

The periodontal host response with diabetes

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In the past decade, periodontal disease has been recognized as not merely a local infectious disease, but as chronic, subclinical, inflammatory disease for the host. Diabetic subjects appear to respond to bacterial challenge in an exaggerated manner as compared with non-diabetic subjects through several possible mechanisms, and develop more severe forms of inflammatory periodontal disease. Severe periodontal disease in such subjects, in turn, acts to reduce insulin sensitivity known as insulin resistance, thereby contributing to the induction of hyperglycemia as well as hyperinsulinemia, important risk factors for diabetic vascular complications. Additionally, recent studies suggested that such subclinical inflammatory states promote renal dysfunction and diabetic dyslipidemia, both of which are important risk factors for atherosclerosis. Finally, all such conditions act to increase the risk for coronary heart diseases, the leading cause of mortality and morbidity in diabetic subjects. Thus, it appears that exaggerated host responses in diabetic subjects ultimately accelerate diabetic vascular disorders, at least partially via periodontal inflammation in subjects with severe periodontitis. The purpose of this review article is to summarize current knowledge on the bidirectional relationship between diabetes and periodontal disease as well as its complications, and to provide future strategies for prevention and treatment of periodontal disease in diabetic subjects.

Pathogenesis of periodontal disease in diabetic subjects

Type 2 diabetes has been postulated as a disease of the innate immune system (59). Evidence for increased inflammation in diabetes includes increased levels of inflammatory marker C-reactive protein (67)

as well as the proinflammatory cytokines tumor necrosis factor- α (93) and interleukin-6 (60). Mild elevation of such acute-phase inflammatory markers predicts the future development of type 2 diabetes in non-diabetic subjects (61). As for type 1 diabetes, it is well known that the pathogenesis of this disease is distinct from that of type 2 diabetes. Autoimmunity against pancreatic β -cells is the major cause of the disease. Thus, during β -cell destruction, the host immune system may be exaggerated, a state very similar to that of chronic inflammation. In fact, it is known that the level of interleukin-6 is also elevated in subjects with type 1 diabetes (77). Besides type 1 diabetes, the innate immune system is similarly activated in obese subjects, an important pre-diabetic state dramatically increasing in both Western and Eastern societies. The observed chronic inflammatory state in obese subjects is largely the result of the increased secretion of adipocytokines as a consequence of the accumulation of mature adipocytes. Several well-characterized adipocytokines are essentially the same as pro-inflammatory cytokines such as tumor necrosis factor- α and interleukin-6. Interleukin-6 is a major inducer of the acute-phase proteins such as C-reactive protein (18). In fact, tumor necrosis factor- α , interleukin-6, and C-reactive protein levels are all elevated in obese subjects regardless of the presence or absence of diabetes, and decrease with successful weight loss (37, 49). Thus, the innate immune system is activated in both type 1 and type 2 diabetics as well as in obese subjects.

What, then, is the major cause of the activated innate immune system in subjects with established diabetes? After developing diabetes, hyperglycemia appears to be a primary cause of an increased innate immune system in both type 1 and type 2 diabetes. Recently, hyperglycemia has been reported to be associated with increased activities of protein kinase

C- α and protein kinase C- β as well as in *in vitro* activities of p38 mitogen-activated protein kinase and the transcription factor nuclear factor- κ B, thereby contributing to the increased transcription and secretion of interleukin-6 (12). Hyperglycemia has also been shown to induce tumor necrosis factor- α via oxidant stress and p38 mitogen-activated protein kinase activity in monocytes (24). Enhanced superoxide release from monocytes under high glucose via protein kinase C- α is also reported (82). Additionally, increased membrane protein kinase C activities were acutely induced in normal subjects when hyperglycemia was induced in such subjects (5). Therefore, the hyperglycemia-protein kinase C axis appears to be a major cause of increased monocyte activity in diabetic subjects.

As described earlier, fat tissues accumulated in obese subjects secrete series of biologically active molecules named adipocytokines, most of which share their natures with pro-inflammatory cytokines (88). In fact, a large repertoire of inflammatory genes was identified in adipose tissue by gene expression analyses (87, 90). Recent studies suggested that macrophage infiltration into adipose tissue in obesity could be integral to these inflammatory changes (88). Adipocytes secrete low levels of tumor necrosis factor- α . This tumor necrosis factor- α then stimulates pre-adipocytes and endothelial cells to express and secrete monocyte chemoattractant protein-1, recruiting monocyte/macrophage cells into adipose

tissues (88). Recruited macrophages, in co-operation with adipocytes, secrete large quantities of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- α , leading to the formation of a vicious inflammatory cycle.

Because of the reasons above, in early stage type 1 diabetes, in the obese non-diabetic stage, which often corresponds to a pre-diabetic stage, and in the established diabetic stage with hyperglycemia, the innate immune system appears to be activated throughout the clinical course of diabetes. Interestingly, all these stages, type 1 diabetes in juveniles (45), the non-diabetic obese state (70), and type 2 diabetes in adults (53), are associated with increased prevalence of periodontal disease. Thus, activated monocyte responses in these conditions are important mechanisms that are closely associated with increased severity of inflammatory periodontal disease (Fig. 1).

Periodontal disease and insulin resistance

Inflammation has been suggested to cause increased insulin resistance (16). To date, several molecules have been demonstrated to be responsible for inducing insulin resistance, e.g. tumor necrosis factor- α (26, 27), resistin (73), and free fatty acid (3). Among these, tumor necrosis factor- α was found to

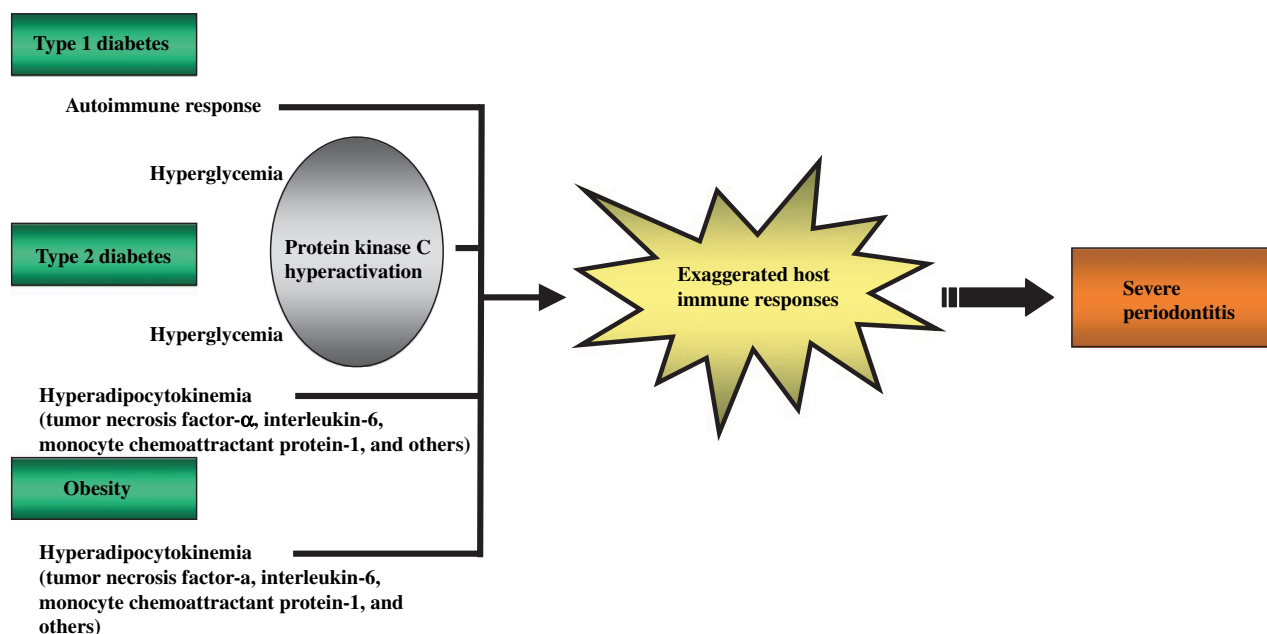


Fig. 1. Hypothetical mechanism indicating exaggerated innate immune system is a key element in inducing more severe forms of periodontal disease in type 1 and type 2 diabetic patients, and in obese subjects.

be abundantly expressed in the adipose tissues of obese diabetic subjects. Mice lacking the tumor necrosis factor- α gene as well as its receptor do not develop insulin resistance even when they are fed a high-fat diet (81). Although tumor necrosis factor- α is one of the best-characterized inflammatory cytokines causing insulin resistance, several studies have reported that interleukin-6 also causes insulin resistance (41, 69). Interestingly, interleukin-6 appears to selectively suppress insulin action in hepatocytes (36, 72).

Monocytes from diabetic subjects are pre-activated by hyperglycemia (5, 12, 24, 82). These subjects tend to develop severe periodontitis as documented. Therefore, it is possible that periodontal infection further stimulates circulating monocyte/macrophage as well as tissue-resident macrophages such as Kupffer cells. Activated circulating macrophages may be recruited to the adipose tissues as documented, and may express further increased amounts of tumor necrosis factor- α , resulting in increased insulin resistance in such subjects. Tissue-resident macrophages as Kupffer cells may also be activated by periodontal infection. Activated Kupffer cells express increased amounts of interleukin-6, leading to the stimulation of hepatocytes, which results in increased synthesis and secretion of acute-phase proteins such as C-reactive protein (18). Activated Kupffer cells also express higher amounts of tumor necrosis factor- α , resulting in increased insulin resistance in the liver. Recently, mimicking chronic, subacute inflammation by low-level activation of nuclear factor- κ B in the liver of transgenic mice has been reported to cause insulin resistance both locally and systemically (4).

Patients with severe periodontitis exhibit increased interleukin-6 and C-reactive protein levels, as compared with systemically and orally healthy controls (46). Additionally, these inflammatory markers as well as tumor necrosis factor- α levels decline with successful periodontal treatment (9, 29, 30). All these data support the fact that severe periodontal disease causes insulin resistance (54). The most probable target organ influenced by periodontal infection is hepatocytes, as it is well known that C-reactive protein is produced by hepatocytes (18). Circulating tumor necrosis factor- α may also cause insulin resistance in muscle cells (8) and adipocytes (75) as well. The role of circulating tumor necrosis factor- α on insulin resistance has also been reported in cases of gestational diabetes (89). Taken together, it is obvious that the reported beneficial effects of periodontal treatment on the metabolic

control of diabetes are mediated by improved insulin sensitivity (22).

Periodontal disease and renal dysfunction

The involvement of inflammation in renal dysfunction, especially in diabetic nephropathy (11, 19, 52), is also suggested (40). Macrophage infiltration in diabetic nephropathy has been reported (17). Monocyte chemoattractant protein-1 expression is observed in the lesions of human diabetic nephropathy (84) and intercellular adhesion molecule-1 (ICAM-1) expression was observed in the kidney of an animal model of nephropathy (74), suggesting that these tissues recruit monocytes/macrophages and that the recruited cells adhere to the tissues. The degree of macrophage infiltration is proportional to the progression of renal injury in diabetic mice (6). In addition, mice lacking ICAM-1 are resistant to renal injury after induction of diabetes (7, 55). Acute-phase inflammatory markers such as C-reactive protein are known to increase with declining kidney function even in pre-dialysis renal failure, suggesting that the innate immune system plays an important role in the pathogenesis not only of diabetic nephropathy but also of chronic kidney disease (40). Most importantly, diabetic subjects with nephropathy have a higher incidence of cardiovascular disease than those without nephropathy, and such renal failure is considered to be an independent risk factor for cardiovascular diseases in both type 1 (48) and type 2 (85) diabetic subjects.

Recently, the association between inflammatory periodontal diseases and diabetic nephropathy as well as kidney dysfunction has been reported. Subjects with renal failure, especially requiring renal dialysis, appear to develop severer periodontal diseases (51). Additionally, severe periodontal inflammation is proportional to the renal disorder in both diabetic populations (39) and in community populations including about 10% diabetic subjects (38). In diabetic subjects, the degree of periodontal infection is associated with microalbuminemia, indicating that periodontal inflammation is associated with the early phase of nephropathy (39). In the community population, periodontal disease is associated with a reduced glomerular filtration rate (38). Thus, the association between periodontal disease and renal disorders appears to be bidirectional. As described earlier, it is well known that kidney dysfunction is a risk factor for atherosclerosis that is independent of

other classic risk factors such as hyperglycemia and hyperlipidemia in subjects needing renal dialysis (44) as well as in diabetic subjects (48, 85), which will be discussed later in this chapter.

Periodontal disease and dyslipidemia

Chronic inflammation and infection may also influence lipid metabolism (34). Traditionally, sepsis caused by gram-negative bacteria has been suggested to cause abnormal lipid profiles including increased concentrations of both very low-density lipoprotein (LDL) and LDL-cholesterol (42). These authors suggested that the changes in the plasma lipoprotein composition might be attributed to altered hepatic synthesis, peripheral metabolism or hepatic uptake of lipoproteins and their remnants, indicating that hepatic function may play a key role in abnormal, infection-induced lipid profiles (42). Endotoxin itself also causes hypertriglyceridemia in an animal model (14, 20).

An association between periodontal disease and abnormal lipid profiles has also been reported. Elevated levels of triglycerides, LDL-cholesterol, and total cholesterol in severe periodontitis subjects have been reported (32, 47). In addition, a recent report indicated that intensive periodontal treatment resulted in decreased total and LDL-cholesterol levels as well as a C-reactive protein value, suggesting that periodontal infection and/or inflammation upregulates the LDL-cholesterol level (10). Furthermore, a recent report indicated that LDL particle size increased after periodontal treatment only in subjects with high serum lipopolysaccharide concentrations, indicating that periodontal treatment has a beneficial effect on highly infected subjects (62). Lipopolysaccharide is a potent stimulator for macrophage activation, leading to the increased oxidation of LDL-cholesterol as well as increased uptake of the product, which comprises an important step for foam cell formation (63). Although some previous reports indicated paradoxical effects of infection and/or inflammation on serum cholesterol concentration between primates and rodents (35), it appears, based on the previous reports, that periodontal disease upregulates cholesterol levels in humans as demonstrated. Such differences might be a feature of periodontal disease as periodontal disease is not a debilitating, direct life-threatening acute infectious disease. Rather, it is a persistent, low-grade infectious disease. Furthermore, it appears that periodontal

infection is associated not only with dyslipidemia, but also with foam cell formation, an early step in atherosclerosis, because co-incubation of some periodontal bacteria, such as *Porphyromonas gingivalis*, with macrophage in the presence of LDL-cholesterol has been reported to transform macrophage into foam cells (64).

Periodontal disease and atherosclerosis

Diabetic subjects are more prone to myocardial infarction than non-diabetic subjects (2). It is estimated that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as non-diabetic patients with previous myocardial infarction (25). Insulin resistance and hyperinsulinemia, as well as hyperglycemia, renal dysfunction, and dyslipidemia, are all independent risk factors for atherosclerosis (2). Thus, if periodontal infection acts as an important risk factor for atherosclerosis in diabetic subjects as suggested (76), the disease promotes vascular changes via several distinct, independent mechanisms (Fig. 2). This may be partially supported by the fact that strict blood glucose control alone is not enough to significantly reduce the risk of developing macrovascular disorders such as myocardial infarction and stroke in diabetic subjects (79). Recent reports indicated that inflammation plays a crucial role in developing atherosclerosis (68). An elevated level of C-reactive protein is a good predictor of the future development of coronary heart disease (66). Additionally, C-reactive protein is now considered as not merely a sensitive marker of inflammation, but as an important molecule that directly participates in the establishment of vascular lesions via several mechanisms (65). C-reactive protein promotes cell surface expression of ICAM-1 and vascular adhesion cell molecule-1 (57) as well as secretion of interleukin-6 (83) and monocyte chemoattractant protein-1 (58) in endothelial cells. C-reactive protein enhances endothelial cell sensitivity to the T-cell-mediated cytotoxicity (50). C-reactive protein also enhances smooth muscle cell proliferation and migration (86). Additionally, C-reactive protein binds to LDL-cholesterol, forming an LDL-cholesterol-C-reactive protein complex (78). This complex is easily taken up by macrophages (94), an important early step for foam cell formation. Lowering inflammation with aspirin is effective in reducing the risk of myocardial infarction, even in apparently healthy men (66),

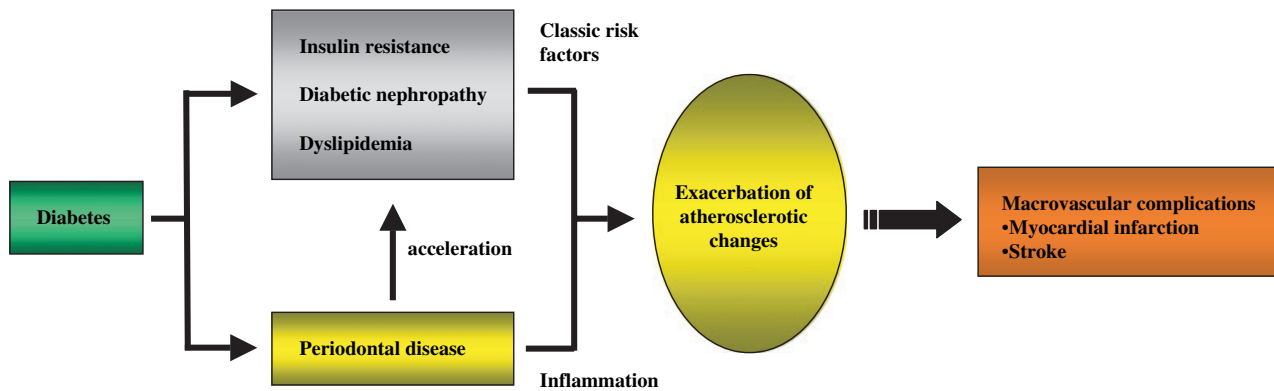


Fig. 2. Hypothetical scheme indicating periodontal disease in diabetic subjects exacerbates vascular atherosclerosis via low grade, persistent inflammation as well as via accelerating insulin resistance, diabetic nephropathy,

and dyslipidemia, all of which are known as classic risk factors. These risk factors ultimately lead to the increased risk of developing macrovascular complications such as myocardial infarction and stroke.

suggesting that anti-inflammatory therapies may be future effective therapeutic strategies in atherosclerosis-prone subjects such as diabetic subjects with severe periodontal disease.

Future strategy for the treatment of periodontal disease with diabetes

As presented, fundamental mechanisms by which diabetic and pre-diabetic obese subjects are prone to severe periodontitis appear to be in the exaggerated host immune responses, especially in high innate immune responses (Fig. 1). Periodontal infection/inflammation further exacerbates the host immune responses, leading to the acceleration of the development of diabetic complications such as nephropathy and macrovascular disorders (Fig. 2). In fact, a recent report demonstrated that severe periodontal disease is a predictor for cardio-renal death in Pima Indians with type 2 diabetes (71). Therefore, prevention of periodontal disease in diabetic patients who are at high risk for periodontitis becomes an important issue.

Recently, new medication was developed to recover insulin sensitivity for diabetic subjects with insulin resistance, especially for obese diabetic subjects. This medication, thiazolidinedione, is known as glitazone. Glitazone essentially activates nuclear receptor, peroxisome proliferator-activated receptor- γ (43). Glitazone acts to change the size of mature adipocytes from large to small, and to increase the number of small pre-mature adipocytes, thereby shutting down the expression of several genes characteristic for mature adipocytes such as tumor necrosis factor- α (56). Glitazone also sup-

presses *P. gingivalis*- and *Fusobacterium nucleatum*-lipopolysaccharide-induced interleukin-6 production in adipocytes (91). Interestingly, glitazone has been demonstrated to act as an anti-inflammatory reagent for the immune cells such as monocytes (31), and has been suggested for the possible beneficial effects in autoimmune disease such as rheumatoid arthritis (33), autoimmune encephalomyelitis (15), and autoimmune myocarditis (92). This reagent has also been suggested to ameliorate diabetic nephropathy (28). Therefore, if it is anti-inflammatory, this drug may also be beneficial for preventing the progression of periodontal disease in diabetic subjects.

Another candidate is the lipid-lowering drug, statin. Statin essentially inhibits the activity of the enzyme 3-hydroxy-3-methyl glutaryl coenzyme A reductase, which is the rate-limiting enzyme for cholesterol synthesis (23). However, the pleiotropic effect, including the anti-inflammatory effect, of this reagent is also reported (13). In fact, the possible effect of statin on the inhibition of diabetic nephropathy is reported (80). Statin lowers C-reactive protein levels, and its anti-inflammatory effect independent of cholesterol-lowering effect has been demonstrated (1). Administration of statin to diabetic mice has been reported to suppress nuclear factor- κ B activity in the kidneys as well as suppression of ICAM-1 expression and subsequent macrophage infiltration (80). Additionally, treating monocytes from patients with Crohn's disease with statin has recently been shown to lower monocyte chemoattractant protein-1 and tumor necrosis factor- α secretion, which was highly enhanced in the monocytes of Crohn's disease patients as compared with monocytes from healthy subjects, suggesting a possible strategy to reduce

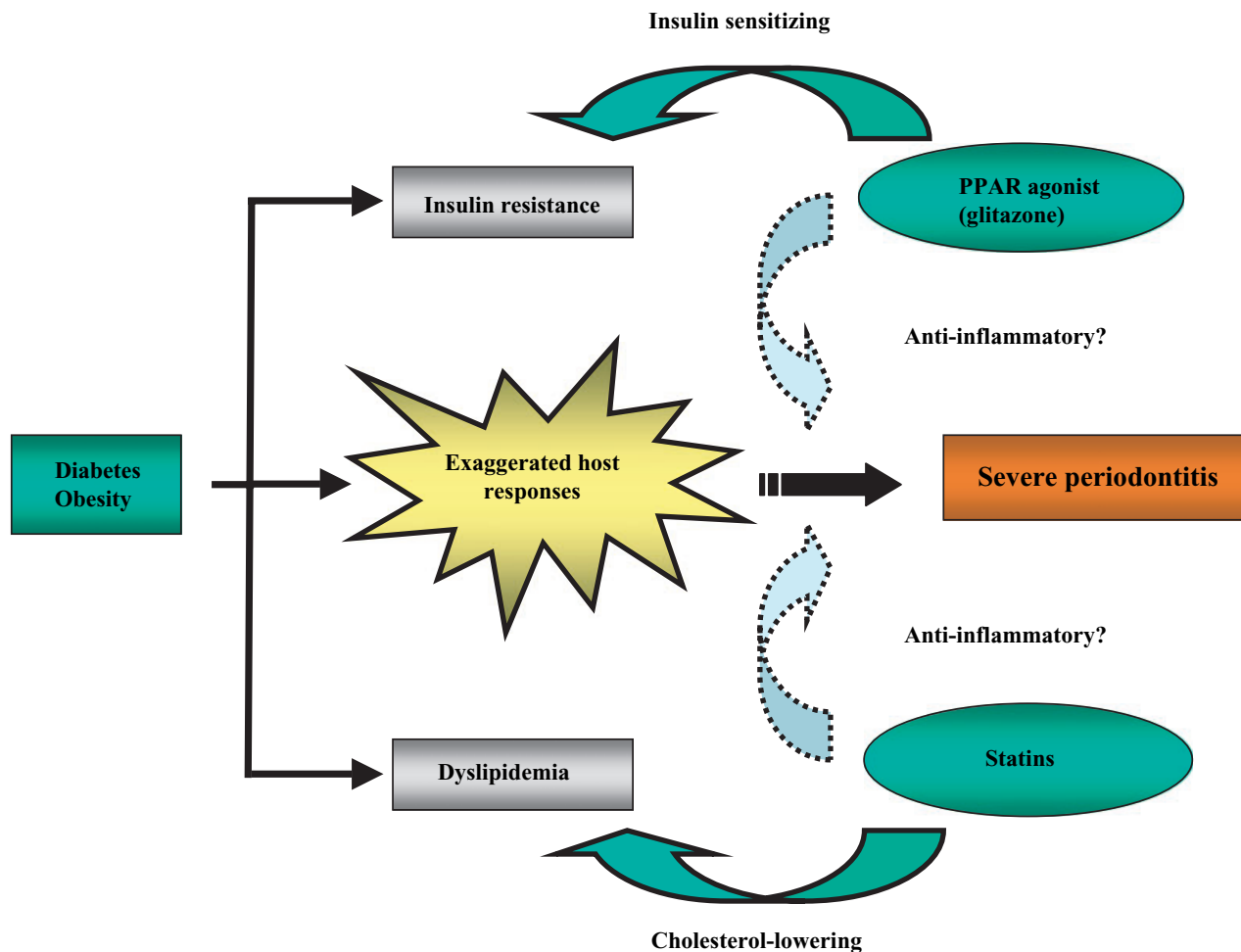


Fig. 3. If we assume that exaggerated host responses are the primary cause of developing more severe forms of periodontal disease in diabetic subjects, anti-inflammatory strategies may protect them from developing severe periodontitis. Peroxisome proliferator-activated receptor (PPAR) agonist, being marketed for treating insulin

resistance, and statins, being marketed for treating hypercholesterolemia, have been suggested to exhibit pleiotropic effects including anti-inflammatory effects. The effects of such medications on the prevention of periodontal disease would, at least partially, give an answer to the question.

macrophage migration to inflamed tissues in such subjects (21).

As these drugs are being marketed already, it would be interesting to see the effects of these drugs on the prevention of onset and the progression of inflammatory periodontal disease in diabetic patients (Fig. 3). If we assume that periodontal disease associated with diabetes is a disease of the innate immunity, such an approach would ultimately give the answer to this assumption.

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