

## Review Article

## The relation of periodontal diseases to systemic diseases

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**Background:** The relationship between systemic disorders and periodontal disease has been studied extensively. With few exceptions, it is more accurate to consider systemic diseases to be contributing factors in the pathogenesis of periodontal disease rather than the primary etiologic factors. The development of periodontal disease cannot be separated from the weakening of immunologic and immunopathological responses. Periodontal disease may enhance susceptibility to certain systemic diseases in several ways. Lipopolysaccharide (LPS) and Gram-positive bacteria in the biofilm and proinflammatory cytokines produced from inflamed periodontal tissues may enter the circulation system causing the development of certain systemic diseases. On the other hand, through immunologic mediators, certain systemic disease may enhance susceptibility to periodontal disease caused by the decrease of immune responses and the increase of proinflammatory cytokines. **Purpose:** The Purpose of this article is to review the immunologic aspect of two way relationship between systemic diseases and periodontal diseases. **Review:** This review studied the relationship between general health status, systemic diseases, and periodontal diseases through immunopathological responses and the weakening of the immune system in the periodontal tissue. **Conclusion:** there is a two-way relationship between periodontal diseases and systemic diseases.

**Key words:** periodontal disease, systemic diseases, immunological, two-way relationship

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**INTRODUCTION**

The rising of human life expectancy has made periodontal diseases and their treatment become more complex. Advanced aging and systemic diseases such as diabetes mellitus and cardiovascular diseases often lead to complications in periodontal tissue. Similarly, patients using medication on a continual basis, such as steroids, anti-coagulants or immunosuppressives often rise manifestations in the periodontal tissue or complications when carrying out actions for treatment. With regard to the increase of systemic diseases experienced by today's population, early identification needs to be done about the potential medical risks related to periodontal diseases and the success of treatment.<sup>1</sup>

The relationship between general health status, systemic diseases, and periodontal diseases has been studied intensively. With few exceptions, it has been shown that the contribution of systemic diseases to the pathogenesis of periodontal diseases is more significant than primary

etiologic factors.<sup>2</sup> The development of periodontal diseases cannot be separated from the immunopathological responses and the weakening of the immune system in the periodontal tissue.<sup>3</sup> Periodontal diseases increase the susceptibility to systemic diseases through various ways. Lipopolysaccharide (LPS) and Gram-positive bacteria in the biofilm and periodontal tissue proinflammatory cytokines may enter the circulation leading to certain systemic diseases such as cardiovascular diseases.<sup>4</sup> On the other hand, through immunologic mediators, some systemic diseases may increase the susceptibility to periodontal diseases or even make them worse. This is generally caused by the declining immune response due to the systemic diseases, while some systemic diseases result in periodontal complications or vice-versa can be explained immunologically. The article focuses on diabetes mellitus and cardiovascular diseases, in consideration that these two systemic diseases are commonly found in today's modern society.

### Immune response of periodontal diseases

The trigger of periodontal diseases is the Gram-negative bacteria on the surface of the roots of teeth, known as biofilm. Lipopolysaccharide (LPS) in the membrane of Gram-negative bacteria and other compounds increase the access to gingival tissue, at first, and give rise to immunoinflammation that causes the production of a high level of proinflammatory cytokines which then induce the metalloproteinase matrix resulting in the destruction of gingival connective tissue and periodontal ligaments. Beside that, prostaglandin as a mediator bone will be produced.<sup>5</sup> The components of the immune response to periodontal diseases include salivary IgA whose function is to eliminate attachment of bacteria colonization on the surface of teeth and mucous membrane. The neutrophil, antibodies, and complements act as bactericides, while lymphocyte, macrophage, and lymphokine act as tissue damager, as well as the immunoregulatory system that controls the immune response.<sup>4</sup> The hypersensitivity reactions that are similar in periodontal diseases are Type I – anafilaxis, Type II – cytotoxic, and Type III – immune complex.<sup>6</sup>

At the onset of periodontal diseases, adhesion and aggregation of bacteria is impeded by antibodies and complements in the fluids of the gaps in the gums at the same time dissolve it so that a reduction in the amount of bacteria occurs. When the host immune response is insufficient, the products of the following bacterial invasion will continue. In this situation, the destruction of bacteria is mediated by antibody-complements as well as chemotaxis and phagocytosis effects, especially by neutrophil polymorphonuclear (PMN) leukocytes. The damage of periodontal tissue is caused by the Type II hypersensitivity reaction, which is mediated by antibodies, cellular immune response, and tissue factor activities, such as collagenase. When the immune response is adequate, repair and fibrosis occur as a result from the fibroblast activity.<sup>3</sup>

The role of PMN neutrophil in the immune response of periodontal diseases is very important. It functions as the maintenance center for the integrity of the periodontal ligaments.<sup>7</sup> In malignant periodontal disease, the capacity of PMN neutrophil seems to decline in controlling the periodontal pathogen.<sup>8</sup> Neutrophil abnormalities, including chemotactic damage, caused deficiency in adhesiveness, and the lack of specific granules as destroyers and neutralizers of microorganisms and their products, will result in malignant periodontal disease. In addition to being a bacteria destroyer through phagocytosis, macrophage is also important in the defence system against the development of periodontal diseases.<sup>7</sup> Cytokines secretes macrophage which not only function in destroying the target cells, but also has a side effect on the host cells.<sup>9</sup> The cytokine and other biochemical compounds that are secreted by the macrophage in response

to the endotoxin stimulation, the immune-complex, or lymphokine, include interleukin-1 (IL-1), IL-6, IL-8, IL-10, Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), stimulator factors, impediments, and growth, as well as prostaglandin and cyclic adenosine monophosphate (cAMP). Collagenase macrophage has a significant role in the destruction of collagen in periodontal diseases. Other cells which play important role in immune responses of periodontal diseases are lymphocyte-T, lymphocyte-B as a precursor of plasma cells, Natural Killer (NK) and Killers (K) cells, and Mast cells<sup>7</sup> that secrete active pharmacological compounds such as histamines, slow-reacting substances of anaphylaxis (SRS-A), heparin, eosinophil chemotactic factor of anaphylaxis (ECF-A), and bradycynine.<sup>3,7</sup>

The important humoral immune response mediators in periodontal diseases are antibodies, especially IgG, and complements. However, potential mediators in inflammation including arachidonate acid derivatives, particularly prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and cytokines, particularly IL-1, IL-2, IL-4, IL-6, and TNF- $\alpha$ . All of these humoral mediators can be used as signs for diagnosis of periodontal diseases.<sup>7</sup> Cytokines are presumed to play an important role in periodontal pathologic changes. The level of IL-1 in gingival tissue and the gum-gap fluids would declined after periodontal treatment,<sup>7</sup> followed by increasing fibroblast procollagen, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and bone resorption activity.<sup>4</sup> IL-2 which stimulates macrophage activity also rises in periodontitis. The same applied to IL-4 as an activator of B cell proliferation and differentiation, growth of T cells, the function of macrophage, and growth of mast cells. The induction of antibody production, IL-6, increases its level in gum inflammation and plays a role in bone resorption.<sup>10</sup> The ability of leukocytes to adhere to endothelium cells will rise because of the TNF- $\alpha$  induction and also the phagocytosis and its chemotaxis. The effect of TNF- $\alpha$  on leukocytes and its induction against macrophage plays a role in vascular changes as occurs in periodontal diseases.<sup>3</sup>

Cytotoxicity of tissue cells can be caused by the direct interaction of lymphocyte with the target cells with specific antigens on their surface. The antigens will be responded by the lymphocyte, which is generally very specifically sensitized, the cytotoxic effect of the host cell-lymphocyte interaction is usually not specific. Therefore, it is estimated that the persistence of the tooth plaque antigen deposits in the periodontal tissue is assisted by the formation of cells that produce lymphotoxin and/or directly because of the lymphocytotoxicity. This incidence can result in tissue damage in cases of periodontal abnormality.<sup>7</sup> In this paradigm, periodontal disease represents a well-regulated response to protracted bacterial infection directed by the inflammatory cells of the host immune system (Figure 1).

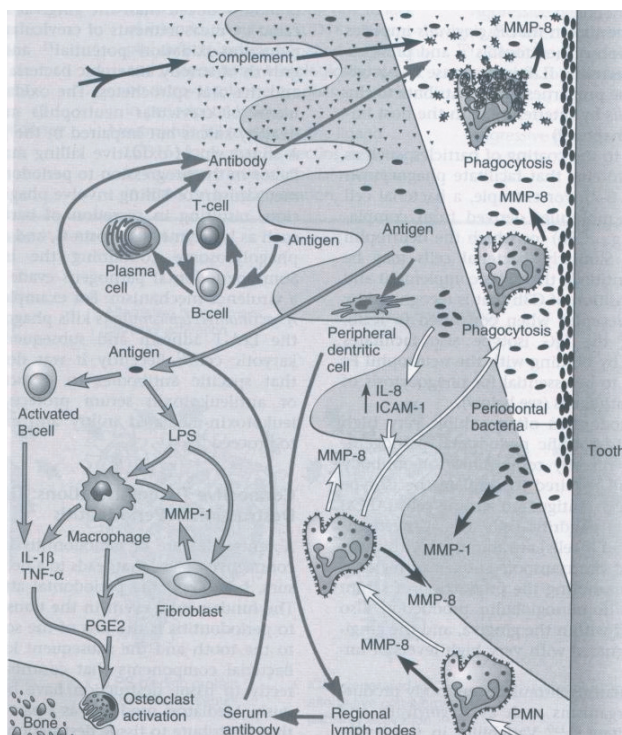


Figure 1. Scheme of the host bacterial interaction in periodontal diseases.<sup>5</sup>

### Neutrophil abnormalities

Neutrophil or PMN leukocytes play a very important role in the defence mechanism against bacterial infection. The production abnormalities and functions of neutrophil will increase the susceptibility to bacterial infection. In the body's defence system, neutrophil is the main phagocyte against extra-cellular bacteria. A person with neutrophil abnormalities, both quantitative (neutropenia) and qualitative (adhesion, chemotaxis, microbicidal activity), often had experiences with the periodontal diseases.<sup>11</sup> A PMN decrease often results in serious periodontal disease<sup>12</sup> and this has implications for its treatment process. Several periodontal diseases that are related to neutrophil can be seen table 1.

Cases showing neutrophil as a key protective cell against periodontal infection support the concept that any disturbance to the functions of neutrophil is a risk factor in the development of periodontal diseases.<sup>9</sup> In immunology, the function of neutrophil response is like a two-edged sword: the main role not only acts as protection to the host tissue, but also as a proinflammation cell that can cause tissue damage. Therefore, neutrophil dysfunction is often related to periodontal diseases, usually through the weakening of host resistance to periodontal pathogens.

### Diabetes mellitus

The relationships between diabetes mellitus and the prevalence and seriousness of periodontal diseases have long been studied. Increased periodontopathic bacteria, the dysfunction of neutrophil, increased cytokine mediators,

**Table 1.** Periodontal abnormalities related to neutrophil<sup>3</sup>

Neutrophil damage related to periodontal disease abnormalities	Periodontal abnormalities with neutrophil damage
Diabetes mellitus	Acute necrotizing ulcerative gingivitis
Papillon-Lefevre Syndrome	Local juvenile periodontitis
Down's Syndrome	Prepuberty periodontitis
Chediak-Higashi Syndrome	Rapidly progressing periodontitis
Granulocytosis due to medication	Refractory periodontitis
Cyclic neutropenia	

and changes in connective tissue in diabetes mellitus have contributions to the seriousness of periodontal diseases. Increasing periodontopathic bacteria colonies are mostly caused by weak body's defence mechanisms as a complement of hyperglycemia.<sup>13</sup> The glucose level in diabetes mellitus saliva rose evidently.<sup>14</sup> These conditions will amplify the growth of microorganisms.

The dysfunction of neutrophil in diabetes mellitus usually increases the susceptibility to periodontitis.<sup>9</sup> Chemotaxis disturbances and phagocytosis also occur in diabetes mellitus.<sup>13</sup> Diabetes mellitus depends on insulin because of the auto-immune reaction, the means being through genes that are related to the HLA-DR3, HLA-DR4, and HLA-DRQ regions. It is very interesting to note that these regions are also related to forms of progressive periodontal diseases. The disturbance of synthetic collagen together with the cellular response failure to injured tissue in diabetes mellitus can result in the slow healing of wounds.<sup>13</sup>

The two-way relationship between periodontal diseases and diabetes mellitus has been developed through a hypothetical model. The connective tissue damage in periodontal diseases is the result of the interaction of the bacteria and their products with the mononuclear phagocyte and fibroblast. This interaction will trigger inflammation mediator activity and local secretions, especially IL-1 $\beta$ , PGE<sub>2</sub>, TNF- $\alpha$ , and IL-6. The biological mechanism that causes diabetes mellitus to contract serious periodontal diseases is mediated by the accumulation of advanced glycation end product (AGE). This product is formed because glycation of protein non-enzymatically as a result of hyperglycemia. Mononuclear phagocyte will take the AGE through the receptor advanced glycation end product (RAGE) or macrophage scavenger receptor (MSR). As a result, the mononuclear phagocyte is stimulated to proliferate and induce free radicals and proinflammatory cytokines. The free radicals will directly damage the tissue, while the cytokines will activate other cell inflammation resulting in tissue damage.<sup>15</sup> In the condition of hyperglycemia, the persistence of the proinflammation

of cells that is activated will increase its adhesiveness as a result of the cytokine stimulation, which will further worsen periodontal tissue damage.<sup>13</sup>

Periodontopathic microorganism parts such as lipopolysaccharide (endotoxin), lipoteichoic acid, short chain fatty acids, and proteinase will activate the synthesis and secretion of especially IL-1 $\beta$ , PGE<sub>2</sub>, TNF- $\alpha$ , and IL-6 by mononuclear phagocyte. TNF- $\alpha$  in particular will induce insulin resistance and reduce its action. Consequently, the condition of serious hyperglycemia will occur with result that protein will be glycosylated and there will be an accumulation of AGE protein. The binding of AGE by RAGE will induce an expressive regulation of cytokine and oxidative pressure. In addition, a hydrolase secretion and metalloproteinase matrix will occur that will worsen the periodontal tissue damage.<sup>13, 15</sup>

### Cardiovascular diseases

Epidemiological studies show that one of the factors that is biologically potential as a cause of vascular disease is infection in the oral cavity have shown that there is a relationship between the bad state of oral health and cardiovascular diseases without being affected by other factors.<sup>1</sup> In the research findings, that there was a relationship between infections in the mouth and arteriosclerosis.<sup>16</sup> This has been backed up by many research reporting the relationship between periodontal and cardiovascular diseases. A long-term study over ten years, has shown that periodontal disease could be used as a predictor of cardiovascular disease.<sup>17</sup>

Periodontal disease is an additional cardiovascular disease risk factor, acting as a predispositional factor because periodontal diseases are a low degree chronic infection.<sup>18</sup> Infections are considered to be risk factors for arteriogenesis and thromboembolism. Periodontal infections and a host response that is not good will lead to chronic inflammation. An *in vitro* thrombosis model showed that certain plaque bacteria such as *S. sanguis* and *P. gingivalis* can induce platelet aggregation.<sup>19</sup> During periodontitis, plaque bacteria, particularly *P. gingivalis*,<sup>5</sup> will invade through the blood, which then infects the vascular endothelium resulting in arteriosclerosis which is a risk factor in the occurrence of ischemia and myocardial infarct. Those two disorders can also be caused by thromboembolism. *In vitro*, plaque bacteria, including *S. sanguis* and *P. gingivalis*, can induce platelet aggregation. Intravenous infusion of *S. sanguis* in rabbits caused changes in the electrocardiogram, heartbeat, blood pressure, and heart contractions. These changes are consistent with what happens in myocardial infarct.<sup>20</sup>

Meurman *et al.* (2004) developed a hypothetical model on the relationship between periodontal diseases and arteriosclerosis, heart attack diseases and stroke. From one individual to another, differences were found in responses to bacterial infections. The differences were found in the T cells and the capacity to secrete monocyte. Some individuals will respond to LPS with an inflammation

response that is reflected through release of inflammation mediators such as IL-1 $\beta$ , PGE<sub>2</sub> and TNF- $\alpha$  at a high level. Individuals with a hyperinflammatory monocyte phenotype (M $\phi$ <sup>+</sup>) will secrete these mediators 3–10 times the normal monocyte phenotype. M $\phi$ <sup>+</sup> is found in patients with early-onset periodontitis, refractory periodontitis and diabetes mellitus depending on insulin. The relationship of M $\phi$ <sup>+</sup> with periodontal infections and arteriosclerosis is mediated by cells that are one channel with monocyte and proinflammatory cytokine that have a critical role in starting and increasing the formation of atheroma and periodontal diseases. The M $\phi$ <sup>+</sup> exists because of genetic factors and environmental changes. Hyper-responsive monocyte to LPS has been mapped to be found in HLA-DR3/4 or -DQ areas that are also the regions, which can increase the susceptibility to diabetes mellitus depending on insulin. Diet that can induce an increase in Low Density Lipoprotein (LDL), such as fat, also affect the monocyte response to LPS resulting in increasing secretion of proinflammatory cytokine that can destroy tissue. Through this mechanism, an increase in the seriousness of periodontal and cardiovascular diseases will occur.<sup>21</sup>

### Hormonal imbalance

Puberty, menstruation, pregnancy, and use of contraception pills show the existence of changes in the composition of microflora in the oral cavity, both quantitatively and qualitatively.<sup>22</sup> At the same time as the decline in the immune response to periodontal pathogens, periodontal diseases will develop. During menstruation, periodic granulocytopenia is found that results in changes in the gingiva. In addition to increased levels of systemic estradiol and progesterone during pregnancy, pressure on the lymphocyte-T response result in increased anaerobic flora<sup>23</sup> that will activate cell inflammation.

### Hematological abnormalities

Hematological abnormalities that cause declines in host immune response will increase bacterial invasions in plaque to periodontal tissue. This is seen in leukemia sufferers because of the occurrence of granulocytopenia.<sup>23</sup> This is the same as what happens in immunodeficiency in cellular, humoral, combinations of cellular and humoral aspects as well as complements with various manifestations.<sup>4</sup> The most evident manifestation is in periodontal tissue in cases of Acquired Immune Deficiency Syndrome (AIDS).<sup>23</sup>

### Use of medication

Cyclosporine, an immunosuppressive that is effective for preventing rejection in kidney, heart or liver transplants,<sup>8</sup> has the side effect of selectively depressing the lymphocyte-T subpopulation and influencing the production of lymphokine, IL-1 and IL-2.<sup>6</sup> Phenacetin, which is used in the control of epilepsy, suppresses serum IgA.<sup>8</sup> Control of malignancy with chemotherapeutic substances has direct effects at the cellular level and not indirectly through myelo-immunosuppression of hematopoietic and lymphoid tissue.<sup>6</sup> Secondary immunodeficiency can also occur in

the use of various types of medicine, such as phenacetin, chloramphenicol, or anti-thyroid and anti-convulsion medicines.<sup>8</sup> Acute periodontal infection in users of these medicines occurs because of exacerbation of chronic conditions due to the increased periodontopathic bacteria during episodes of granulocytopenia.

### Stress

Resorption of the alveolar bone, degeneration of periodontal ligaments, decline of osteoblast activity, the formation of periodontal pockets, and the slow healing of connective tissue and bones can be related to conditions of stress. A weak inflammation response and low periodontium resistance accompanied by ischemia will increase the invasion of periodontopathic bacteria.<sup>6</sup> In states of chronic stress the sIgA level declines, and in states of acute stress the level rises. This is possibly caused by the increased cortisol in saliva during stress.<sup>24</sup> In addition, the rising cortisol will affect the immune response by reducing the chemotactic and phagocytic PMN response.<sup>6</sup>

### DISCUSSION

Until now, the general opinion is that systemic diseases will result in periodontal diseases. However, the new paradigm on the relationship of periodontal and systemic diseases is that there is a two-way relationship, even that periodontal diseases may cause and worsen diabetes mellitus and cardiovascular diseases. It could be said that the majority of periodontal diseases are related to the immune response and therefore every systemic disease that has implications for a decline in host immune response has a connection with periodontal disease. Besides the decline in the phagocytic amount and functions, both neutrophil and mononuclear phagocyte, proinflammatory cytokines, such as IL-1 $\beta$ , PGE<sub>2</sub>, TNF- $\alpha$ , and IL-6 that are secreted by mononuclear phagocyte, plays a big role as mediators of periodontal disease with diabetes mellitus<sup>13</sup> and cardiovascular diseases.<sup>21</sup>

The old paradigm showed that periodontal diseases are a manifestation of diabetes mellitus, but the hypothetical model recently developed<sup>13</sup> shows that periodontal diseases increase the insulin resistance so that hyperglycemia occurs and diabetes mellitus arises or is worsened. The seriousness of diabetes mellitus increases the serious of periodontal diseases. This two-way relationship is mediated by the AGE protein. The macrophage of diabetes mellitus sufferers will bind the AGE so that it activates the synthesis and secretion of local proinflammatory cytokines that lead to the destruction of connective tissue and bone resorption in periodontal diseases. Simultaneously, periodontal infection induces a chronic condition of insulin resistance resulting in hyperglycemia.

The presence of the M $\phi$ <sup>+</sup> phenotype will place certain individuals in the risk position of contracting arteriosclerosis/cardiovascular diseases and periodontal

diseases.<sup>25</sup> The critical control roles of the activity channel, LPS with microorganism and cytokine mediators, are very important in the process of the occurrence of periodontal diseases and arteriosclerosis as well as thromboembolism which is caused by infection. In addition to genetical factors, diet can exacerbate the hyperinflammatory monocyte phenotype that contributes to the occurrence of arteriosclerosis and periodontal diseases. Periodontal infections have a direct contribution on the pathogenesis of arteriosclerosis and thrombosis through continuous stimulation of LPS and proinflammatory cytokines. Periodontal pathogens themselves can also be a factor of the etiology of thromboembolism that can cause arteriosclerosis which is a risk factor in the occurrence of ischemia and myocardial infarct.<sup>21</sup>

The relationships between hormonal imbalances, hematological abnormalities, medication, and stress and periodontal diseases are more caused by pressure on the host immune response. Hormones and certain medicines, immunodeficiency, or stress will reduce the host's endurance so that the normal flora in the oral cavity will change, both quantitatively and qualitatively. The result, the development of periodontal diseases cannot be held off any longer.

Based on the matters discussed, it can be seen that periodontium tissue health cannot be separated from general health. Chronic infections in the oral cavity, particularly periodontal infections, have a wide impact. Periodontal diseases are particularly connected to the seriousness of diabetes mellitus and the increased incidence of cardiovascular diseases. The problem that remains is how dentists can convince the patients, community, and other health personnel about the relationships between periodontal diseases and diabetes mellitus and cardiovascular diseases.

In conclusion, there is a two-way relationship between periodontal diseases and diabetes mellitus: the latter causes the former and vice-versa, and the mediator is the AGE protein. The two-way relationship between periodontal and cardiovascular diseases occurs because of the similarity of pathogenesis in the critical control path of LPS activity with microorganism create cytokine mediators. In both the relationships of periodontal diseases with diabetes mellitus and with cardiovascular diseases, the head of the spear is the proinflammatory cytokines. The occurrence of periodontal diseases is because of hormonal imbalances, hematological abnormalities, medication, and stress is more caused by pressure on the host immune response.

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