

# Association of TNF- $\alpha$ , IL-1 $\beta$ with chronic periodontitis and type 2 diabetes mellitus

## Abstract

The most common endocrine disease, Diabetes Mellitus (DM), a metabolic disorder characterized by hyperglycemia, occurs due to the interaction of some environmental factors such as a high-fat diet, genetic history, and obesity. DM is classified into two categories: type-1 and type-2 DM.

- A. **Type-1 DM (T1DM):** occurs due to a reduction in insulin production as a result of autoimmune destruction of pancreatic cells, and is observed mostly in children and young adults.
- B. **Type-2 DM (T2DM):** is generally observed in adults and is characterized by the reduction in insulin resistance due to the failure in pancreatic beta cells to create a sufficient amount of insulin secretion.

Volume 6 Issue 1 - 2017

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**Received:** December 30, 2016 | **Published:** January 19, 2017

## Mini review

T2DM constitutes 70-95% of DM patients.<sup>1,2</sup> IL-1 $\beta$  levels in GCF are lower in T2DM patients with gingivitis or slight periodontitis than in patients with moderate or severe periodontitis. Also, the levels of IL-1 $\beta$  in GCF in T2DM patients were higher than in systemically healthy patients.<sup>3</sup> Clinically healthy DM patients with pocket depth of not more than 3 mm have a more common form of periodontitis and have higher levels of prostaglandin E2 and TNF- $\alpha$  than systemically healthy patients.<sup>4</sup> Microorganism toxins are known to stimulate connection epithelium cells to secrete various inflammatory mediators in IL-1 $\beta$ , IL-6, TNF- $\alpha$ , and matrix metalloproteinases (MMPs). All of these mediators may pass over the connection of epithelium and reach the GCF. The normal flora of the body blocks the development of microorganisms and may act as an effective buffer against infections.<sup>5</sup> Cytokines that pioneer inflammation, such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , play a very significant role in the initiation, regulation, and prolongation of natural immune response.<sup>6</sup> These cytokines cause vascular changes and the migration of cells such as from neutrophilia to periodontium. It is revealed that IL-1 $\beta$ , IL-6, and TNF- $\alpha$  have various activities that may cause tissue destruction, including chronic inflammation such as periodontitis.<sup>7</sup> IL-1 $\beta$ , IL-6, and TNF- $\alpha$  are the basic mediators of chronic inflammatory disease, and have the potential to destroy tissue and initiate bone loss.<sup>7,8</sup> It is revealed that IL-1 $\beta$ , IL-6, and TNF- $\alpha$  stimulate fibroblasts in cultures to produce collagenase.<sup>7-9</sup> Moreover, osteoblasts suppress alkaline phosphatase expression and matrix synthesis, and inhibit bone construction.<sup>10</sup> IL-1, which is the most powerful inducer of bone demineralization, exhibits a synergistic impact with TNF- $\alpha$  in stimulating bone resorption, as well as significant changes in collagen tissue matrix.<sup>11,12</sup> According to bone resorption trials, IL-1 $\beta$  is 100-fold more potent than TNF- $\alpha$ .<sup>13</sup> TNF- $\alpha$  molecules induce multiplication and differentiation of osteoclast pioneer cells and stimulate bone resorption by indirectly activating matured osteoclasts.<sup>14</sup> TNF- $\alpha$  also induces IL-6 production, which stimulates osteoclast formation, direct osteoclastic bone resorption, and T-cell differentiation.<sup>8</sup>

The duty of the host defense system is to protect against infectious agents. Skin and mucous membranes create physical barriers against microorganism attacks and toxins and enable host defense. The flushing impact of liquids such as saliva and GCF is removed from organisms that invade in mucosal surfaces, and enables protection with bactericidal agents. The strict epithelial barrier of gingival sulcular epithelium and connection epithelium is known to block the invasion of microorganisms and products in periodontal tissues. Besides being complements to GCF, saliva and serum act as elements of host defense.<sup>15,16</sup> As a result of an immuno-inflammatory response developed in periodontal tissue that coincides to periodontal pathogen microorganisms, an increase occurs in the construction of inflammatory cytokines (IL-1 $\beta$  and TNF- $\alpha$ ), chemotactic cytokines (IL-6), and tissue-destructive enzymes (MMPs). These proinflammatory mediators and enzymes are responsible for a great part of the destruction observed in periodontal disease.<sup>17</sup> The balance between inflammatory-anti-inflammatory cytokines and enzymes is more significant than the level of each inflammatory mediator found in periodontal tissues. The imbalance between cytokines and their inhibitors is the greatest factor responsible for the destruction of periodontal tissues.<sup>18</sup> Periodontal diseases may be defined as the inflammatory response of periodontal tissues against oral bacterial changes. Bacterial biofilm is very significant in gingival inflammation in periodontal tissues and periodontal tissue destruction. IL-1 $\beta$  and TNF- $\alpha$  are known to be cytokines that play a rather significant role in alveolar bone destruction.<sup>19</sup> Cytokines that play a significant role in periodontal diseases play a significant role in the initiation, regulation, and prolongation of natural immune response.<sup>20</sup> IL-1 $\beta$  and TNF- $\alpha$  cause vascular changes and also the migration of effector cells such as neutrophilia to periodontium. Thus, periodontal pathogens are suppressed and diminished. However, when the persistent nature of subgingival plaque combines with non-compliant cytokine response, the combination may cause inflammation and tissue destruction. The induction of primary mediators such as IL-1 $\beta$  and TNF- $\alpha$  stimulates the release of secondary mediators such as cyclooxygenase that cause the production of prostaglandins or chemokine acting as chemotactic

cytokines. This enables inflammatory response in two routes, including the release of enzymes that cause collagen tissue destruction, and the resorption of osteoclastic bone resorption. Gelatinases (MMP-2 and MMP-9) act by destroying type IV collagen, laminin, and other basal membrane components. MMP-9 is an enzyme that allows insulin degradation. High levels of glucose contribute to the activation of latent MMP-9. Also, MMP-9 cells are considered to increase T-cell proliferation.<sup>21</sup> MMP-1, MMP-8, MMP-13, and MMP-18 is included in the collagenase group of enzymes. The basic property of these enzymes is the ability to destroy type I, II, and III collagens from a special region.<sup>22</sup>

## Acknowledgments

None.

## Funding

None.

## Conflicts of interest

The authors declare there is no conflict of interests.

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