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Commonality in chronic inflammatory diseases: periodontitis, diabetes, and coronary artery disease

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Diabetes, coronary artery disease, and adult periodontitis are common chronic diseases observed in a significant proportion of the adult US population. Diabetes is a metabolic disease that, due to disturbances in insulin production, leads to abnormal fat, sugar, and protein metabolism and resultant hyperglycemia that can ultimately induce diverse multiple systems pathologies (164). This disease affects approximately 18 million individuals with an increase of approximately 1.3 million new cases a year in people aged 20 years and older (106). Global estimates by Zimmet & McCarty (173) predicted 216 million diagnosed cases of Type 2 diabetes by 2010. The American Diabetes Association reports a direct medical cost in 2002 of $92 billion, with combined direct and indirect expenditures (disability, work loss, premature mortality) attributable to diabetes estimated at $132 billion (4, 59).

Overall, these cost figures underscore the enormous economic impact related to the treatment and control of diabetes in this country. In addition to a monetary burden, diabetes patients are also at increased risk of premature death related to vascular disease manifested as coronary heart disease, cerebrovascular accidents, and peripheral vascular disease (5, 108). The magnitude of the need for additional research initiatives and clinical interventions for diabetes is very apparent with expenditures climbing higher and higher and no cure available. There are a number of chronic disease processes associated with the development of long-term hyperglycemia, with cardiovascular diseases and periodontal infection among the most common. According to WHO estimates, cardiovascular diseases are responsible for 16.6 million deaths around the world (67). Of these diseases, coronary artery disease caused 7.1 million deaths. In addition, cardiovascular disease is the leading cause of diabetes-related deaths, diabetes resulting in a 2–4 times greater risk of developing cardiovascular disease (76, 171).

Like coronary heart disease, periodontitis is also exacerbated by the diabetic state, which leads to more severe and rapid disease progression (153). Periodontitis is an infection caused predominately by gram-negative organisms in the plaque biofilm that affects 7–15% of the adult population (115). Periodontal research over the last 30–40 years has been instrumental in providing an insight into the impact of severe periodontitis on systemic health. Although bacteria must be present for periodontal disease to occur, a susceptible host is also required. The immune response that develops in the gingival and periodontal tissues in response to the chronic presence of plaque bacteria results in the destruction of structural components of the periodontium, leading, ultimately, to the clinical signs of periodontitis (118). The host response is determined primarily by genetic, environmental, and acquired factors. The host response is essentially protective in nature. However, a hyper-responsive inflammatory trait associated with an impaired host immune response could result in enhanced tissue destruction.

An abnormal inflammatory response, which has been referred to as a hyper-inflammatory trait (114, 133), has been linked to diabetes, where there is an increased susceptibility to infections, such as periodontal disease, and also to cardiovascular disease, which is more inflammatory in nature. The

'hyper-inflammatory trait' is associated with an exaggerated secretion of innate inflammatory mediators and systemic markers of inflammation. It is suggested that this process mechanistically contributes to the pathology associated with these chronic disease processes. Traditionally, diabetic complications have been attributed to the hyperglycemic state, which over time results in the irreversible covalent modification (glycosylation) of structural proteins and lipids that make up the extracellular matrix and connective tissues, as well as the vascular tissues (18, 62, 151). These structural changes result in impaired capillary function, poor blood perfusion of tissues and organs, and the release of reactive oxygen species (oxidative stress), triggering a systemic inflammatory process. The activation of inflammation at a systemic level results in chronic elevation of inflammatory mediators and acute phase reactants such as C-reactive protein, elevated fibrinogen, and lowered albumin – all hallmarks of the acute phase reaction observed in diabetes, coronary heart disease, and periodontitis (9, 58, 125, 139, 145). Thus a hyper-inflammatory trait may predispose an individual to more severe systemic disease as a result of over-expression of inflammatory mediators and may ultimately lead to metabolic dysregulation in the person who has diabetes or who are at risk for developing the disease.

Acute infection is a metabolic stressor, resulting in an increased demand for insulin, glucose, and lipids (28, 41, 70). Infection results in the systemic challenge of pyrogenic cytokines such as interleukin (IL)-1β, tumor necrosis factor-α and IL-6, which block lipoprotein lipase activity, leading to decreased transportation of blood lipids from the circulation into the cells (16, 36, 50, 54, 141). This elicits hyperlipemia, reflected clinically as an increase in low-density lipoprotein and total cholesterol (37). Tumor necrosis factor-α and IL-1β promote glycogenolysis and impaired glucose uptake by cells in the periphery, presumably by an effect on glucose transport receptor expression, leading to hyperglycemia (26, 38, 45, 50, 130, 148). These cytokines also induce insulin resistance by inhibiting the insulin receptor tyrosine kinase and other signaling proteins (16, 97, 117, 165), further increasing the physiological demand for insulin secretion. Clinically, this insulin resistance manifests as elevations in fasting and postprandial serum insulin, increased C-peptide (the N-terminus pro-peptide region of the insulin molecule that accumulates when excess insulin is synthesized and released), and impaired glucose tolerance. Therefore, an infectious challenge can induce a metabolic diabetic state, which, if the infection is ephemeral, is generally considered reversible. However, it is not known what metabolic changes occur when this process is not acute, but chronic and asymptomatic in nature. Since coronary heart disease and periodontitis both possess inflammatory components that result in the production of a similar cytokine profile, these chronic disease processes could serve as a stimulus to a systemic-based inflammatory response that may represent a previously underestimated metabolic stressor in diabetic patients, enhancing insulin resistance and impairing insulin secretion and leading to increased morbidity associated with diabetic complications. Further, the inflammatory component provides an important linkage of diabetic metabolic dysregulation, periodontal disease severity, and the development of coronary heart disease. In this review, we propose an overall hypothetical working model that is illustrated in Fig. 1. This model suggests a connection between the complex association of diabetes, coronary heart disease, and periodontal disease. The inflammatory component provides an important linkage of diabetic metabolic dysregulation, periodontal disease severity, and development of coronary heart disease. This model depicts interactions between chronic oral and systemic infectious / inflammatory processes. A clearer understanding of these interactions should lead to the development of better primary prevention strategies to reduce possible comorbidities that have been identified with cardiovascular events and periodontitis, and provide better glycemic control in individuals with diabetes.

Effects of hyperglycemia

Metabolic dysregulation in diabetes as a result of prolonged exposure to chronic levels of glucose can lead to the glycosylation of long-lived proteins and lipids found in the blood and in the tissues. These glycosylation products, referred to as advanced glycosylation endproducts (AGEs), have been implicated as a primary causal factor in the development of complications associated with diabetes and cardiovascular disease in individuals with diabetes (17, 116). AGEs were identified in 1912 by Louis Mallard, who reported that this reaction of reducing sugars with amino acids led to development of a yellow-brown color and the formation of CO_2 (27, 66). Decades later, scientists have hypothesized that nonenzymatic glycosylation of proteins and lipids may explain many of the sequelae of diabetes,

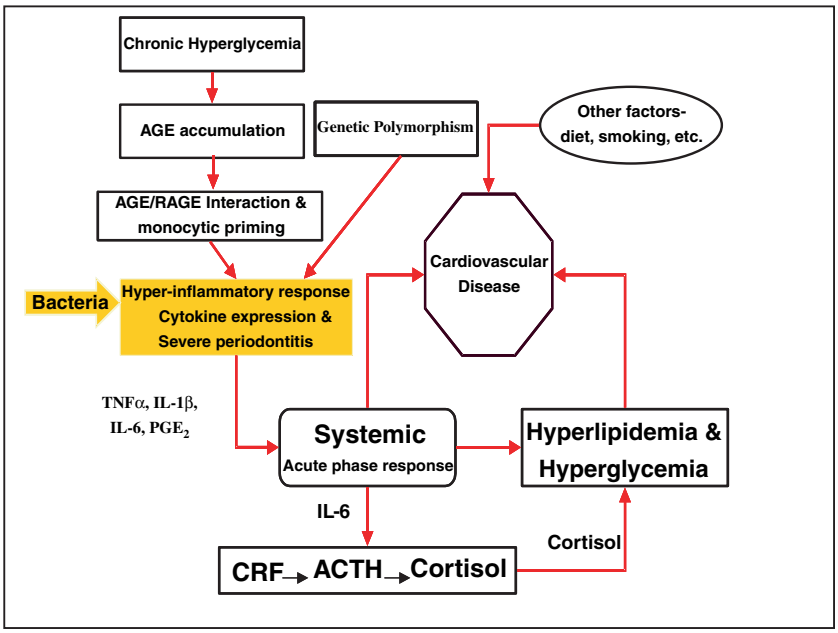

Fig. 1. This model suggests a connection between the complex associations between diabetes, coronary heart disease, and periodontal disease. The inflammatory component provides an important linkage between diabetic metabolic dysregulation, periodontal disease severity, and development of coronary heart disease. This model depicts interactions between chronic oral and systemic infectious/inflammatory processes. AGE, advanced glycosylation endproducts; RAGE, receptors for AGEs; CRF, corticotropin-releasing factor; ACTH, adrenocorticotropin.

such as vascular lesions, neuropathy, and impaired immunologic function, and that circulating levels of certain AGEs are also useful in monitoring glycemic control. The chronic hyperglycemia state promotes glycosylation of hemoglobin to form the A_{1c} product. The measure of glycosylated hemoglobin A_{1c} has been a reliable measure of glycemic control at 3-month intervals. However, compared to tissue matrix AGEs with slower turnover rates, the half-life of glycosylated hemoglobin A_{1c} is relatively short. AGEs are a heterogeneous class of structures irreversible in nature, which are characterized by their yellow-brown color, fluoresce, have a propensity to form cross-links, and interact with cellular receptors (18, 20). During normal states of metabolism, early reversible intermediates of AGEs, called Amadori products, are formed; with time and/or abnormal glucose metabolism, these products become irreversible (98). Subsequently, there is an increase in AGE deposition in matrix tissues as well as an increase in the number of receptors for AGEs on these tissues and on target cells (27, 107). Receptors for AGEs (RAGEs) have also been identified and characterized in the literature (15, 137). RAGE is a multiligand receptor that propagates cellular dysfunction in several inflammatory disorders, in tumors, and in diabetes. RAGE is expressed at low levels in normal tissues, but becomes up-regulated at sites where its ligands accumulate. RAGE may play a dual role in the inflammatory response:

- interaction of RAGE on leukocytes or endothelial cells with its ligands results in cellular activation involving the transcription factor nuclear factor κB;
- RAGE on endothelial cells may also function as an adhesive receptor that directly interacts with leukocyte β2-integrins, and are thereby directly involved in inflammatory cell recruitment (22).

Data available on AGEs and diabetic complications suggests three general mechanisms of action: alteration of signal transduction pathways involving ligands on extracellular matrix, alteration of the levels of cytokines, hormones, and free radicals through interaction with RAGEs, and intracellular glycation of proteins and nucleic acids that directly alters protein function (160). The binding of AGEs to monocyte receptors has been shown by investigators to induce production of IL-1, insulin-like growth factor-1, tumor necrosis factor-α, and platelet-derived growth factor (30, 138). It has been documented that the interaction of AGEs with their receptors has a potentially important role in altering cellular function via binding to cultured endothelial cells and mononuclear phagocytes (87, 124, 161). Thus, the binding of AGEs to macrophages and other cell types contributes greatly to increased cytokine production, which can lead to vascular damage such as atherosclerosis or coronary heart disease, and a more severe and progressive form of periodontal disease (77). Although the accumulation of AGEs and monocyte hypersecretion provide a plausible explanation for enhanced periodontitis severity in this high risk group, several alternative hypotheses have been proposed involving other mechanisms that could explain the periodontal disease susceptibility in patients with diabetes. These include abnormality in neutrophil chemotaxis, chronic bacterial infection

with lipopolysaccharide up-regulation of monocytes, abnormalities of T-cell activation via the Th1 response, and genetic alteration of the HLA-DR region (3, 7, 24, 32, 109). The role of these mechanisms is still not well delineated and may be particularly involved in the exacerbation of periodontal disease in the patient with diabetes. Some of these alternate mechanisms may also induce a monocytic hyper-responsiveness. However, the chronic hyperglycemic state (AGEs), systemic exposure to inflammatory molecules as a result of oral infection, and the cumulative role of these factors are the most plausible mechanism linking the presence of chronic periodontal infection with diabetic coronary heart disease and glycemic control. S100A12, also called EN-RAGE (extracellular newly identified receptor for AGE-binding protein) or calcium-binding protein in amniotic fluid-1, is also a ligand for RAGE (95). It has been shown that S100A12 induces adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in the vascular endothelial cell and mediates migration and activation of monocytes/macrophages through RAGE binding. Furthermore, infusion of lipopolysaccharide into mice causes time-dependent increase of S100A12 in the plasma (55, 72). Results from that study suggest that plasma S100A12 protein levels are regulated by factors related to subclinical inflammation and glucose control in patients with type 2 diabetes.

Recent studies have also identified potential therapies that may be effective in lowering RAGE expression in human endothelial cells, thus reducing cardiovascular complications associated with diabetes. Marx and colleagues (90) demonstrated that thiazolidinediones, antidiabetic agents used clinically to treat patients with Type 2 diabetes, can modulate endothelial RAGE expression, limiting the cells' susceptibility to the proinflammatory effects of AGEs. These data provide new information on therapies that may be beneficial against complications associated with diabetes such as coronary heart disease and potential periodontal disease in the patient with diabetes. In addition, the metabolic effects of these drugs could modulate the development of vascular dysfunction in diabetic patients (90). Other therapies under investigation include cross-link breakers, or AGE breakers, that react with and cleave the covalent AGE-derived protein cross-links. A study by Wolffenbuttel et al. (166) showed that treatment of rats with streptozotocin-induced diabetes with the AGE-breaker ALT-711 for 1–3 weeks reversed the diabetes-induced increase of large artery stiffness as measured by systemic arterial compliance, aortic impedance, and carotid artery compliance and distensibility. The effects of ALT and aminoguanidine have also been studied in a rat model of periodontitis; the results showed a reduction of the inflammatory parameters measured and demonstrated a protective effect against tissue damage associated with periodontitis (29). Future therapies such as ALT and aminoguanidine may prove useful in reducing complications such as coronary heart disease and periodontitis that are associated with diabetes.

Diabetes and periodontal disease

Historically, diabetic patients have been shown to be at increased risk for infections (73, 79, 86). Past and present studies have reported periodontal disease to be one of the most prevalent complications of diabetes (52, 61, 88, 94). The classic presentation of periodontal progression has been associated with accumulation of plaque and calculus on the tooth surfaces and potent virulence factors produced by bacteria, causing destruction of periodontal tissues and resorption of alveolar bone (83, 146). Studies demonstrating the relationship between diabetes and the association of microbial organisms for the prevalence and severity of periodontal disease have shown that the flora associated with diabetes does not appear to differ from non diabetic flora (68, 172). Comprehensive evaluation of the literature indicates that diabetes carries a two to three times higher risk for both severe periodontitis and the incidence of periodontal disease progression (152).

Over the past decade, research targeting periodontal diseases has focused on the host immune response that is triggered by bacteria found in periodontal lesions (69, 143). Components of bacteria, such as lipopolysaccharide found in their cell membranes, have been shown to be potent stimulators of cellular secretion of a variety of cytokines and growth factors via Toll-like receptor-mediated response (44, 135) Lipopolysaccharide binds to the Toll-like receptor 4 (113, 119). Downstream signaling from this interaction involves MyD88, IL-1 receptor associated kinase, and tumor necrosis factor receptor associated factor 6, which activates the IκB kinase complex (103, 163). The activation of the Toll-like receptor by bacterial products leads to the production of innate inflammatory cytokine responses, ultimately contributing to tissue damage and destruction.

In addition to virulence factors that activate the Toll-like receptor, inflammatory mediators of the

immune response appear to play an important role in the local tissue destruction observed in periodontal disease (151). Cytokines most often associated with tissue destruction following stimulation of macrophages include IL-1β, IL-6, tumor necrosis factor-α, and the lipid mediator prostaglandin E_2. These mediators are very potent in inducing major alterations in the connective or extracellular matrix tissues. Thus, the enhanced secretion of these mediators of destruction, as seen in peripheral blood monocytes isolated from diabetics, may provide one possible mechanism for increased periodontal tissue destruction seen in these patients. In diabetics, an abnormal inflammatory response to lipopolysaccharide challenge has been shown to preset monocytes, resulting in an exaggerated secretion of inflammatory lipid mediators such as prostaglandin E_2 and the cytokines IL-1β and tumor necrosis factor-α (133, 134, 143). The monocytic hyper-responsive phenotype has also been reported to occur in patients with refractory, early onset, and diabetes-associated periodontal disease and may have a genetic component (132). The severity of periodontal disease experience in diabetics might also reflect an alteration in connective tissue metabolism and subsequent impairment of wound healing (35). The diagram in Fig. 2 illustrates a possible linkage between diabetes and periodontal disease severity. Thus, local periodontal tissue destruction may be a consequence of an exaggerated monocytic inflammatory response induced by AGE accumulation and may result in increased secretion of local and systemic mediators, leading to severe periodontitis.

Potential mechanisms associated with diabetic periodontal disease progression

Nuclear factor κB is a protein transcription factor that is known to initiate the transcription of a variety of genes such as cytokines, growth factors, adhesion molecules, and immunoregulatory and acute phase proteins (13, 47). In addition, nuclear factor κB is required for maximal transcription of tumor necrosis factor-α, IL-1, IL-6, and IL-8 genes, which are thought to be important in mediating acute inflammatory responses (1, 10, 74). Transcriptional regulation is important for cytokine production, and transcriptional factors play an important role in regulating cytokine-mediated inflammation. Nuclear factor κB is also regulated by a number of reactive oxygen species. The activation of nuclear factor κB by

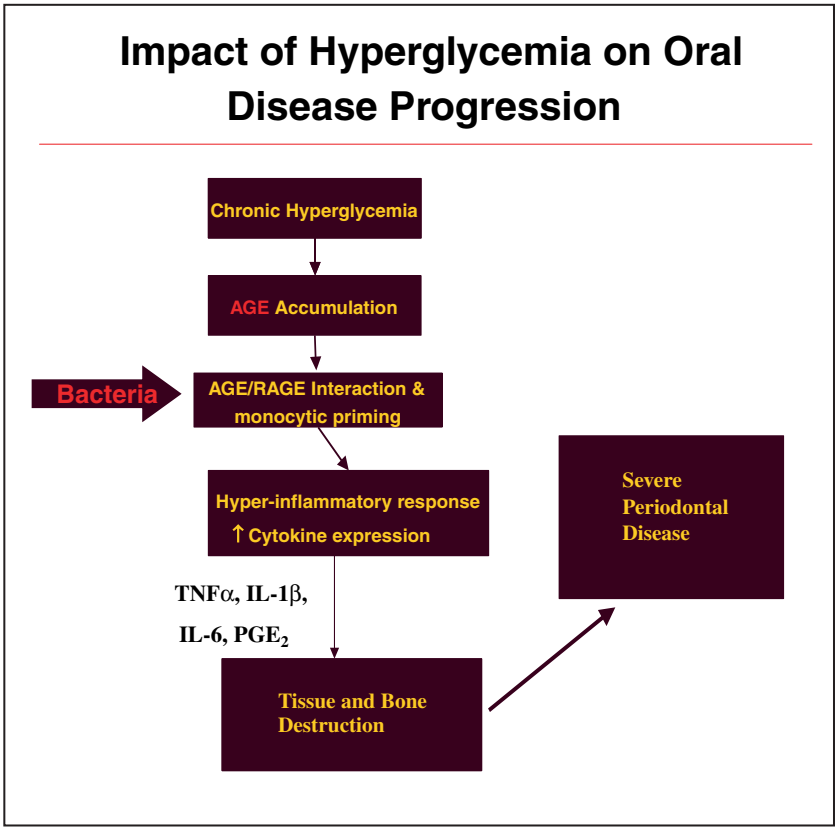

Fig. 2. Possible linkage between diabetes and periodontal disease severity. Thus, local periodontal tissue destruction may be a consequence of an exaggerated monocytic inflammatory response induced by AGE accumulation and result in exaggerated secretion of local and systemic mediators leading to severe periodontitis. AGE, advanced glycosylation endproducts; RAGE, receptors for AGEs.

hydrogen peroxide is cell-specific and distinct from cytokine activators such as IL-1 and tumor necrosis factor and is cell- and stimulus-specific, involving diverse and unexpected targets that may be distinct from redox modulation (14).

Interestingly, cell surface ligation of RAGE, the immunoglobulin superfamily cell surface receptor for AGE, modulates gene expression centrally by triggering a signal transduction cascade that converges on a nuclear factor κB and involves multiple signaling pathways, including $p21^{RAS}$, ERK 1/2 kinases [P44–P42, P38 and Sin3-associated protein–c-Jun N-terminal (SAP-JNK) kinases], and CDC42–RAC (63, 150, 169). Subsequent to this signaling, a series of phosphorylation events takes place. Nuclear factor κB-associated inhibitory molecules, IκB, retain nuclear factor κB in the cytoplasm (167). Upon phosphorylation and ubiquitination of these proteins, they become degraded by the 26s proteosome, which enables translocation of nuclear factor κB to the nucleus. Nuclear factor κB activity is mediated by a family of transcription factor subunits that bind DNA as homo- or heterodimers (31). Specific nuclear factor κB complexes in the monocyte have been identified as p50/p65 (56). In general, the subunits are identified as p50/nuclear factor κB1, p65/Rel, c-Rel, Rel B, and p52/nuclear factor κB2. Although various combinations of these subunits exist within the cell, classic nuclear factor κB is characterized by the p50/p65 subunits. The p50 and p52 units are derived from precursor molecules, the p105 and p100, respectively (12, 131). There are multiple proteins associated with this group that include IκBα, β, ε (IκBα weak association with p50 and does not stop nuclear translocation), IκBγ/p105 (serves as an inhibitor of Rel A), IκBδ/p100, and Bcl-3 (92). These inhibitors contain ankyrin repeat domains that mask nuclear factor κB nuclear localization sequences (13). A variety of stimuli have been shown to activate nuclear factor κB. These include lipopolysaccharide, tumor necrosis factor-α, IL-1β, mitogens, viral proteins, ionizing radiation, UV light, some chemical agents, and AGE (139). Once stimulated, phosphorylation, ubiquitination, and degradation of the inhibitory units follow, allowing the nuclear localization signal to be recognized and nuclear factor κB to be translocated to the nucleus (154).

Of the stimuli that activate gene transcription by nuclear factor κB, the presence of lipopolysaccharide and AGE may be very important in mediating severe periodontal destruction and systemic disease progression in diabetics. In the case of the *Cox-2* gene (the rate-limiting enzyme for prostaglandin E_2), activated nuclear factor κB is able to bind to one or both of the consensus sequences located within the Cox-2 promoter region and initiate mRNA transcription (25). This results in transcriptional up-regulation of the Cox-2 enzyme with subsequent arachidonic acid processing and increased prostaglandin E_2 levels. Elevation of prostaglandin E_2 levels in gingival crevicular fluids has been shown to be associated with periodontal disease progression and severity in diabetes patients (6, 132, 134). Unpublished studies from our group show that combined AGE and *Porphyromonas gingivalis* lipopolysaccharide stimulation of THP-1 cells results in up-regulation of nuclear factor κB and Cox-2 promoter activity over time compared to either treatment alone. In addition, we were able to demonstrate sustained IκBβ degradation and increased IKK activity compared to either treatment alone in this model. The role of nuclear factor κB in the promotion of inflammation in the diabetic patient with coronary heart disease and periodontal disease is far from being well understood but this review provides a framework for understanding the mechanism by which chronic hyperglycemia and periodontal infection may enhance inflammatory mediator expression via nuclear factor κB and facilitate oral and systemic disease progression in the diabetic patient.

Diabetes, oxidative stress, and coronary heart disease

Micro- and macrovascular diseases of the cardiovascular system present major complications in diabetics. An increased frequency of hyperglycemia and dyslipidemia in this population is thought to be a major contributor to vascular alteration and atherogenesis (48, 142). Atherosclerosis is responsible for about 75% of the deaths in diabetic patients (85), compared to 55% of all US deaths (122). The accelerated morbidity associated with coronary heart disease in diabetes has been well documented in the literature (53, 110, 162). Seventy percent of individuals with Type 2 diabetes die from premature cardiovascular disease (101). Even with this demonstrated association of diabetes and coronary heart disease, there is still much speculation about the mechanism of the atherogenic process in this group. Past investigations have implicated the advanced glycosylation process and the resultant production of oxidative stress in tissues as important mechanisms of coronary heart disease progression in diabetics

(8, 136, 139). Glycosylation of long-lived proteins occurs normally with age; however, the hyperglycemic state accelerates the process, which leads to alteration of tissue and cell function, particularly in diabetics. In addition to proteins, lipid moieties are also glycosylated and oxidized (27, 104, 112).

The metabolic syndrome has emerged as an important cluster of risk factors for atherosclerotic disease. Common features are central (abdominal) obesity, insulin resistance, hypertension, and dyslipidemia, namely high triglycerides and low high-density lipoprotein cholesterol. It has been estimated that one out of four adults living in the United States merits the diagnosis (according to the clinical criteria developed by ATP III). The presence of the metabolic syndrome is highly prognostic of future cardiovascular events. Esposito & Giugliano (34) suggest that this process may involve a number of factors such as chronic inflammation, insulin resistance, and adipose tissue. Chronic inflammation may represent a triggering factor in the origin of the metabolic syndrome: stimuli such as overnutrition, physical inactivity, and aging would result in cytokine hypersecretion and eventually lead to insulin resistance and diabetes in genetically or metabolically predisposed individuals. Alternatively, resistance to the anti-inflammatory actions of insulin would cause enhanced circulating levels of proinflammatory cytokines, resulting in persistent low-grade inflammation. A generally enhanced adipose tissue-derived cytokine expression may be another plausible mechanism for the inflammation/metabolic syndrome relationship. The role of adipose tissue as an endocrine organ capable of secreting a number of adipose tissue-specific or enriched hormones, known as adipokines, is being increasingly appreciated. Although the precise role of adipokines in the metabolic syndrome is still being debated, an imbalance between increased inflammatory stimuli and decreased anti-inflammatory mechanisms may be an intriguing working hypothesis. The proinflammatory state that accompanies the metabolic syndrome is associated with both insulin resistance and endothelial dysfunction, providing a connection between inflammation and metabolic processes that is highly deleterious for vascular functions (34). Individuals with the metabolic syndrome are at risk of developing type 2 diabetes and coronary heart disease. Of the components of the metabolic syndrome, obesity and abnormal carbohydrate metabolism are the most significant predictors of the development of diabetes (149). Dyslipidemia involving hypertriglyceridemia and low levels of high-density lipoproteins is a common finding in diabetics that is thought to be predictive of cardiovascular mortality (75, 126). Lipoproteins (low-density, high-density lipoproteins and very-low-density), particularly low-density lipoproteins, are thought to be intimately associated with the development of atherosclerosis (46, 65, 71). However, oxidized forms of these lipids are believed to be the most pathogenic forms. Oxidative stresses including products of oxidized arachidonic acid (prostaglandin E_2 and malonyldialdehyde) are potent catalytic inducers of oxidized low-density lipoprotein formation (57, 140). Infection and poor oxygen perfusion represent two potential causes of oxidative stress (80, 158, 170). The peroxidation process involving lipoproteins is thought to contribute to atheroma formation by the following interactions:

- impairment of the low-density lipoprotein receptor recognition of modified low-density lipoprotein, and cholesterol transport by high-density lipoproteins;
- stimulation of platelet aggregation, and foam cell formation;
- the formation of immune complexes and reactive oxygen species (21, 157).

The cumulative effects of these mechanisms may subsequently contribute to vascular wall injury and atherogenesis.

In conjunction with the role of low-density lipoproteins in lesion formation, glycosylation and oxidation of low-density lipoproteins (ox-LDL) have been shown to alter gene expression for several cytokines and growth hormones *in vitro* (23). The unsaturated fatty acid core of lipoproteins has been shown to be particularly susceptible to oxidative damage (65, 85). The ox-LDL molecule is cytotoxic to cells in culture and is a potent stimulator of macrophage foam cell formation (64, 100, 140). Along with direct cell injury, glycated and oxidized lipoproteins may have a role in altering tissue and cell function, in particular 'monocytic priming'. Lopes-Virella et al. demonstrated that the uptake of low-density lipoprotein-immune complexes by macrophages leads to activation and release of proinflammatory cytokines, which have been implicated in tissue destruction, especially vascular and potentially periodontal disease (82, 159). The release of these monocyte-derived macrophage mediators is not only associated with periodontitis but may also be involved in the early and later stages of atheroma formation. Transformed monocytes in advanced atherosclerotic lesions have also been shown to secrete other mediators such as interferon,

fibroblast growth factor, platelet-derived growth factor (30, 105), prostaglandin E_2 (40), proteases (102), and collagenases (111, 129). Other studies have shown that glucose-oxidized low-density lipoproteins resulted in phosphorylation of extracellular signal-regulated kinase and protein kinase B/Akt and stimulated proliferation of isolated macrophages (78). This effect was mediated by CD36 and induced by protein kinase C-dependent and phosphatidylinositol 3-kinase-dependent pathways in the study. Thus, hyperglycemia is not sufficient to stimulate macrophage proliferation in lesions of atherosclerosis or in isolated macrophages. A combination of hyperglycemia and hyperlipidemia stimulates macrophage proliferation by a pathway that may involve the glucose-dependent oxidation of low-density lipoproteins (75, 78, 127). As mentioned in the discussion of periodontal disease severity and progression in diabetics, AGEs once formed can bind to monocytic receptors (RAGEs) and alter the cell phenotype. The primed monocyte upon stimulation during an infectious challenge (i.e. by lipopolysaccharide) may produce excessive amounts of cytokines or inflammatory products. In addition to AGEs, markers of coronary heart disease such as unsaturated fatty acids and modified lipoproteins are capable of inducing a similar increase in monocytic secretion of cytokines (11, 49, 123, 144). The effects of these metabolic hormones are not only observed locally in the oral cavity but also systemically and may significantly contribute to a more progressive periodontal infection, and increased morbidity and mortality associated with coronary heart disease in the individual with diabetes.

Diabetes, periodontitis, and coronary heart disease

Periodontal infection is involved in the local destruction of underlying bone and connective tissues and, as the disease progresses, loss of the integrity of the periodontal attachment, which can result in transient bacteremias. The systemic challenge of bacterial toxin derived from periodontal lesions represents an important link between periodontitis, the monocytic inflammatory response, and metabolic dysregulation in certain disease states. Studies have implicated bacteria in the occurrence and progression of coronary heart disease as well (11, 33, 91). Cytokines common to the pathology of periodontitis, such as tumor necrosis factor-α and IL-6, have been shown to have important effects on glucose and lipid metabolism, especially following an infectious challenge or trauma (36, 37). Tumor necrosis factor-α, a proinflammatory cytokine, is well known for its systemic effects on lipid metabolism during a condition known as cachexia (96). It has been shown to interfere with lipid metabolism by increasing serum triglyceride levels primarily by stimulating hepatic lipid secretion (39). In addition to these other functions, tumor necrosis factor-α is important for signaling the release of another metabolic hormone, IL-6. Unlike tumor necrosis factor-α, IL-6 is thought to have mostly an inhibitory action in the presence of inflammation (89). However, IL-6 is considered a pleiotropic mediator and is involved in the regulation of hematopoiesis and the acute phase response (155). Because IL-6 and tumor necrosis factor-α may share a role in promoting the hyperglycemic state during an inflammatory response, it is important to account for the systemic as well as local effects of these mediators and their effect on periodontal and diabetic status. The majority of clinical and epidemiologic evidence suggests that individuals with Type 1 and Type 2 diabetes tend to have a higher prevalence of both vascular disease (43, 84, 128, 147) and more severe and rapidly progressive periodontal disease than people without diabetes (152, 156). The relationship between diabetes and coronary heart disease (2, 108, 122) and diabetes and periodontal disease is well described in the literature (42, 51, 60, 81, 99, 156, 168). Periodontal infection is also thought to have a role in cardiovascular and atherosclerotic disease progression (120) and periodontal pathogens have been identified in atherosclerotic plaques (19, 93, 121). There are components of periodontitis and coronary heart disease that are similar in terms of pathophysiology. For example, they both are multifactorial and have been associated with infectious agents and have a characteristic inflammatory component. The similarities in disease presentation and supporting evidence from epidemiologic studies suggest a possible adverse interaction between coronary heart disease and periodontal disease. The combined effect of chronic periodontitis and diabetes could potentially constitute an even greater risk for developing subclinical coronary artery disease than would be predicted by either diabetes or periodontal disease alone.

Although diabetes is well established as a major risk factor for periodontal disease and cardiovascular disease, the cellular and molecular basis for this association is not clear. It is important to determine whether the combined effect of AGEs and bacterial endotoxins exacerbates diabetic oral and systemic disease through inflammatory responses to a number

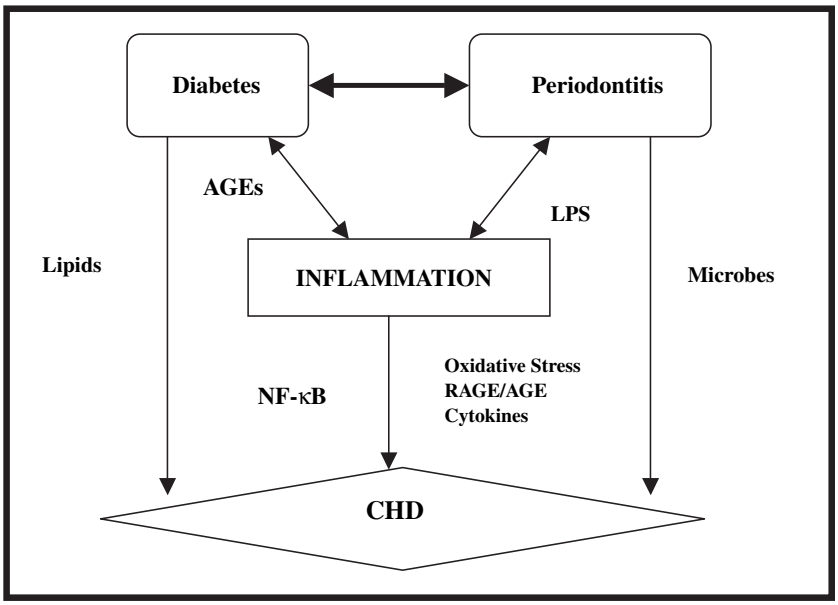

Fig. 3. Key components that need to be closely examined, placing inflammation at the core of these processes, if we are to make any progress in continuing to unravel the very complex relationship between diabetes, coronary heart disease, and periodontitis. AGE, advanced glycosylation endproducts; RAGE, receptors for AGEs; LPS, lipopolysaccharide.

of pathogenic stimuli. A bacterial infectious challenge can induce a metabolic diabetic state that is generally considered reversible. However, it is not known what metabolic changes occur when this process is not acute, but chronic and asymptomatic in nature, and occurs in an already compromised system, such as that observed in the individual with diabetes. Future studies should examine the following:

- the impact of periodontal infection on glycemic control;
- the role of periodontal disease and diabetes in development and progression of coronary heart disease;
- the molecular mechanisms that may be involved in the interaction between AGE- and lipopolysaccharide-induced hyper-inflammatory responses.

To better understand the relationship between these chronic disease processes (diabetes, coronary heart disease, and periodontitis) it is important to delineate the interactions between and among all three processes. Additional studies are needed both on an epidemiologic and on a molecular level. Fig. 3 provides an illustration of key components that need to be closely examined, placing inflammation at the core of these processes, if we are to make any progress in continuing to unravel the very complex relationship of diabetes, coronary heart disease, and periodontitis.

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