of clinical trials.

| No. | Name of drug | Mechanism of action | Phase | Identifier (Trial registration) | Outcome |
|-----|--------------|---------------------|-------|--------------------------------|---------|
| 1.  | Canakinumab  | Binds to IL-1β resulting in blocking the interaction between IL-1β and IL-1 receptor | Phase 3 | NCT01327846 | Reduction in cardiovascular events, hospitalization for heart failure, and heart failure-associated death |
| 2.  | Colchicine   | Prevents microtubule formation resulting in tubulin disruption | Phase 3 | NCT02551094 | Emergence of death due to sepsis |
| 3.  | Metoprolol   | Attenuates neutrophil migration and infiltration by impairing the neutrophil-platelet interaction that is crucial during early phases of neutrophil recruitment | Phase 4 | NCT01311700 | Reduction of infarct size |
| 4.  | AZD5069 (a CXCR2 antagonist) | Prevents neutrophil recruitment to the site of inflammation | Phase 1 | ISRCTN48328178 | No adverse events and safety concerns |
| 5.  | AMY-101 (a complement C3 inhibitor) | Inhibits downstream activation of the anaphylatoxin C3a and C5a receptors | Phase 2a | NCT03894444 | Reduction in gingival inflammation |

reviewed elsewhere (129). These clinical trials indicate that therapies with alternative strategies are required to achieve outcomes in which the benefits outweigh the risks.

Besides the necessity of different strategies to reduce the risk–benefit ratio, a refined understanding of the potential role of periodontitis-induced neutrophil alteration in the pathology of ASCVD and its retained phenotypes following successful periodontitis treatment highlights the importance of selectively targeting neutrophils during the treatment of periodontitis. This therapeutic approach is warranted to mitigate the potential impact of periodontitis on ASCVD. The main endpoint of this intervention is to either manipulate the number of neutrophils and/or their functional activities. We only discuss the approaches to block neutrophil recruitment and prevent NET-driven inflammation, while other neutrophil-targeted therapeutics have been extensively reviewed elsewhere (130).

While the results of neutrophil recruitment blockage are promising in preclinical studies, clinical trials exhibit unsuccessful outcomes due to the redundancy of signals during neutrophil recruitment and off-target effects caused by receptor cross-linking. Recent studies have provided strategies for overcoming such difficulties. The combined inhibition of several endothelial cell molecules interrupts redundant signals that recruit neutrophils (131). Intravenous injection of nanoparticles carrying small interfering RNAs (siRNAs) that target endothelial adhesion molecules including ICAM-1, E-, P-selectin, and vascular celular adhesion molecule-1 (VCAM-1) decreased leukocyte recruitment to ischemic myocardium in a mouse model of post-myocardial infarction (131). Moreover, specific blockage of neutrophils that traffic to certain vascular tissue requires a refined understanding of recruitment patterns at particular sites (16). A neutrophil granule protein, cathepsin G promotes myeloid cell adhesion to only arterial but not microvascular tissue (73). Indeed, antibody-assisted cathepsin G neutralization in an atherosclerotic mouse model specifically alleviated neutrophil recruitment to the carotid artery, resulting in reduced atherosclerotic plaque size. However, a similar treatment did not affect neutrophil adhesion in lung microcirculation following an LPS-induced lung inflammation model in mice (73). Furthermore, the elucidation of heteromeric interactions between neutrophil-derived human neutrophil peptide-1 (HNPI) and platelet-borne CCL5 that must stimulate monocyte adhesion via CCR5 ligation allows the design of a peptide that can disturb these neutrophil–platelet interactions. This specifically designed short peptide alleviated inflammation in a mouse model of myocardial infarction (20). Finally, inducing endogenous inhibitors in leukocytes can overcome integrin activation by chemokine, thereby suppressing myeloid cell adhesion. For example, growth differentiation factor-15 (GDF-15) and annexin A1 inhibit chemokine-induced β2 integrin activation and subsequently reduce neutrophil recruitment in a mouse model of chronic inflammation (72, 132). Moreover, recombinant developmental endothelial locus-1 (DEL-1), the first identified endogenous inhibitor of the leukocyte adhesion cascade (133), inhibited neutrophil recruitment in mouse and non-human primate models (17, 134).

Important roles of NETs in both atherosclerosis progression (atherogenesis, plaque destabilization and erosion) and complication (atherothrombosis) stand out as a potential therapeutic target to manipulate cardiovascular inflammation. Peptidyl arginine deiminase 4 (PAD4) citrullinates histone to disrupt electrostatic bonds in nucleosomes, decondensing chromatin that leads to NET release (135). Cl-amidine, a PAD inhibitor administered intravenously in an atherosclerotic mouse model, prevented NET formation, leading to reduced atherosclerotic lesion area and thrombosis (136). However, the mechanism of NETosis in mice is different from that in humans as ex vivo experiments of human neutrophils showed that PMA-induced NETosis of the cells was not affected following the PAD4 inhibitor, Cl-amidine (137). Meanwhile, DNase 1 treatment might be considered to mitigate ASCVD complications like
thrombosis due to NET deposition in the vascular lumen. This notion is supported by a study where the treatment protected mice from deep vein thrombosis following an inferior vena cava stenosis model (138). A reduction in lesion size was also observed in an atherosclerosis mouse model after DNase injections (84). In humans, DNase 1 treatment to eliminate NET deposition might need a combination with other substances, as DNase 1 alone was not adequate to degrade NETs in vitro (139). Lastly, NET chromatin can stimulate macrophages by activating AIM2 inflammation, causing the release of IL-8 and IL-1β in atherosclerotic lesions. The use of an AIM2 inhibitor could also attenuate ASCVD complications because reduced plaque vulnerability through the thickening of the fibrous cap was observed in an atherosclerotic mouse model after the treatment of an AIM2 inhibitor (140). ApoE-deficient mice on a 6-week high fat diet and injected with anti-chromatin antibodies also showed a reduced plaque area per lumen, suggesting the potential of chromatin blockage to hinder atherosclerosis (141). The use of substances to block NETs in humans should be implemented with caution because studies about the pro-inflammatory features of NETs in humans are still conflicting, as in vitro NET clearance by human macrophages did not induce pro-inflammatory cytokines (139), but NET transfection to mouse macrophages did (142).

Targeting neutrophils as an approach to mitigate the potential impact of periodontitis on ASCVD is appealing considering the numerous efforts outlined previously. This targeted strategy can not only have direct effects on ASCVD but also reduce periodontitis, which triggers inflammation that primes neutrophils for ASCVD pathology. However, safety and specificity issues are challenges that need to be solved as neutrophils interact with other myeloid lineages (130). The solution to the former concern is that the intervention should consider the therapeutic window, where the attenuation of the inflammatory process mediated by neutrophils does not interfere with neutrophil capacity during host defense (130). Recent studies revealed that the use of antibodies to inhibit NET-derived histones reduced the amplification of NET-induced inflammation rather than completely blocking NETosis or inflammation (141). Few studies have presented strategies to obtain the specificity to therapeutically target neutrophils. For example, the conjugation of siRNA targeting Bruton’s tyrosine kinase (BTK) to the F(ab’)2 fragment of an anti-neutrophil monoclonal antibody specifically targeted alveolar neutrophils in an acute lung injury mouse model. This treatment was administered locally using a technique called intranasal instillation (143). Meanwhile, others harness nanoparticle technology to enhance specificity. One of them reported that neutrophils adhered to activated endothelium-engulfed albumin nanoparticles carrying piceatannol, leading to the inactivation of these adherent neutrophils and consequently preventing vascular inflammation (144). Additionally, another report exhibited lipid-based nanoparticles that were successfully incorporated with identified peptides that interact with the neutrophil-specific surface marker, CD177 (145).

A clinical trial targeting neutrophils to lower ASCVD risk is still lacking. However, two randomized clinical trials reported that metoprolol provides a cardio-protective effect following acute myocardial infarction, which is one of the atherosclerosis complications (Table 2). Specifically, intravenous administration of metoprolol reduced infarct size and improved cardiac function in patients with acute myocardial infarction (146, 147). Studies using a myocardial infarct mouse model revealed the mechanism of this protection in which metoprolol attenuates neutrophil migration and infiltration by impairing the neutrophil–platelet interaction that is crucial during early phases of neutrophil recruitment (148, 149). Another drug candidate, AZD5069, a CXCR2 antagonist, could be a potent drug candidate in treating patients with advanced atherosclerotic lesions. CXCR2 is a chemokine receptor 2 in neutrophils that regulates neutrophil migration, and the inhibition of this receptor successfully prevents neutrophil recruitment to the site of inflammation (150). No adverse effects on neutrophil function were observed, and no safety concerns were raised in participants receiving oral administration of AZD5069 (151). The CICADA trial was proposed to investigate the effect of a CXCR2 antagonist (administered orally) on coronary flow, structure, and function in patients with coronary heart disease (152).

Mechanical intervention in periodontitis management with adjunctive neutrophil-targeted therapeutic approach could also provide benefit in reducing periodontal-induced systemic inflammation that can implicate all stages of atherosclerosis. A phase IIA clinical trial of the complement C3 inhibitor, AMY-101, summarized in Table 2, shows promising results in reducing local inflammation in periodontal tissue (153). The pharmacological blockade of the central complement component, C3, inhibits downstream activation of the anaphylatoxin C3a and C5a receptors (C3aR and C5aR, respectively), which induce inflammatory bone loss in a preclinical model (154). C5aR and TLR2 coactivation in neutrophils contribute to oral microbiota dysbiosis leading to overt periodontal inflammation and subsequent periodontal tissue destruction (155). Local injection of AMY-101 to the gingiva reduced gingival inflammation without adverse events, warranting phase III clinical trials for further investigation (153, 156). Importantly, AMY-101 significantly reduced the gingival crevicular levels of MMP-8 and MMP-9 (152), which are the major neutrophil-derived proteases and are considered biomarkers of periodontal tissue destruction (157). Meanwhile, other local neutrophil-targeted treatments, including resolvin E1, developmental endothelial locus-1, and milk fat globule epidermal growth factor 8, are still in pre-clinical studies. These proteins reduce neutrophil recruitment to the site of inflammation and prevent animal models of ligature-induced periodontitis (134, 158, 159). Additionally, resolving E1 also promotes neutrophil apoptosis and its clearance (efferocytosis), resulting in the resolution of periodontal inflammation (157). Focusing on the termination of periodontitis may prevent its systemic impact, which is heightened systemic inflammation. These strategies of local intervention potentially further improve...
the current periodontal treatment in providing a sustained protection to cardiovascular health.

CONCLUSION

Periodontitis triggers systemic inflammation which could modulate hematopoietic tissue activity in the bone marrow, resulting in trained myelopoiesis. Clinical studies demonstrating increased numbers as well as enhanced inflammatory responsiveness in neutrophils back this notion. The evidence of persistent elevated neutrophil numbers and their altered phenotypes, despite the resolution of periodontitis following local treatment, also supports the speculation that periodontitis-induced systemic inflammation can induce long-term myelopoiesis bias, a hallmark of innate immune training in the bone marrow. The quantitative and qualitative alterations in neutrophils may contribute to all stages of the ASCVD pathology, atherosclerosis (Figure 3). Although clinical intervention studies suggest that periodontal therapy improves surrogate markers of ASCVD, the long-term effects of this oral treatment to maintain such improvement and convincing evidence that successful periodontitis treatment can reduce the risk or incidence of ASCVD are yet to be investigated. Meanwhile, targeting neutrophils is warranted to improve local periodontal therapy, eliminate periodontitis effectively, that can reduce periodontitis-triggered systemic inflammation and reverse the periodontitis-induced neutrophil changes. Such targeted approaches can be harnessed as a direct treatment for ASCVD and indirect intervention of the disease through the reduction of heightened systemic inflammation triggered by periodontitis.

AUTHOR CONTRIBUTIONS

RI wrote the original draft. RI, SC, GH, VP, JD, and FD provided critical revisions to the article. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This work was undertaken at the UCL Biomedical Research Centre which receives funding from the UK National Institute for Health and Care Research. GH receives a grant from the US National Institutes of Health (DE031206). RI receives funding from the Indonesia Endowment Fund for Education (S-1692/LPDP.4/2019—LPDP—Indonesia Scholarship). The figures were created using Biorender.com

REFERENCES

1. Ellulu MS, Patimah I, Khaza’ai H, Rahmat A, Abed Y, Ali F. Atherosclerotic Cardiovascular Disease: A Review of Initiators and Protective Factors. Inflammopharmacology (2016) 24(1):1–10. doi: 10.1007/s10778-015-0255-y
2. Sanz M, Marco del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D’Aiuto F, Bouchard P, et al. Periodontitis and Cardiovascular Diseases: Consensus Report. J Clin Periodontol (2020) 47(3):268–88. doi: 10.5334/jcp.600
3. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. J Am Coll Cardiol (2020) 76(25):2982–3021. doi: 10.1016/j.jacc.2020.11.010
4. Libby P. The Biology of Atherosclerosis Comes Full Circle: Lessons for Conquering Cardiovascular Disease. Nat Rev Cardiol (2021) 18(10):683–4. doi: 10.1038/s41569-021-00609-1
5. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal Diseases. Nat Rev Dis Primers (2017) 3(1):17038. doi: 10.1038/nrdp.2017.38
6. Graziani F, Music L, Bozic D, Tsakos G. Is Periodontitis and Its Treatment Capable of Changing the Quality of Life of a Patient? Br Dent J (2019) 227(7):621–5. doi: 10.1038/s41415-019-0735-3
7. Kassebaum N, Bernabe E, Dahiya M, Bhandari B, Murray C, Marceunes W. Global Burden of Severe Periodontitis in 1990-2010: A Systematic Review and Meta-Regression. *J Dent Res* (2014) 93(11):1045–53. doi: 10.1177/ 0022034514524901

8. Dye BA. Global Periodontal Disease Epidemiology. *Periodontol 2000* (2012) 58(1):10–25. doi: 10.1111/j.1600-0757.2011.00413.X

9. Baehni P, Tonetti M. Group 1 of the European Workshop on Periodontology. Conclusions and Consensus Statements on Periodontal Health, Policy and Education in Europe: A Call for Action--Consensus View 1: Consensus Report of the 1st European Workshop on Periodontal Education. *Eur J Dent Educ* (2010) 14:2–3. doi: 10.1111/j.1600-0759.2010.00619.X

10. Geerts SO, Nys M, De Mol P, Charpentier J, Albert A, Legrand V, et al. Systemic Release of Endotoxins Induced by Gentle Mastication: Association With Periodontitis Severity. *J Periodontol* (2002) 73(1):73–8. doi: 10.1902/jop.2002.73.1.73

11. Forner I, Larsen T, Kilian M, Holmstrup P. Incidence of Bacteremia After Chewing, Tooth Brushing and Scaling in Individuals With Periodontal Inflammation. *J Clin Periodontol* (2006) 33(6):401–7. doi: 10.1111/j.1600-051X.2006.00924.x

12. Hajishengallis G, Chavakis T. Local and Systemic Mechanisms Linking Periodontal Disease and Inflammatory Comorbidities. *Nat Rev Immunol* (2021) 21(7):426–40. doi: 10.1038/s41577-020-00488-6

13. Konkel JF, O’Boyle C, Krishnan S. Distal Consequences of Oral Inflammation. *Front Immunol* (2019) 10:1403. doi: 10.3389/ fimmu.2019.01403

14. Schenken HA, Papapanou PN, Genco R, Sanz M. Mechanisms Underlying the Association Between Periodontitis and Atherosclerotic Disease. *Periodontol 2000* (2020) 83(1):90–106. doi: 10.1111/prd.12304

15. Rosales C. Neutrophil: A Cell With Many Roles in Inflammation or Several Cell Types. *Front Physiol* (2018) 9:113. doi: 10.3389/fphys.2018.00113

16. Soehnlein O, Steffens S, Hidalgo A, Weber C. Neutrophils as Protagonists and Targets in Chronic Inflammation. *Nat Rev Immunol* (2017) 17(4):248–61. doi: 10.1038/nri.2017.10

17. Eskan MA, Jotwani R, Abe T, Ghmelar J, Lim J-H, Liang S, et al. The Leukocyte Integrin Antagonist Del-1 Inhibits IL-17-Mediated Inflammatory Bone Loss. *Nat Immunol* (2012) 13(5):465–73. doi: 10.1038/ni.2260

18. Dutzan N, Kajikawa T, Abusleme L, Greenwell-Wild T, Zuazo CE, Ikeuchi T, et al. A Dysbiotic Microbiome Triggers T(H)17 Cells to Mediate Oral Inflammation. *Cell* (2017) 170(6):1324–38. doi: 10.1016/j.cell.2017.12.013

19. Orlandi M, Suvan J, Petrie A, Donos N, Masi S, Hingorani A, et al. Periodontitis is Associated With Hypertension: A Nationwide, Population-Based, Cohort Study. *PLoS One* (2016) 11(10):e0165601. doi: 10.1371/journal.pone.0165601

20. Lee Y-L, Hu H-Y, Chou P, Chu D. Dental Prophylaxis Decreases the Risk of Acute Myocardial Infarction: A Nationwide Population-Based Study in Taiwan. *Clin Interv Aging* (2015) 10:175–82. doi: 10.2147/CIA.S67854

21. Holmlund A, Lampa E, Lind L. Poor Response to Periodontal Treatment May Predict Future Cardiovascular Disease. *J Dent Res* (2017) 96(7):768–73. doi: 10.1177/0022034517019090

22. Machado V, Botelho J, Escalda C, Hussain SB, Luthra S, Mancarenhas P, et al. Serum C-Reactive Protein and Periodontitis: A Systematic Review and Meta-Analysis. *Front Immunol* (2021) 12:706432. doi: 10.3389/ fimmu.2021.706432

23. Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, et al. Periodontitis is Associated With Hypertension: A Systematic Review and Meta-Analysis. *Cardiovasc Res* (2020) 116(1):28– 39. doi: 10.1093/cvr/cvz201

24. Muñoz Aguilera E, Suvan J, Orlandi M, Muro Catalina Q, Nart J, D’Aiuto F. Association Between Periodontitis and Blood Pressure Highlighted in Systemically Healthy Individuals: Results From a Nested Case-Control Study. *Hypertension* (2021) 77(5):1765–74. doi: 10.1161/HYPERTENSIONAHA.120.16790

25. Sharma S, Sridhar S, Mcintosh A, Messow C-M, Aguilar EM, Del Pinto R, et al. Periodontal Therapy and Treatment of Hypertension—Alternative to the Pharmacological Approach. *A Systematic Review and Meta-Analysis*. *Pharmacol Res* (2021) 166:105511. doi: 10.1016/j.phrs.2021.105511

26. Orlandi M, Suvan J, Petrie A, Donos N, Masi S, Hingorani A, et al. Association Between Periodontal Disease and Its Treatment, Flow-Mediated Dilatation and Carotid Intima-Media Thickness: A Systematic Review and Meta-Analysis. *Atherosclerosis* (2014) 236(1):39–46. doi: 10.1016/j.atherosclerosis.2014.06.002

27. Chavakis T, Wielock B, Hajishengallis G. Inflammatory Modulation of Hemopoiesis: Linking Trained Immunity and Clonal Hemopoiesis With Chronic Disorders. *Ann Rev Physiol* (2021) 84:183–207. doi: 10.1146/ annurev-physiol-052521-013627

28. Bekkering S, Arts RJW, Novakovic B, Kourtzelis I, van der Heijden C, Li Y, et al. Western Diet Triggers NLRP3-Dependent Inflaming Reprogramming. *Cell* (2018) 172(1–2):162–75. doi: 10.1016/j.cell.2017.12.013

29. Poller WC, Nahrendorf M, Swirski FK. Hemopoiesis and Cardiovascular Disease. *Circ Res* (2020) 126(8):1061–85. doi: 10.1161/ CIRCRESAHA.120.435115

30. Radvan M, Tavakkol-Afshari J, Bajestan MN, Naseh MR, Arab HR. The Effect of Periodontal Treatment on IL-6 Production of Peripheral Blood Monocytes in Aggressive Periodontitis and Chronic Periodontitis Patients. *Iran J Immunol* (2008) 5(2):100–6.

31. Dietrich T, Sharma P, Walter C, Weston P, Beck J. The Epidemiological Evidence Behind the Association Between Periodontitis and Incident Atherosclerotic Cardiovascular Disease. *J Periodontol* (2013) 84(4 Suppl): S70–84. doi: 10.1902/jop.2013.134008

32. Sen S, Giambardino LD, Moss K, Morelli T, Rosamond WD, Gottesman R, et al. Periodontal Disease, Regular Dental Care Use, and Incident Ischemic Stroke. *Stroke* (2018) 49(2):355–62. doi: 10.1161/ STROKEAHA.117.018990

33. Chen D-Y, Lin C-H, Chen Y-M, Chen H-H. Risk of Atrial Fibrillation or Flutter Associated With Periodontitis: A Nationwide, Population-Based, Cohort Study. *PLoS One* (2016) 11(10):e0165601. doi: 10.1371/journal.pone.0165601

34. Tofighi D, Pellowes MA, Lusby CA, Dujovny M, Firth S, Brown JW, et al. Effect of Periodontal Treatment on IL-6 Production of Peripheral Blood Monocytes in Aggressive Periodontitis and Chronic Periodontitis Patients. *Eur J Oral Sci* (2017) 125(3):225–31. doi: 10.1111/eos.12235

35. Christ A, Günther P, Lauterbach MAR, Duewell P, Biswas D, Pelka K, et al. Neutrophils Potentiate Endothelial Stress, Apoptosis and Detachment: A Pathway. *Annu Rev Physiol* (2016) 78:171–94. doi: 10.1146/ annurev-physiol-052521-013627

36. Silvestre-Roig C, Braster Q, Ortega-Gomez A, Soehnlein O. Neutrophils as Regulators of Cardiovascular Inflammation. *Nat Rev Cardiol* (2020) 17 (6):327–40. doi: 10.1038/s41569-019-0326-7
Randomized Controlled Trial of Non-Surgical Periodontal Therapy. *Eur Heart J* (2019) 40(42):3459–70. doi: 10.1093/eurheartj/ehz2646

45. Shires DJ, Marchitelli LL. Nitric Oxide Synthases. *Biochim Biophys Acta* (1999) 1411(2-3):217–30. doi: 10.1016/s0005-2728(99)00016-x

46. Palmer RM, Ferrige AG, Moncada S. Nitric Oxide Release Accounts for the Functional Expression of the Rat Liver Interleukin 6 Receptor. *J Biol Chem* (1990) 265(32):19853–62. doi: 10.1001/s0021-9258(97)84541-2

47. Yoshizumi M, Perrella MA, Burnett JCJr., Lee ME. Tumor Necrosis Factor Dependent Dilatation in Human Veins. *In Vivo Circ* (1997) 99(6):3042–7. doi: 10.1016/0196.9.3042

48. Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jainal I. Demonstration That Interleukin-8 in Smokers and Nonsmokers With Chronic Periodontitis. *J Periodontol* (2000) 71(10):1528–9. doi: 10.1902/jop.2000.71.10.1528

50. Clapp BR, Hingorani AD, Kharbanda RK, Mohamed-Ali V, Stephens JW, et al. Randomized Controlled Trial. *J Periodontol* (2017) 88(8):711–7. doi: 10.1902/jop.2017.160447

51. Higashi Y, Goto C, Jitsuiki D, Umemura T, Nishioka K, Hidaka T, et al. Cathepsin G Controls Arterial But Not Venular Myeloid Cell Recruitment. *Circ Res* (2015) 116(5):827–35. doi: 10.1161/CIRCRESAHA.115.305825

52. Ortega-Gomez A, Salvermoser M, Rossaint J, Pick R, Brauner J, Lemmitzer P, et al. Cathepsin G Controls Arterial But Not Venular Myeloid Cell Recruitment. *Circulation* (2016) 134(16):1176–88. doi: 10.1161/CIRCULATIONAHA.116.024790

53. Shitara R, Gregorek H, Kowalski J, Laskus-Perendyk A, Syczewska M, Madalinski K. Relationship Between Clinical Parameters and Cytokine Profiles in Inflamed Gingival Tissue and Serum Samples From Patients With Chronic Periodontitis. *J Clin Periodontol* (2003) 30(12):1046–52. doi: 10.1034/j.1399-0039.2003.00425.x

54. Van Dyke TE, Kholy KE, Ihai A, Takra RA, Mezue K, Abobashem SM, et al. Inflammation of the Periodontium Associates With Risk of Future Cardiovascular Events. *J Periodontol* (2021) 92(3):348–58. doi: 10.1002/jper.19-0441

55. Moutopoulos NM, Madiansan PN. Low-Grade Inflammation in Chronic Infectious Diseases: Paradigm of Periodontal Infections. *Ann N Y Acad Sci* (2006) 1088:251–64. doi: 10.1196/annals.1366.032

56. Górska R, Gregorek H, Kowalski J, Laskus-Perendyk A, Syczewska M, Madalinski K. Relationship Between Clinical Parameters and Cytokine Profiles in Inflamed Gingival Tissue and Serum Samples From Patients With Chronic Periodontitis. *J Clin Periodontol* (2000) 30(12):1046–52. doi: 10.1002/jper.19-0441

57. Loos BG, Braumick J, Hoek FJ, PMwv D, van der Velden U. Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients. *J Periodontol* (2000) 71(10):1528–34. doi: 10.1902/jop.2000.71.10.1528

58. Türer C, Durmus D, Balli U, Güven B. Effect of Non-Surgical Periodontal Treatment on Gingival Crevicular Fluid and Serum Endocan, Vascular Reactive Protein. *J Periodontol* (2017) 88(5):493–8. doi: 10.1902/jop.2017.160447

59. Higashi Y, Goto C, Jitsuiki D, Umemura T, Nishioka K, Hidaka T, et al. Cathepsin G Controls Arterial But Not Venular Myeloid Cell Recruitment. *Circ Res* (2015) 116(5):827–35. doi: 10.1161/CIRCRESAHA.115.305825

60. de Oliveira C, Watt R, Hamer M. Toothbrushing, Inflammation, and Risk of Cardiovascular Disease: Results From Scottish Health Survey. *BMJ* (2010) 327(14):3040. doi: 10.1136/bmj.c2451

61. Loos BG, Craandijk J, Hoek FJ, PMwv D, van der Velden U. Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients. *J Periodontol* (2000) 71(10):1528–34. doi: 10.1902/jop.2000.71.10.1528

62. Botelho J, Machado V, Hussain SB, Zehra SA, Proença L, Orlando M, et al. Periodontal and Circulating Blood Cell Profiles: A Systematic Review and Meta-Analysis. *Exp Hematol* (2021) 93:1–13. doi: 10.1016/j.exphem.2020.10.001

63. Herrera D, Molina A, Buhlin K, Klinge B. Periodontal Diseases and Inflammation, and Risk of Cardiovascular Disease. *J Periodontol* (2021) 92(3):348–58. doi: 10.1002/jper.19-0441

64. Van Dyke TE, Kholy KE, Ihai A, Takra RA, Mezue K, Abobashem SM, et al. Inflammation of the Periodontium Associates With Risk of Future Cardiovascular Events. *J Periodontol* (2021) 92(3):348–58. doi: 10.1002/jper.19-0441

65. Moutopoulos NM, Madiansan PN. Low-Grade Inflammation in Chronic Infectious Diseases: Paradigm of Periodontal Infections. *Ann N Y Acad Sci* (2006) 1088:251–64. doi: 10.1196/annals.1366.032

66. Górska R, Gregorek H, Kowalski J, Laskus-Perendyk A, Syczewska M, Madalinski K. Relationship Between Clinical Parameters and Cytokine Profiles in Inflamed Gingival Tissue and Serum Samples From Patients With Chronic Periodontitis. *J Clin Periodontol* (2000) 30(12):1046–52. doi: 10.1002/jper.19-0441

67. Loos BG, Crandajck J, Hoek FJ, PMwv D, van der Velden U. Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients. *J Periodontol* (2000) 71(10):1528–34. doi: 10.1902/jop.2000.71.10.1528

68. Botelho J, Machado V, Hussain SB, Zehra SA, Proença L, Orlando M, et al. Periodontal and Circulating Blood Cell Profiles: A Systematic Review and Meta-Analysis. *Exp Hematol* (2021) 93:1–13. doi: 10.1016/j.exphem.2020.10.001

69. Loos BG, Craandijk J, Hoek FJ, PMwv D, van der Velden U. Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients. *J Periodontol* (2000) 71(10):1528–34. doi: 10.1902/jop.2000.71.10.1528
Cytokine Production in Human Monocytes and Adhesion Molecule Expression in Endothelial Cells. *Eur Cytokine Newsl* (2000) 11(2):257–66.

81. Sun R, Iribarren P, Zhang N, Zhou Y, Gong W, Cho EH, et al. Identification of Neutrophil Granule Protein Cathespin G as a Novel Chemotactic Agonist for the G Protein-Coupled Formyl Peptide Receptor. *J Immunol* (2004) 173(1):428–36. doi: 10.4049/jimmunol.173.1.428

82. Carr AC, McCall MR, Frei B. Oxidation of LDL by Myeloperoxidase and Reactive Nitrogen Species: Reaction Pathways and Antioxidant Protection. *Arterioscler Thromb Vasc Biol* (2000) 20(7):1716–23. doi: 10.1161/01.ATV.20.7.1716

83. Bekkerk S, Quintin J, Joosten LA, van der Meer JW, Netea MG, Riksen NP. Oxidized Low-Density Lipoprotein Induces Long-Term Proinflammatory Cytokine Production and Foam Cell Formation via Epigenetic Reprogramming of Monocytes. *Arterioscler Thromb Vasc Biol* (2014) 34(8):1731–8. doi: 10.1161/ATVBAHA.113.303887

84. Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Neutrophil Extracellular Traps License Invasive Capacity for Cytokine Production in Atherosclerosis. *Science* (2015) 17:349(6245):316–20. doi: 10.1126/science.aaa8064

85. Silva-estreig C, Braster Q, Wichapong K, Lee EY, Teulon JM, Berrebeh N, Gopalkrishna S, Johnson J, Jaggers RM, Dahdah A, Murphy AJ, Hanssen et al. Externalized Histone H4 Orchestrates Chronic Inflammation by Inducing Lytic Cell Death. *J Immunol* (2011) 187(1):428–37. doi: 10.4049/jimmunol.1100081

86. Horckmans M, Ring L, Duchene J, Santovito D, Schloss MJ, Drechsler M, Mitroulis I, Ruppova K, Wang B, Chen LS, Grzybek M, Grinenko T, et al. Reactive Nitrogen Species: Reaction Pathways and Antioxidant Protection. *Arterioscler Thromb Vasc Biol* (2015) 35(1):428–37. doi: 10.1161/ATVBAHA.114.310906

87. Franck G, Mawson TL, Folco EJ, Molinaro R, Ruvkun V, Engelbertsen D, Marinkovic et al. S100A9 Links Inflammation to a Hyperactive Neutrophil Granule Protein Cathepsin G. *Nat Commun* (2016) 7:13490. doi: 10.1038/ncomms13490

88. Carr AC, McCall MR, Frei B. Oxidation of LDL by Myeloperoxidase and Reactive Nitrogen Species: Reaction Pathways and Antioxidant Protection. *Arterioscler Thromb Vasc Biol* (2000) 20(7):1716–23. doi: 10.1161/01.ATV.20.7.1716

89. Warnatsch A, Ioannou M, Wang Q, Papayannopoulos V. Neutrophil Extracellular Traps License Invasive Capacity for Cytokine Production in Atherosclerosis. *Science* (2015) 17:349(6245):316–20. doi: 10.1126/science.aaa8064

90. Gopalkrishna S, Johnson J, Jaggers RM, Dahdah A, Murphy AJ, Hanssen NM, et al. Neutrophils in Cardiovascular Disease: Warmongers, Peacemakers or Both? *Cardiovasc Res* (2018) 112(12):1656–66. doi: 10.1093/cvr/cvy130

91. Franck G, Mawson TL, Folco EJ, Molinaro R, Ruvkun V, Engelbertsen D, Marinkovic et al. S100A9 Links Inflammation to a Hyperactive Neutrophil Granule Protein Cathepsin G. *Nat Commun* (2016) 7:13490. doi: 10.1038/ncomms13490

92. Nagareddy PR, Abo-Aly M, Athmanathan B, Annabathula R, Dhyani A, Noothi et al. Neutrophils Recruit by Leukotriene B4 Induce Features of Plaque Reactive Erosion. *Circ Res* (2018) 122:2271–73. doi: 10.1161/circresaha.117.312494

93. Horckmans M, Ring L, Duchene J, Santovito D, Schloss MJ, Drechelur M, et al. Neutrophils Orchestrating Post-Mycocardial Injury Healing by Polarizing Macrophages Towards a Reparative Phenotype. *Eur Heart J* (2017) 4:138(3):187–97. doi: 10.1093/eurheartj/ehw002

94. Marinkovic G, Koenis DS, de Camp L, Jablonowski R, Graber N, de Waard et al. Integrative Hubs for Adaptation to and Fine-Tuning of Inflammation: Novel Paradigms From Studying Periodontitis. *J Leukoc Biol* (2015) 98(4):539–48. doi: 10.1189/jlb.0414-468R

95. Ishai A, Osborne MT, El Kholi K, Takx RA, Ali A, Yuan N, et al. Periodontal Inflammation: Novel Paradigms From Studying Periodontitis. *J Leukoc Biol* (2015) 98(4):539–48. doi: 10.1189/jlb.0414-468R

96. Wright HJ, Matthews JB, Chapple IL, Ling-Mountford N, Cooper PR. Periodontitis Associates With A Type I IFN Signature in Peripheral Blood Neutrophils. *J Immunol* (2008) 181(8):5775–84. doi: 10.4049/jimmunol.181.8.5775

97. Ju Y, Zhang T, Lu H, Ma Q, Zhao D, Sun J, et al. Granulocyte Colony-Stimulating Factor (G-CSF) Mediates Bone Resorption in Periodontitis. *BMC Oral Health* (2021) 21:1(299). doi: 10.1186/s12903-021-01658-1

98. Hajishengallis G, Chavakis T, Hajishengallis E, Lambris JD. Neutrophil Homeostasis and Inflammation: Novel Paradigms From Studying Periodontitis. *J Leukoc Biol* (2015) 98(4):539–48. doi: 10.1189/jlb.0414-468R

99. Manz MG, Boetcher S. Emergency Granulopoiesis. *Nat Rev Immunol* (2014) 14(5):302–14. doi: 10.1038/nri3660

100. Li X, Wang H, Yu X, Saha G, Kalafati L, Ioannidis C, et al. Maladaptive Innate Immune Training of Myelopoiesis Links Inflammatory Comorbidities. *Cell* (2022) 185(10):1709–27.e18. doi: 10.1016/j.cell.2022.03.043

101. Yamashita M, Passeggi E. TNF-α Coordinates Hematopoietic Stem Cell Survival and Myeloid Regeneration. *Cell Stem Cell* (2019) 25(3):357–72.e7. doi: 10.1016/j.stem.2019.05.019

102. Schürch CM, Riether C, Ochesenin AF. Cytotoxic CD8+ T Cells Stimulate Hematopoietic Progenitors by Promoting Cytokine Release From Bone Marrow Mesenchymal Stromal Cells. *Cell Stem Cell* (2014) 3(4):460–72. doi: 10.1016/j.stem.2014.01.002

103. Kalafati L, Kourtzis E, Schulz-Schrepp J, Li X, Hatzianagnostou A, Grinenko T, et al. Innate Immune Training of Granulopoiesis Promotes Anti-Tumor Activity. *Cell* (2020) 183(3):771–85.e12. doi: 10.1016/j.cell.2020.09.05

104. Matatall KA, Jeong M, Chen S, Sun D, Chen F, Mo Q, et al. Chronic Infection Depletes Hematopoietic Stem Cells Through Stress-Induced Terminal Differentiation. *Cell Rep* (2016) 17(10):2584–95. doi: 10.1016/j.celrep.2016.11.031

105. Christopher MJ, Rao M, Liu F, Wołoszynek JR, Link DC. Expression of the G-CSF Receptor in Monocytic Cells is Sufficient to Mediate Hematopoietic Progenitor Mobilization by G-CSF in Mice. *J Exp Med* (2021) 208(2):251–60. doi: 10.1084/jem.20210170

106. Hérault A, Binnewies M, Leong S, Calero-Nieto FJ, Zhang SY, Kang Y-A, et al. Myeloid Progenitor Cluster Formation Drives Emergency and Leukemic Myelopoiesis. *Nature* (2017) 544(7648):53–8. doi: 10.1038/nature21693

107. Wright HJ, Matthews JB, Chapple IL, Ling-Mountford N, Cooper PR. Periodontitis Associates With A Type I IFN Signature in Peripheral Blood Neutrophils. *J Immunol* (2008) 181(8):5775–84. doi: 10.4049/jimmunol.181.8.5775

108. Yu H, Zhang T, Lu H, Ma Q, Zhao D, Sun J, et al. Granulocyte Colony-Stimulating Factor (G-CSF) Mediates Bone Resorption in Periodontitis. *BMC Oral Health* (2021) 21:1(299). doi: 10.1186/s12903-021-01658-1
117. Figueredo C, Gustafsson A, Åsman B, Bergström K. Expression of Intracellular Elastase Activity in Peripheral Neutrophils From Patients With Adult Periodontitis. *J Clin Periodontol* (2000) 27(8):572–7. doi: 10.3109/0300978003009572x

118. Guenther A, Poldo M, Preshaw PM, Glockmann E, Pfister W, Potempa J, et al. Neutrophils in Chronic and Aggressive Periodontitis in Interaction With Porphyromonas Gingivalis and Aggregatibacter Actinomycetemcomitans. *J Periodontal Res* (2009) 44(3):368–77. doi: 10.1111/j.1600-0765.2008.01113.x

119. Fine N, Chadwick JW, Sun C, Parbhakar KK, Khoury N, Barbou A, et al. Periodontal Inflammation Primers the Systemic Innate Immune Response. *J Dent Res* (2021) 100(3):318–25. doi: 10.1177/0022034520963710

120. Welsh C, Welsh P, Mark PB, Celis-Morales CA, Lewsey J, Gray SR, et al. Association of Total and Differential Leukocyte Counts With Cardiovascular Disease and Mortality in the UK Biobank. *Arterioscler Thromb Vasc Biol* (2018) 38(6):1415–23. doi: 10.1161/ATVRAHA.118.310945

121. Lassale C, Curtis A, Abele I, van der Schouw YT, Verschuren WM, Lu Y. Elements of the Complete Blood Count Associated With Cardiovascular Disease Incidence: Findings From the EPIC-NL Cohort Study. *Sci Rep* (2018) 8(1):3290. doi: 10.1038/s41598-018-12661-x

122. White P, Sakellari D, Roberts H, Risaf I, Ling M, Cooper P, et al. Peripheral Blood Neutrophil Extracellular Trap Production and Degradation in Chronic Periodontitis. *J Clin Periodontol* (2016) 43(12):1041–9. doi: 10.1111/jcpe.12628

123. Lee R, Rodriguez-Vélez M, Arias S, López-Dequidt I, Campos F, Sobořín T, et al. Periodontitis as a Risk Indicator and Predictor of Poor Outcome for Lacunar Infarct. *J Clin Periodontol* (2019) 46(1):20–30. doi: 10.1111/jcc.13032

124. Medara N, Lenzo JC, Walsh KA, Reynolds EC, O’Brien-Simpson NM, Darby IB. Peripheral Neutrophil Phenotypes During Management of Periodontitis. *J Periodontal Res* (2021) 56(1):58–68. doi: 10.1111/jcpe.12793

125. Rüdler PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antinflammatory Therapy With Canakinumab for Atherosclerotic Plaque Circulation (2018) 138(3):321–3. doi: 10.1161/CIRCULATIONAHA.117.033098

126. Shin J, Maekawa T, Abe T, Hajishengallis G, Hosur K, Pyaram K, et al. DEL-1 Regulates of LFA-1-Dependent Inflammation Primes the Systemic Innate Immune Response. *Cell Mol Physiol* (2014) 307(6):L435–42. doi: 10.1152/ajplung.00234.2013

127. Wang Z, Li J, Cho J, Malik A.B. Prevention of Vascular Inflammation by Nanoparticle Targeting of Adherent Neutrophils. *Nat Nanotechnol* (2014) 9(5):204–10. doi: 10.1038/nnano.2014.17

128. Miettinen HM, Gripen Borg J, Lord CI, Nagy JO. CD147-Mediated Nanoparticle Targeting of Human and Mouse Neutrophils. *PLoS One* (2018) 13(7):e0200444. doi: 10.1371/journal.pone.0200444

129. Ibáñez B, Macaya C, Sánchez-Bruneet V, Pizarro G, Fernández-Friera L, Mateos A, et al. Effect of Early Metoprolol on Infarct Size in ST-Segment-Elevation Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention: The Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD–CNIC) Trial. *Circulation* (2013) 128(14):1495–503. doi: 10.1161/CIRCULATIONAHA.113.003653

130. Pizarro G, Fernández-Friera L, Fuster V, Fernández-Jiménez R, García-Ruiz JM, García-Alvarez A, et al. Long-Term Benefit of Early Pre-Reperfusion Metoprolol Administration in Patients With Acute Myocardial Infarction: Results From the METOCARD–CNIC Trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction). *J Am Coll Cardiol* (2014) 63(22):2356–62. doi: 10.1016/j.jacc.2014.03.014

131. García-Prieto J, Villena-Gutierrez R, Gómez M, Bernardo E, Pun-García A, García-Lunar I, et al. Neutrophil Stowing by Metoprolol Reduces Infarct Size. *Nat Commun* (2017) 8:14780. doi: 10.1038/ncomms14780

132. Clemente-Moragón A, Gómez M, Villena-Gutierrez R, Lalama DV, García-Prieto J, Martínez F, et al. Metoprolol Exerts a Non-Class Effect Against Ischaemia-Reperfusion Injury by Abrogating Exacerbated Inflammation. *Eur Heart J* (2020) 41(46):4245–40. doi: 10.1093/eurheartj/ehaa733

133. Herz J, Sabellek P, Lane TE, Gunzer M, Herrmann DM, Doepner TR. Role of Neutrophils in Excavation of Brain Injury After Focal Cerebral Ischemia in Hyperlipidemic Mice. *Stroke* (2015) 46(10):2916–25. doi: 10.1161/STROKEAHA.115.010620

134. Jurcevic S, Humfrey C, Uddin M, Warrington S, Larsson B, Keen C. The Effect of a Selective CXCR2 Antagonist (AZD9069) on Human Blood Neutrophil Count and Innate Immune Functions. *Br J Clin Pharmacol* (2015) 80(6):1324–36. doi: 10.1111/bcp.12724

135. Joseph JP, Reyes E, Guzman J, O’Doherty J, McConkey H, Arri S, et al. CXCR2 Inhibition - a Novel Approach to Treating Coronary Heart Disease (CICADA): Study Protocol for a Randomised Controlled Trial. *Trials* (2017) 18(1):473. doi: 10.1186/s13063-017-2210-2
153. Hasturk H, Hajishengallis G, Lambris JD, Mastellos DC, Yancopoulou D. Phase IIa Clinical Trial of Complement C3 Inhibitor AMY-101 in Adults With Periodontal Inflammation. J Clin Invest (2021) 131(23):e152973. doi: 10.1172/JCI152973

154. Hajishengallis G, Liang S, Payne MA, Hashim A, Jotwani R, Eskan MA, et al. Low-Abundance Biofilm Species Orchestrates Inflammatory Periodontal Disease Through the Commensal Microbiota and Complement. Cell Host Microbe (2011) 10(5):497–506. doi: 10.1016/j.chom.2011.10.006

155. Maekawa T, Krauss JL, Abe T, Jotwani R, Triantaflou M, Triantaflou K, et al. Porphyromonas Gingivalis Manipulates Complement and TLR Signaling to Uncouple Bacterial Clearance From Inflammation and Promote Dysbiosis. Cell Host Microbe (2014) 15(6):768–78. doi: 10.1016/j.chom.2014.05.012

156. Hajishengallis G, Hasturk H, Lambris JD. C3-Targeted Therapy in Periodontal Disease: Moving Closer to the Clinic. Trends Immunol (2021) 42(10):856–64. doi: 10.1016/j.it.2021.08.001

157. Räisänen IT, Lahteenmäki H, Gupta S, Grigoriadis A, Sahni V, Suojanen J, et al. An aMMP-8 Point-Of-Care and Questionnaire Based Real-Time Diagnostic Toolkit for Medical Practitioners. Diagnostics (Basel) (2021) 11(4):711. doi: 10.3390/diagnostics11040711

158. Lee CT, Teles R, Kantarci A, Chen T, McCafferty J, Starr JR, et al. Resolvin E1 Reverses Experimental Periodontitis and Dysbiosis. J Immunol (2016) 197(7):2796–806. doi: 10.4049/jimmunol.1600859

159. Kajikawa T, Meshikhes F, Maekawa T, Hajishengallis E, Hosur KB, Abe T, et al. Milk Fat Globule Epidermal Growth Factor 8 Inhibits Periodontitis in Non-Human Primates and Its Gingival Crevicular Fluid Levels Can Differentiate Periodontal Health From Disease in Humans. J Clin Periodontal (2017) 44(5):472–83. doi: 10.1111/jcpe.12707

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Irwandi, Chiesa, Hajishengallis, Papayannopoulos, Deanfield and D’Aiuto. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.