

CLINICAL REVIEW

Oral Infections, Metabolic Inflammation, Genetics, and Cardiometabolic Diseases

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Abstract: *Although several epidemiologic studies reported plausible and potentially causal associations between oral infections and cardiometabolic diseases (CMDs), controversy still lingers. This might be due to unrecognized confounding from metabolic inflammation and genetics, both of which alter the immune responses of the host. Low-grade inflammation termed metaflammation is the hallmark of obesity, insulin resistance, type 2 diabetes, and CMDs. According to the common soil theory, the continuum of obesity to CMDs is the same pathology at different time points, and early metaflammations, such as hyperglycemia and obesity, display many adverse cardiometabolic characteristics. Consequently, adipose tissue is now considered a dynamic endocrine organ that expresses many proinflammatory cytokines such as TNF- α , IL-6, plasminogen activator inhibitor 1, and IL-1 β . In metaflammation, IL-1 β and reactive oxygen species are generated, and IL-1 β is a pivotal molecule in the pathogenesis of CMDs. Note that the same cytokines expressed in metaflammation are also reported in oral infections. In metabolic inflammation and oral infections, the innate immune system is activated through pattern*

recognition receptors—which include transmembrane receptors such as toll-like receptors (TLRs), cytosolic receptors such as nucleotide-binding oligomerization domain–like receptors, and multiprotein complexes called inflammasome. In general, TLR-2s are presumed to recognize lipoteichoic acid of Gram-positive microbes—and TLR-4s, lipopolysaccharide of Gram-negative microbes—while nucleotide-binding oligomerization domain–like receptors detect both Gram-positive and Gram-negative peptidoglycans on the bacterial cell walls. However, a high-fat diet activates TLR-2s, and obesity activates TLR-4s and induces spontaneous increases in serum lipopolysaccharide levels (metabolic endotoxemia). Moreover, genetics controls lipid-related transcriptome and the differentiation of monocyte and macrophages. Additionally, genetics influences CMDs, and this creates a confounding relationship among oral infections, metaflammation, and genetics. Therefore, future studies must elucidate whether oral infections can increase the risk of CMDs independent of the aforementioned confounding factors.

Key Words: TLRs, NODs, NLRP3 inflammasomes, metabolic endotoxemia, gut microbial dysbiosis, Fcy.

Although several epidemiologic studies report plausible and potentially causal associations between oral infections and cardiovascular mortality (Janket et al. 2014), a number of well-conducted randomized trials did not demonstrate unequivocal improvements in cardiometabolic disease (CMD) outcomes following periodontal treatment. This discordance prompted the American Heart Association to issue a guideline stating that “there is no evidence to support a causative relationship” between chronic periodontitis (PD) and cardiovascular disease (CVD; Lockhart et al. 2012). A summary of randomized clinical trials evaluating the impacts of periodontal treatment on CMDs is presented in the Appendix Table. Randomized clinical trials with small sample sizes and various flaws presented significant improvement, and large, well-conducted studies presented equivocal results. If there truly is a causal relationship between PD and CMDs, these conflicting results might have arisen from unrecognized confounding.

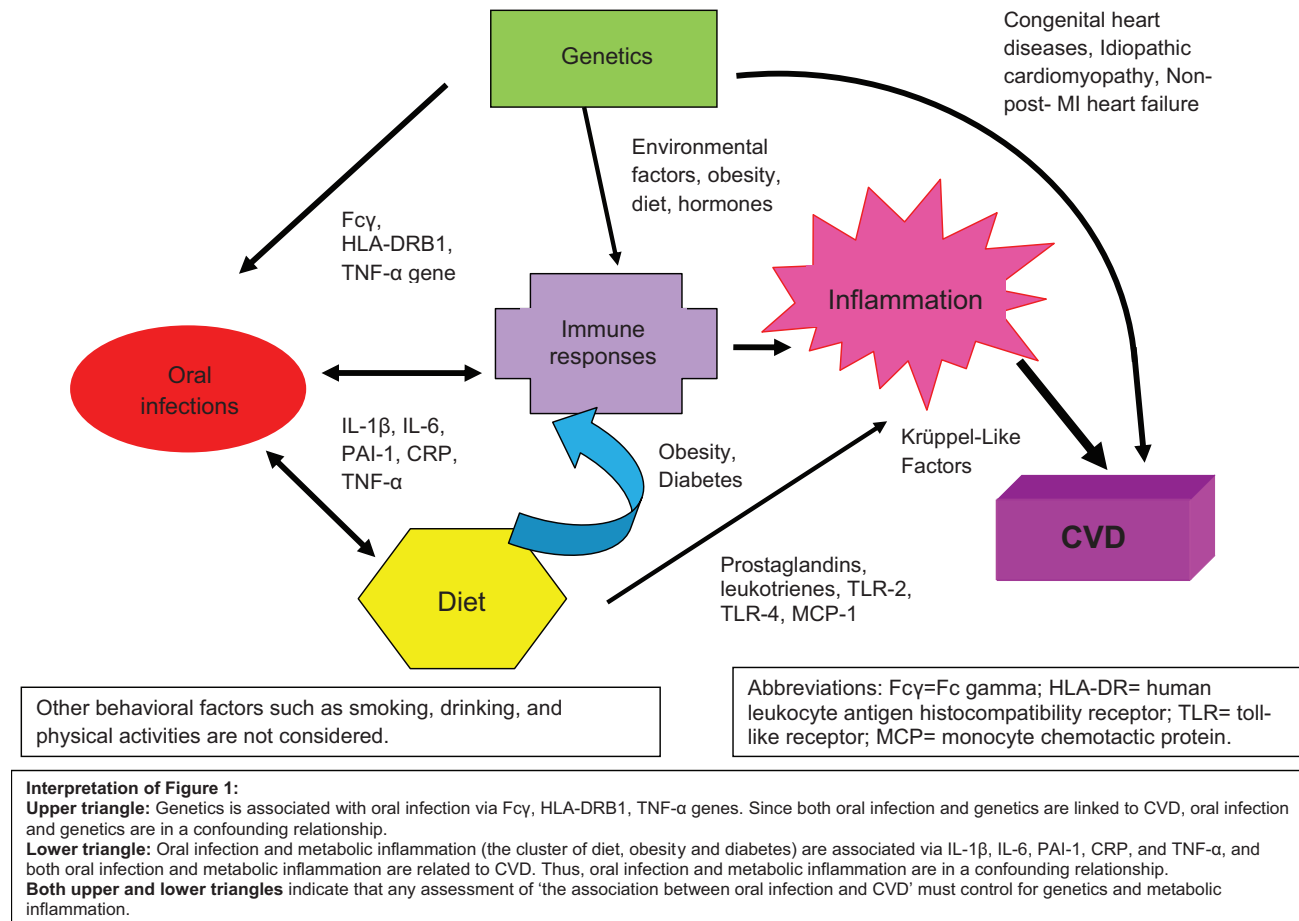
The critical role of immune responses rather than the mere presence of pathogens in the relationship between PD and CVD has long been recognized (Beck et al. 2005). As illustrated in the putative pathogenic pathways in Figure 1, the molecules expressed in oral infections are also produced by diet and

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Figure 1.

Putative pathogenic pathways to cardiometabolic diseases by oral infections, diet, and genetics.



obesity, creating a confounding situation (Jin and Flavell 2013).

Based on the common soil theorem (Stern 1995)—which regards hyperglycemia, insulin resistance, diabetes, and atherosclerosis as 1 pathology at different stages—obesity and insulin resistance should be considered as the early stages of inflammatory CMDs. When 2 factors (oral infections and obesity) are associated with the same outcome (CMDs) and they themselves are associated, the relationship forms a triangle. This triangular relationship is called *confounding*. Oral infections in this context include PD, gingivitis, mucositis, aphthous ulcers, herpes- or *Candida*-related infections, dental caries, and pulpitis. Henceforth, we critically examine the pathways linking oral infections and metabolic inflammation to

CMDs. To highlight the main theme of this review—metabolic inflammation—we will not discuss the impacts of smoking, although its deleterious effects are well established. For this narrative review, we conducted 4 separate searches using Medline/PubMed, Web of Science, and Cochrane databases: the first search with the terms “oral infection,” “periodontitis”; the second with the terms “diet,” “obesity,” “metabolic,” “hyperglycemia,” “diabetes,” “cardiovascular”; the third with the terms “innate immunity,” “adaptive immunity,” “inflammation”; and the fourth with the terms “pattern recognition receptors,” “toll-like receptors,” “nucleotide-binding oligomerization domain,” “NODs,” “inflammasomes,” and combined all. Subsequently, we further searched manually after reading several references.

Metabolic Inflammation and Innate Immunity

Atherosclerosis, diabetes, obesity, and insulin resistance are linked to dysregulated lipid and carbohydrate metabolism. It is now an accepted paradigm that low-grade systemic inflammation termed *metainflammation* is a pathogenic process leading from obesity to insulin resistance, type 2 diabetes, and CMDs (Hotamisligil 2006). Obesity increases systemic inflammation and expression of many inflammatory markers and cytokines, such as TNF-α, IL-6, and IL-1β. Thus, adipose tissue is now considered an endocrine organ that actively participates in the metabolic processes (You et al. 2004). In metainflammation, excess nutrients trigger inflammation and cause stress

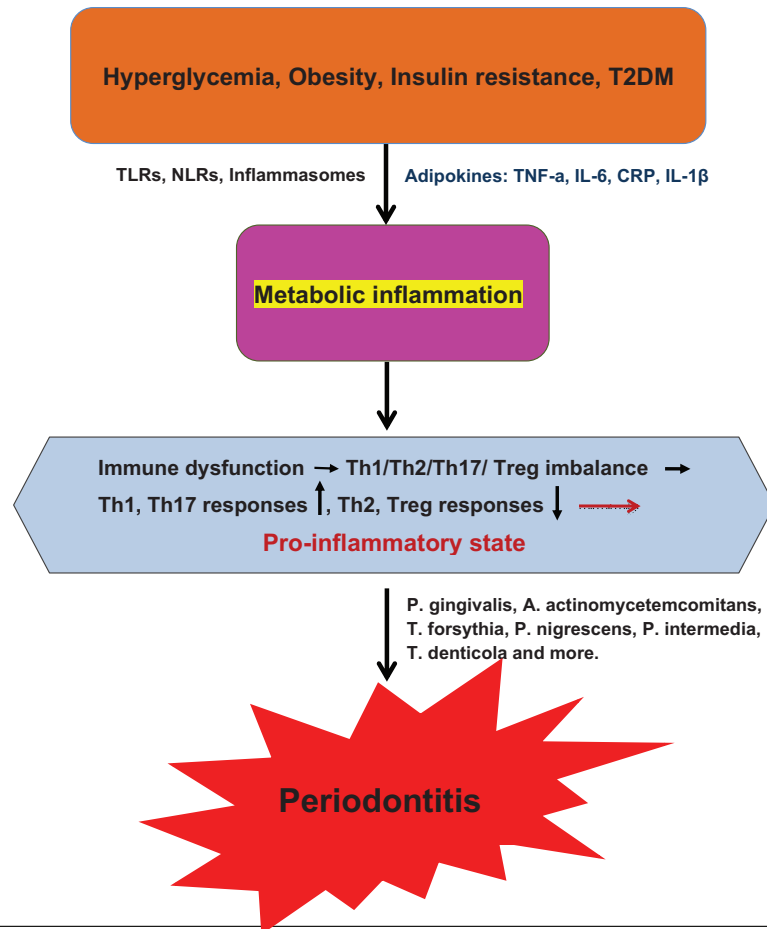
in cells and especially the endoplasmic reticulum. This endogenous stress activates the immune system and recruits immune cells to the sites of metabolic inflammation—namely, adipose and pancreatic tissues (Hotamisligil 2006).

PD is known to cause low-grade inflammation (Beck and Offenbacher 2005); it is also associated with obesity and diabetes. Hence, metabolic inflammation is a confounding or collinear factor in the relationship of PD to atherosclerotic inflammatory diseases (Janket et al. 2008). Although the same mediators, such as TNF- α , IL-6, and IL-1 β , are expressed in both PD (Salvi et al. 1998) and metainflammation (Schroder et al. 2010), metainflammation is distinctly different from the classic inflammation (including infectious inflammation) that elicits the 5 cardinal signs. Metainflammation does not generate fever, redness, or pain (Hotamisligil 2006). Metainflammation involves adipose tissue, liver, and pancreas, while infectious inflammation can occur in any tissue. Metainflammation mobilizes immune cells, such as macrophages, monocytes, dendritic cells, monocytes, T- and B-cells, adipocytes, hepatocytes, and pancreatic β cells, while oral infections involve immune cells, epithelial cells, fibroblasts, osteoblasts, and osteoclasts. The cytokines generated in metainflammation, such as IL-1b, IL-6, TNF- α , and C-reactive protein (Chae et al. 2013), are also produced in PD and other oral infections (Gonzales et al. 2014). Some scholars view PD as the result of immune cell dysfunction induced by obesity and diabetes (Zhu et al. 2014). The potential mechanism of PD pathogenesis in relation to metabolic inflammation is illustrated in Figure 2.

Obesity activates innate immunity via chemokine signaling that expresses monocyte chemoattractant protein 1 (MCP1) and recruits macrophages (Kanda et al. 2006). In turn, macrophages express cytokines, such as TNF- α , IL-1 β , and IL-6 (You et al. 2004). Because MCP1 is expressed in oral infections (Gupta et al. 2013), it is not clear whether metabolic inflammation (metainflammation) or oral infections are the source for

Figure 2.

Potential mechanism linking metabolic inflammation and periodontitis.



Abbreviations:

T2DM: type 2 diabetes; **TLR:** Toll-like receptors; **NLRs:** nucleotide-binding oligomerization domains like receptors; **Th1:** Type 1 helper T cells; **Th2:** Type 2 helper T cells; **Th17:** T helper 17 cells; **Treg:** Regulatory T cells.

MCP1. It is clear, however, that several pathways converge, expressing the same cytokines in innate immunity: via metainflammation, infectious inflammation, or genetics that controls immune responses.

Metainflammation generates IL-1 β and reactive oxygen species that lead to the pathogenesis of CMDs (Schroder et al. 2010). Thus, several large-scale randomized trials attempted to counteract reactive oxygen species by administering exogenous antioxidants but resulted in null findings (Sesso et al. 2008). Similarly, exogenous antibodies to TNF- α or IL-1 β did not alter the cardiovascular sequelae following lipopolysaccharide (LPS) infusion (Gardiner et al. 1998). These results suggest that endogenous cytokines may not be neutralized by exogenous supplements

or antibodies. Even the early stage of metabolic inflammation, hyperglycemia, was associated with periodontal pathogens (Merchant et al. 2014).

It is well known that diabetes is associated with PD, and a bidirectional relationship between PD and diabetes has been suggested. Diabetes manifesting in periodontal tissue has strong, convincing evidence, but results showing periodontal treatment improving glycemic control need better-designed and large-scale randomized clinical trials, as suggested by several researchers (Vergnes 2010). Periodontal treatment utilizing antibiotics elicited more salient improvement in glycemic control, but administration of antibiotics may be biased through the coinciding alteration in the intestinal microbiome.

Metabolic Inflammation and Insulin Resistance

The current paradigm in the prevention of CMDs centers on the molecular blockade of IL-1 β : the key element in innate immunity associated with obesity, insulin resistance, and more advanced CMDs. Abundant evidence linked IL-1 β to pancreatic β -cell failure (Maedler et al. 2002). Moreover, β -cell apoptosis occurs in an IL-1 β -dependent manner (Maedler et al. 2002). IL-1 β is an obesity-related adipokine expressed by pancreatic islet β cells in response to prolonged elevated glucose exposure (Boni-Schnetzler et al. 2008). Therefore, the role of IL-1 β is evident in the pathogenesis of type 2 diabetes via dysglycemic pathway. The inflammation associated with β -cell failure can be attributed to multiple factors, such as infections, cellular stress, physical elements, diet, and obesity (Schroder et al. 2010). Moreover, IL-1 β blockade reduced endotoxin production in human peripheral blood mononuclear cells, suggesting that endotoxemia may be a by-product of metabolic inflammation that generated IL-1 β (Porat et al. 1992).

Oral Infections and Innate Immunity

The biological link between oral infections and inflammatory vascular diseases may be via innate immunity that elicits inflammation. Inflammation is a nonspecific response in the innate immune system to any injury or stimuli, be it pathogens, allergens, or physical elements (Schroder et al. 2010). Alternatively, obesity and other perceived dangers, such as overindulgent dietary intake, also elicit inflammation (Jin and Flavell 2013).

PD is a phenotype-based definition and may reflect systemic immune dysfunction originating from smoking or diabetes, as the American Heart Association stated (Lockhart et al. 2012). Some periodontal pathogens may cause PD by taking advantage of the systemic immune dysfunction caused by obesity or diabetes (Zhu et al. 2014). Notably, when PD was separately assessed from other minor oral infections, it was not a significant predictor of cardiovascular mortality (Tuominen et al. 2003).

However, an oral inflammation marker, numbers of teeth, significantly predicted CVD mortality (Janket et al. 2014). Because of the diverse sources of oral infections, one single molecule may not explain all. To bypass this obstacle, we have used salivary molecules that may represent innate immune activation—namely, salivary immunoglobulin A or salivary lysozyme. The innate immune system is activated by recognition of danger signals through the pattern recognition receptors (PRRs), such as toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and multiprotein NLRP3 inflammasome (discussed in detail later). Salivary lysozyme (muramidase) assesses the enzymatic action on muramyl dipeptides, the constituents of Gram-positive and Gram-negative bacterial cell walls that NODs recognize (Jin and Flavell 2013; Neves et al. 2013). Salivary immunoglobulin A measures oral inflammation via NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), a universal inflammatory activity marker. The “kappa-light-chain” in NF- κ B is an important moiety of immunoglobulins and the fragment crystallizable (Fc) region of immunoglobulins’ impact on immune effector cells that elicit inflammatory responses.

Conversely, ample in vitro evidence indicates that PD is associated with elevated inflammatory markers such as TNF- α , IL-1 β , and IL-6 (Gonzales et al. 2014). However, in vitro studies using cells harvested from PD patients do not determine whether underlying obesity-induced metabolic inflammation or smoking that primed the innate immunity were responsible for these results. Furthermore, these cytokines are expressed in obesity and metabolic inflammation (Jin and Flavell 2013), and supplementation with docosahexaenoic acid suppressed the transcription of NF- κ B and attenuated the production of IL-1 β and IL-6 that were induced by *Prevotella intermedia* LPS (Choi et al. 2014). These results indicate that nutrition and oral infection both express IL-1 β and that nutrition alters infection-related

IL-1 β expression. Thus, to prove that oral infections increase systemic inflammation via IL-1 β leading to CMDs, metabolic inflammation has to be controlled.

Danger Signaling in Innate Immunity

When exposed to stimuli, the sentinel cells, such as macrophages and dendritic cells in the innate immune system, determine quickly whether the stimulus is true danger, harmless, or part of self by utilizing PRRs. Several PRRs can be activated by metabolic danger signals, and they actively participate in the development of obesity-related inflammation (Jin and Flavell 2013). Figure 3 shows a simplified categorization of PRRs.

The most well-known PRRs are transmembrane receptors, TLRs, and lesser-known membrane receptors include C-type lectin receptors (CLRs). Cytoplasm also contains PRRs: better-known cytosolic receptors are NLRs and retinoic acid-inducible genelike receptors (RLRs). NODs include NOD1 and NOD2. NOD1 recognizes Gram-negative bacterial peptidoglycan, and NOD2 recognizes both Gram-negative and Gram-positive bacteria. If bacteria are the leading pathogens, then TLRs or NLRs are relevant; however, if fungi are the pathogens in question, then CLRs are relevant. Generally, it is accepted that TLR2 responds to Gram-positive bacterial peptidoglycan and lipoteichoic acid, while TLR4 recognizes Gram-negative LPS, including that of *Porphyromonas gingivalis* when bound to myeloid differentiation factor 2. Interestingly, salivary TLR-4, a sentinel receptor for LPS, was not elevated by 6 Gram-negative periodontopathogens: *Tannerella forsythia*, *Lysobacter enzymogenes*, *P. intermedia*, *Prevotella oris*, and 2 strains of *P. gingivalis* (Lappin et al. 2011). Note that high-fat diet can activate TLR-2s (Jang et al. 2013) and obesity can activate TLR-4s, leading to endotoxemia (Neves et al. 2013). Furthermore, a high-energy diet even for several days has been shown to induce spontaneous endotoxemia with elevated serum LPS levels, suggesting that the source of elevated serum LPS could be metabolic inflammation (Amar et al. 2008).

NLRP3 Inflammasome

A new concept in innate immune activation in metabolic inflammation centers on the cytosolic inflammasome, which is involved in maturation and secretion of IL-1 β , the key player in metainflammation. NLRP3 inflammasome is the most extensively researched among the inflammasomes, and this protein complex consists of 3 parts: apoptosis-associated speck-like protein containing a CARD; the interleukin-1 converting enzyme, caspase 1; and NLRP3 (Schroder et al. 2010). NLRP3 belongs to the receptor family discussed in the previous section (NLR). Various exogenous or host-driven danger signals—including pathogens, endotoxins, hyperglycemia, obesity, and other factors—activate inflammasome (Kim and Jo 2013).

As described in the previous section, IL-1 β is the key mediator associated with glucose metabolism, insulin resistance, and metainflammation (Schroder et al. 2010). IL-1 β is a potent cytokine and is tightly controlled, requiring at least 2 independent signals for induction and maturation: the induction of proform IL-1 β is via proinflammatory signaling through TLRs or cytokines, such as TNF- α or IL-1 β itself. The maturation requires a modification process by caspase 1, also called interleukin-1 converting enzyme (Schroder et al. 2010; Kim and Jo 2013).

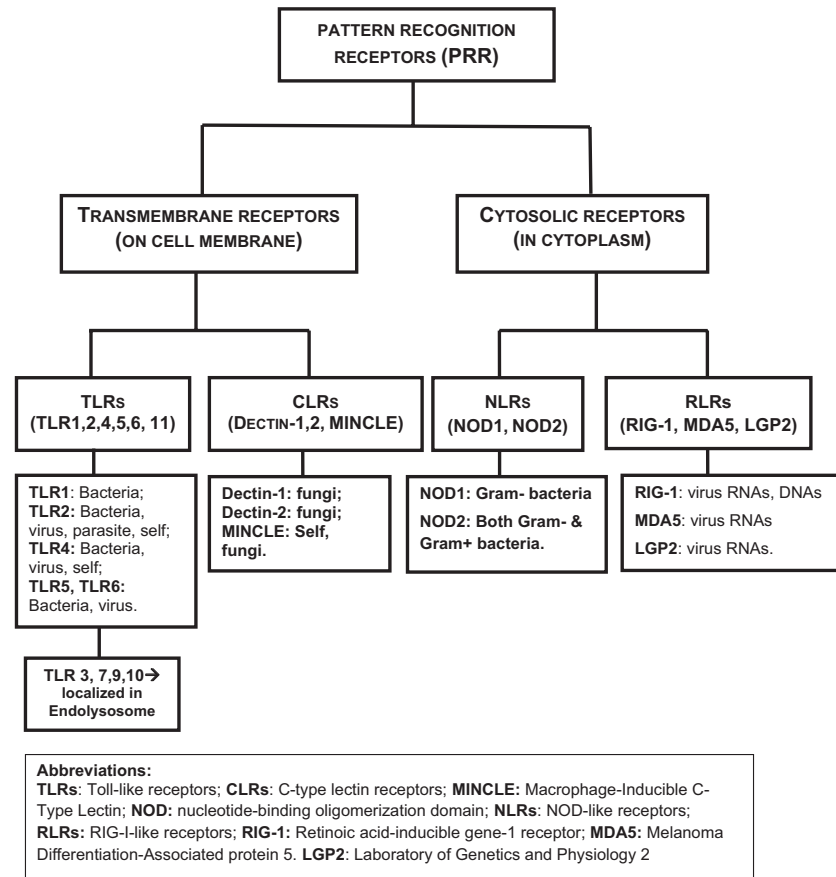
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IL-1 β was elevated in gingival crevicular fluids of PD patients (Gonzales et al. 2014). However, IL-1 β expression is not unique to PD, and many other microorganisms, such as *Candida*, *Staphylococcus*, and virus, all express IL-1 β . Moreover, not only does infection activate inflammasome and express IL-1 β , but so do physical irritants such as ultraviolet light, asbestos, and silica, as well as endogenous danger signals, including ATP, glucose, and amyloid β (Schroder et al. 2010; Kim and Jo 2013).

Additional support for the potential confounding by metainflammation in the oral infection pathway can be derived from a study where periodontal treatment did not change serum IL-1 β levels

Figure 3.

Categories of pattern recognition receptors.



(Michalowicz et al. 2009). We interpret this as follows: (1) systemic IL-1 β may originate from underlying systemic immune modifiers, such as smoking, pregnancy, diabetes, or genetics; (2) PD might be one of the manifestations of systemic immune dysfunction.

Metabolic Inflammation and Metabolic Endotoxemia

LPS is a cell wall component of Gram-negative bacteria, and it is reasonable to hypothesize that LPS is originated from periodontal pathogens that are predominantly Gram-negative anaerobic bacteria. Thus, the dental research community naturally considers that PD may be the source of elevated serum LPS levels in obesity (Janket and Ackerson 2015). However, metainflammation can increase intestinal cell permeability and alter gut microbiota (Lam et al. 2012). Thus, subsequent LPS translocation from

gut microbiota into the serum is possible (Neves et al. 2013).

Other examples corroborate that this assumption of LPS originating from oral infections may be flawed. After 4 wk of a high-fat diet in mice, the proportion of LPS-expressing bacteria in the gut increased and elevated plasma LPS concentration 2 to 3 times (Cani et al. 2007). In humans, only 3 d of high-fat and high-carbohydrate diet increased circulating LPS (Amar et al. 2008). Metabolic inflammation can spontaneously increase plasma LPS, and this observation challenges the assumption that elevated serum LPS originates from Gram-negative oral pathogens.

Even before obesity fully develops, excess dietary intake can change the intestinal microbiota, which in turn affects the innate immune system (Amar et al. 2008). Obesity further changes the intestinal microbial community,

and that is called *microbial dysbiosis* (Ley et al. 2005). Obesity increased the Firmicutes:Bacteroidetes ratio, while weight loss decreased this ratio (Evans et al. 2014). Thus, obesity is associated with intestinal dysbiosis, but obesity in turn is dependent on dietary intakes of certain nutrients. Additionally, arginine supplementation—an amino acid involved in immune responses and wound healing—shifted the gut Firmicutes:Bacteroidetes ratio favoring Bacteroidetes. This shift in microbiota ratio is similar to the effects of weight loss and significantly reduced the expression of TLR-4, NF- κ B, and mitogen-activated protein kinase, suggesting less inflammation (Ren et al. 2014). Thus, dietary intake can affect the cytokine expression, innate immune activation, and inflammation. Moreover, omega-3 polyunsaturated fatty acid intakes suppressed the expression of inflammatory cytokines, IL-1 β , or TNF- α (Endres et al. 1989). The mechanism for metabolic endotoxemia is presumed to be that microbiota-associated molecules are fat soluble and absorbed by chylomicrons with dietary fat in a similar manner as fat-soluble vitamins. Hence, it appears that diet can change the intestinal microbiota and further alter the innate immune responses.

Alternatively, the altered microbiome due to high-energy intake can increase the energy harvest and exacerbate obesity and insulin resistance (Backhed et al. 2007). This has been proven in the experiments with germ-free mice (Backhed et al. 2007) or with TLR-4 knockout mice that were immune to weight gain even with high-fat diet (Pierre et al. 2013). However, the opposite results were also published suggesting that lack of TLR signaling could induce obesity (Vijay-Kumar et al. 2010). Thus, whether TLR signaling is protective or detrimental to the development of obesity is not conclusive.

Convergence of Infectious and Metabolic Inflammation

Potential causal inference can be made only when the predictor (oral infections) occurred prior to the outcome

(CMDs) and all established confounding factors are controlled. Regrettably, many periodontal studies have been conducted as bivariate analyses without adjusting for any confounding factors or have used cross-sectional data. Thus, we do not have adequate evidence to determine whether the increased level of IL-1 β from the oral cavity is due to PD, obesity/diabetes, or smoking that induced PD. PD fulminates in immune-compromised states caused by smoking, pregnancy, and diabetes (Blasco-Baque et al. 2012). Therefore, it is essential to control the hosts' immune capability if we wish to estimate the unbiased contribution of oral infection to CMDs.

Oral Infections versus Metabolic Inflammation

TNF- α , IL-1, and IL-6 were expressed in periodontal tissue in patients with diabetes (Salvi et al. 1998), but these cytokines are also expressed by the adipocytes in patients with diabetes or insulin resistance. Moreover, weight loss by diet (Chae et al. 2013), bariatric surgery, and increased physical activity all reduced these cytokines (Wasinski et al. 2013). These results strongly suggest that cytokine expression is a function of metainflammation, and research in oral infections in relation to these cytokines must control for metabolic inflammations to arrive at an unbiased conclusion.

Genetic Influence on Inflammatory Diseases

Genetics in CMDs

Genetics determines the cell differentiation and the interactions among the cellular milieu, the extracellular milieu, and the metabolic environment. The Krüppel-like family of transcription factor (KLF) is a set of DNA-binding proteins that regulate gene expression. KLFs were reported to be associated with CVD, which has strong inheritability. Among the 17 known KLFs, KLF4 and KLF5 are of particular interest in CVD. KLF4 is upregulated in vascular injury and repairs endothelial damage generated by shear stress. KLF4 is anti-inflammatory because it neutralizes

NF- κ B, the universal inflammatory transcription factors (Yoshida et al. 2014).

Diabetes is a polygenetic disease, and single-nucleotide polymorphisms in 18 loci were associated with the disease. However, when lifestyle factors were adjusted, genetics improved only a fraction of prediction ability, suggesting that epigenetics through lifestyle changes is more important in the development of diabetes (Meigs 2009). Gene expression is highly regulated by adiposity-related transcription factors (Wallner et al. 2014), and lipid-related transcriptome regulates the differentiation of monocyte and macrophages (Wallner et al. 2014). These facts bring metabolic inflammation, infectious inflammation, and genetics together.

Genetics in Oral Infection

PD is an inflammatory disease (Van Dyke 2007), and genetics plays an important role in PD. Thus, any genetic factor that affects inflammatory response will alter the relationship of PD with metabolic inflammation (Larsson et al. 2014). In PD, as in many other infections, the manifestation of the disease depends on the host's immune response, which is under genetic control (Hajishengallis and Lamont 2012). Furthermore, 4 genes highly related to severe chronic PD—namely, NIN, ABHD12B, WHAMM, and AP3B2—were linked to an endoplasmic reticulum-controlling gene (Rhodin et al. 2014), suggesting a potential connection between PD and metainflammation. As stated earlier, metabolic inflammation is caused by endoplasmic reticulum stress (Hotamisligil 2006). The general assumption is that the dysfunctional innate immune responses due to genetic polymorphism may allow the periodontopathogens to manifest more severe forms of PD. We acknowledge, however, the methodological difficulties because PD and CMD are both polygenetic diseases and the complex interplay of genetic variants and epigenetic modifications alters the disease manifestation on systemic outcomes (Genco and Loos 1991).

Genetic mutation in alleles LTA1633c, HLADRB1*01, and HLA-

B*35 was associated with increased susceptibility for PD (Palikhe et al. 2008), while carriers of HLA-B*57, HLA-DQB1*08, or the combination HLA-DRB1*04;DRB4*;DQB1*0302 were at a lower risk of having PD (Reichert et al. 2013). Also, polymorphism of Fcγ receptor gene is involved in PD (Chai et al. 2010). Fcγ receptors are membrane glycoproteins expressed on immune response cells that bind with the Fc moiety of immunoglobulins A and G and elicit immune responses. FcγRIIb is known to inhibit B-lymphocyte activation, thus causing low antibody formation and increased disease risk. Also known is the anti-inflammatory action of intravenous IgG (Nimmerjahn and Ravetch 2008). This is in agreement with our report of low coronary artery disease prevalence in patients with high IgG (Janket et al. 2010).

Microbial Dysbiosis, Nutrients, and Inflammation

Microbial dysbiosis was suggested as a new paradigm of PD pathogenesis (Hajishengallis and Lamont 2012). Would microbial dysbiosis in the oral cavity be the results of metabolic inflammation as observed in the gut (Ley et al. 2005)? What roles do oral infections and diet play in innate immunity and inflammation? These are the key queries that can be answered in future studies.

Some nutrient intake, such as inorganic nitrate, can improve endothelial dysfunction. The mechanism was speculated to be the modulation of nitric oxide (NO) bioavailability through the nitrate-nitrite-NO pathway. Phagocytes such as monocytes, macrophages, and neutrophils during the immune response also generate NO. Oral commensal bacteria can generate NO from the nitrate-nitrite-NO pathway. However, caution must be exercised in administering nitrates because they can be converted to carcinogens under certain conditions. Nitrates are plentiful in green leafy vegetables, and good mastication is a prerequisite for the intake of these vegetables. This underscores our conclusion that good oral health is required in the maintenance of good systemic health.

Recently, citicoline (CDP-choline) has been reported to restore endothelial permeability and dysfunction. Moreover, choline-deficient diet induced gut microbiome dysbiosis and nonalcoholic fatty liver disease, a form of metabolic syndrome. However, intestinal microorganisms metabolize dietary phosphatidylcholine and generate trimethylamine N-oxide (TMAO), which was reported to increase major adverse cardiac events (Tang et al. 2013). These facts further highlight the need for elucidating the relationship of oral infections, nutrition, microbiome, and innate immunity to CMD. To establish causality in humans, they have to be tested sequentially.

Concluding Remarks and Future Directions

So far, it has been proven that a high-fat diet and obesity activated the innate immune system via TLR-associated pathways (Shi et al. 2006) and expressed cytokines such as TNF-α, IL-1β, and IL-6 (You et al. 2004). The same cytokines were expressed in oral infections (Salvi et al. 1998). In addition, CMD and PD have pleiotropic characteristics, and systemic statin administration improved periodontal condition (Subramanian et al. 2013), suggesting that PD may be a cluster in pleiotropy of cardiometabolic inflammation. Similar effects were reported with systemic administration of the anti-inflammatory drug telmisartan, which decreased IL-1β and TNF-α in the periodontal tissue (Araujo et al. 2013).

Thus, answering the question whether PD is an independent risk factor for CMD or a result of underlying metainflammation will require sequential evaluation of oral infection, nutrition, gut microbiome, and innate immunity. Finally, good oral health is a prerequisite in healthy dietary intake and the maintenance of good systemic health regardless of the role that it plays in the inflammation/immunity pathways.

Author Contributions

S.-J. Janket, contributed to conception, design, data acquisition, and interpretation, drafted and critically revised the manuscript; H. Javaheri,

contributed to data acquisition and interpretation, critically revised the manuscript; L.K. Ackerson, S. Ayilavarapu, contributed to design and data interpretation, critically revised the manuscript; J.H. Meurman, contributed to data interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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