



## Role of TNF- $\alpha$ in Periodontal Disease and Its Implication on Systemic Health

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**ABSTRACT:** Periodontal disease is a polymicrobial infection, characterized by gingival inflammation, pocket formation, loss of connective tissue attachment and supporting alveolar bone. Though the etiology of periodontal disease has been established and micro-organisms have been implicated, pathology of these inflammatory lesions have been attributed not only to bacterial products, that have adverse effects on the tissues, but also to chemical mediators released by the host cells, as a result of inflammatory and immune reactions. Oral micro-organisms trigger the endogenous pathways of tissue degradation by activating host cells to produce and release inflammatory mediators and cytokines. These inflammatory mediators and cytokines manifest potent pro-inflammatory and catabolic activity and may play a key role in local amplification of the immune response as well as in periodontal tissue breakdown.

Apart from playing an important role in periodontal destruction, systemic elevation of TNF -  $\alpha$  levels is extremely toxic to the host and hence has been termed as the "Suicide hormone". TNF -  $\alpha$ , has been postulated to mediate wasting during chronic infections. This review aims to explore the role of TNF -  $\alpha$  in periodontal disease & its implication on systemic health.

**KEY WORDS:** Tumor Necrosis Factor-Alpha

### INTRODUCTION

Periodontal disease is a polymicrobial infection, characterized by gingival inflammation, pocket formation, loss of connective tissue attachment and supporting alveolar bone<sup>1</sup>. Though the etiology of periodontal disease has been established and micro-organisms have been implicated, pathology of these inflammatory lesions have been attributed not only to bacterial products, that have adverse effects on the tissues, but also to chemical mediators released by the host cells, as a result of inflammatory and immune reactions<sup>2</sup>. Oral micro-organisms trigger the endogenous pathways of tissue degradation by activating host cells to produce and release inflammatory mediators and cytokines. These inflammatory mediators and cytokines manifest potent pro-inflammatory and catabolic activity and may play a key role in local amplification of the immune response as well as in periodontal tissue breakdown<sup>3</sup>.

Among the chemical mediators released by the host cells in response to antigenic stimulus, the most important mediators that have a crucial role in the pathogenesis are cytokines. Prominent among them are interleukin - 1  $\beta$  ( IL- $\beta$ ), prostaglandin - E2 (PGE2) and tumor necrosis factor -  $\alpha$  (TNF- $\alpha$ )<sup>4</sup>. Cytokines refer to a large and diverse group of small proteins and glycoproteins that have a vast range of potent biological functions and are released from immune cells and other cells of the body, in response to virulence factors of periodontopathic bacteria. <sup>5</sup>

Currently cytokines have been classified into 6 groups Tumor necrosis factor is one among them. Tumor necrosis "family" includes 2 structurally and functionally related proteins, TNF - $\alpha$  or Cachectin and TNF -  $\beta$  or lymphotoxin. TNF -  $\alpha$  is secreted by macrophages or monocytes in response to bacterial lipopolysaccharides, including those from periodontal bacteria<sup>8</sup>.

Rossomando, Kennedy et al., 1990<sup>11</sup>, in their study have found that TNF -  $\alpha$  in GCF may be found in sites prior to clinically observable disease and therefore may prove to be a suitable indicator of periodontal disease. They suggested that TNF -  $\alpha$  may be found in sites that, if left untreated, would experience the inflammation associated with gingivitis and subsequent loss of attachment associated with periodontitis.



In Dentistry, particularly in Periodontics, tests for host - derived factors have been performed using saliva, gingival crevicular fluid, blood serum, blood cells and urine<sup>12</sup>. Gingival crevicular fluid, an exudate that can be harvested from the gingival sulcus offers a great potential as a source of factors associated with disease and destruction<sup>13</sup>.

Apart from playing an important role in periodontal destruction, systemic elevation of TNF -  $\alpha$  levels is extremely toxic to the host and hence has been termed as the "Suicide hormone"<sup>5</sup>. TNF -  $\alpha$ , has been postulated to mediate wasting during chronic infections. There is evidence that, over production of TNF -  $\alpha$  during infection leads to systemic toxicity and even death.

In the light of above mentioned facts, the present Review is designed to know the association between periodontal disease and the level of TNF -  $\alpha$ .

## CYTOKINES:

Cytokines are soluble proteins produced by various cell types, such as structural and inflammatory cells, into the extracellular fluid, where they exert their effects on the same cells (autocrine activity) or on neighboring cells (Paracrine activity) and by interacting with specific receptors<sup>14</sup>.

Cytokines play an important role in numerous biological activities including proliferation, development, differentiation, homeostasis, regeneration, repair and inflammation. Evidence has revealed that cytokines play important role not only in tissue homeostasis but also in the pathogenesis of many infectious diseases. Cytokines play crucial role in the maintenance of tissue homeostasis, a process which requires a delicate balance between anabolic and catabolic activities.

### A. CLASSIFICATION OF THE CYTOKINES<sup>14</sup>

1. They are classified into 6 groups as follows:

- Interleukins.
- Cytotoxic cytokines.
- Colony stimulating factors
- Interferons.
- Growth factors
- Chemokines.

### TUMOR NECROSIS FACTOR<sup>15</sup>:

Tumor necrosis factor "family" includes two structurally and functionally related proteins. TNF -  $\alpha$  or cachectin mainly produced by monocytes and / or macrophages and TNF-beta or lymphotoxin, a product of lymphoid cells. TNF have shown to be cytostatic and cytotoxic for neoplastic cells and they exert broad hormone like activities on various target cells including leukocytes, endothelial cells and fibroblasts. TNS are grouped among the "major inflammatory cytokines" which are characteristically produced at the sites of inflammation by infiltrating mononuclear cells. They play a beneficial role as immuno stimulants and important mediators of host resistance to many infectious agents.

### FUNCTIONS OF TNF - $\alpha$

1. TNF -  $\alpha$  is a pro inflammatory cytokine that is secreted mainly by monocytes and macrophages.
2. It induces the secretion of collagenase by fibroblasts, resorption of cartilage and bone, and has been implicated in the destruction of periodontal tissues in periodontitis.
3. It induces macrophages to secrete IL - and PGE 2.
4. TNF -  $\alpha$  activates osteoclasts and thus induces bone resorption.
5. TNF -  $\alpha$  has synergistic effects with the bone resorptive actions of IL -1  $\beta$
6. LPS from periodontal Gram negative bacteria can initiate the production of TNF -  $\alpha$  by peripheral blood monocytes, which in turn leads not only to alveolar bone resorption but also to enhance the synthesis of collagenase by human gingival fibroblasts.



7. TNF -  $\alpha$  is a cytokine that appears to have a key role in orchestrating the inflammatory response. TNF -  $\alpha$  , by affecting many target cell types, is capable of inducing a wide spectrum of proinflammatory activities and has been implicated in mediating a variety of disease states.
8. TNF -  $\alpha$  , originally defined because of its ability to induce hemorrhagic necrosis of tumors.
9. TNF -  $\alpha$  is identical to cachectin and it causes anorexia ensuing weight loss, it has pyrogenic and has catabolic effects on energy storage tissues contributing to the metabolic changes that leads to cachexia.
10. TNF -  $\alpha$  plays an important role in a activation of neutrophils. It mobilizes the mature neutrophils from bone marrow into the peripheral blood. It results in enhanced adherence of neutrophils to endothelial cells by the regulation of expression of cell surface molecules both on neutrophils and on vascular endothelial cells.
11. TNF -  $\alpha$  is involved in the endotoxin induced disseminated intravascular coagulation responsible for hemorrhagic necrosis of tumors.
12. TNF -  $\alpha$  can induce the antiviral effect, which is mediated by IFN-  $\beta$
13. TNF -  $\alpha$  plays an essential role in septic shock induced by LPS or live bacteria.
14. TNF -  $\alpha$  has many parasitocidal and bactericidal activity.
15. TNF -  $\alpha$  plays an important role in graft versus host reaction and graft rejection.
16. Injection of TNF -  $\alpha$  has been found to enhance glomerular damage in some forms of experimental glomerulonephritis.
17. TNF -  $\alpha$  has shown to take part in autoimmune diseases like systemic lupus erythematoses, diabetes in mice.

#### TNF - $\alpha$ IN PERIODONTAL DISEASE

TNF -  $\alpha$  is a proinflammatory cytokine that is secreted mainly by monocytes and macrophages. It induces the secretion of collagenase by fibroblasts, resorption of cartilage and bone, and has been implicated in the destruction of periodontal tissues in periodontitis<sup>14</sup>.

In resting macrophages, TNF -  $\alpha$  induces the synthesis of IL - 1 and PGE 2, also activates osteoclasts and thus induces bone resorption<sup>5</sup>. TNF -  $\alpha$  has synergistic effects with the bone resorptive actions of IL - 1  $\beta$ <sup>5</sup>.

Lipopolysaccharide obtained from periodontal Gram negative bacteria can initiate the production of TNF -  $\alpha$  peripheral blood monocytes, which in turn leads not only to alveolar bone resorption but also to enhanced synthesis of collagenase by human gingival fibroblasts to degrade collagen. TNF -  $\alpha$  has been shown to induce the secretion of collagenase, PGE2 and interleukin - 6 by human fibroblasts and bone culture cells<sup>10</sup>.

Both IL - 1  $\beta$  and TNF -  $\alpha$  have been demonstrated in increased amounts in GCF at periodontal disease sites and in periodontal tissues of patients with different forms of disease<sup>10</sup>

Meyle - J 1993<sup>8</sup>, has reported that serum levels of TNF -  $\alpha$  were found to be elevated in patients with periodontitis. A recent report has shown that specific local blockage of IL - 1 and TNF -  $\alpha$  significantly reduced periodontal destruction in a monkey periodontitis model<sup>4</sup>. Matsuki et al<sup>16</sup>, used in situ hybridization and immunohistochemistry to show that TNF -  $\alpha$  mRNA was abundant in macrophages and T-cells of the gingival tissues of patients with moderate to severe periodontitis.

These findings support the hypothesis that TNF -  $\alpha$  could provide a mechanistic bridge between the inflammatory process and tissue destruction.

#### DISCUSSION

Periodontitis is characterized by inflammatory destruction of connective tissues, loss of periodontal attachment and resorption of alveolar bone<sup>1</sup>. Cytokine synthesis and release by cells in the affected tissues possesses bioactivities, which are consistent with a causative or contributory role in the destruction of bone and connective tissue in periodontitis<sup>48</sup>. Several cytokines have been detected in GCF and gingival tissues of patients with periodontitis, reflecting the possibility of evaluating the contents of GCF as "Indicators" or "Markers" of periodontal disease<sup>2</sup>.



## CONCLUSION

TNF -  $\alpha$ , in GCF is a result of localized phenomenon arising out of inflammation and cellular destruction within the periodontium and serum levels of TNF -  $\alpha$ , may be the result of systemic “Spill” of cytokine via the circulation.

The above mentioned observations suggest that, there is a positive association between periodontal disease and TNF -  $\alpha$ , level in GCF and serum and that there is a possibility of using the levels of TNF -  $\alpha$ , in GCF as a “marker” of periodontal disease.

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