Endothelin-1 in Periodontal Diseases: A Mini-Review

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ABSTRACT

Endothelin-1 (ET-1) is a 21 amino acid peptide and is a potent vasoconstrictor produced by endothelial cells. It plays a role in the development of diseases such as hypertension and atherosclerosis. Reports have suggested the identification of ET-1 in chronic periodontitis and gingival overgrowth. Thus, there is a need to appraise the role of ET-1 in periodontal disease. Further research is needed to confirm its use as a biomarker and to incorporate endothelin-antagonists in periodontal therapy.

KEYWORDS: Endothelins, endothelin-1, cytokines, chronic periodontitis, gingival overgrowth

INTRODUCTION:

Endothelins were originally identified by Yangisawa in 1988. It is of three different sub-types which include ET-1, ET-2 and ET-3. ET-1 is the most common type of endothelin seen in humans. It is a peptide of 21 amino acid residues and is a potent vasoconstrictor. It is mostly secreted by endothelial cells, epithelial cells, macrophages, smooth muscle cells and fibroblasts. It is involved in various diseases such as cardiovascular diseases, atherosclerosis, hypertension, inflammatory and sclerotic diseases.

Chronic Periodontitis is a host mediated inflammatory disease which is provoked by pathogenic microorganisms, and is characterized by elevated levels of various cytokines and inflammatory mediators. Drug induced gingival overgrowth is seen as one of the side effects elevated in patients receiving cyclosporine, phenytoin and nifedipine. Studies have reported an expression of ET-1 in these periodontal diseases. Thus, a need to assess the role of ET-1 in periodontal disease arises. This review aims to evaluate the role of ET-1 in periodontal disease.

Endothelin-1 in periodontal health and disease:

The concentration of ET-1 has been estimated in both human and animal studies. Various human studies had shown increased levels of ET-1 in chronic periodontitis and one animal study was found to show increased levels of ET-1 mRNA expression. The reasons for the elevated endothelin levels in diseased groups than the healthy groups can be attributed to various factors.

One among these factors could be due to Porphyromonas gingivalis (P. gingivalis), a key pathogen causing chronic periodontitis. In the study by Shuji Awano et al it has been found that a novel endopeptidase gene from P. gingivalis called as PgPepO was similar in structure and function with endothelin-convertase-1 (ECE-1). ECE-1 is responsible for conversion of big ET-1,-2 and -3 to ET-1,-2 and-3 respectively. Similarly, an in vitro study by Toshihiro et al showed up-regulated mRNA expression of ET-1 on exposure to P. gingivalis strains. Cross-sectional studies by Yamamoto et al, Fujioka et al, and Toshihiro et al, also revealed an elevated ET-1 expression in diseased condition compared to healthy controls.

Elevated expression of proinflammatory cytokines in periodontitis may play a role in the expression of ET-1. Fujioka et al found that the exposure of the cell lines with interleukin-1β (IL-1β) and transforming necrosis factor-α (TNF-α) enhanced the expression of ET-1 and its receptors. The results were concurrent with the study by Tetsuya et al, where a positive correlation existed between the concentrations of ET-1 and IL-1β in gingival tissues. The findings by Lester et al also revealed a positive correlation between ET-1 and IL-6, IL-18, TNF-α. Another study by Endo et al found an up-regulation of ET-1 as a result of IL-1β, -6 and -8 in cultured porcine respiratory epithelial cells.

It has also been reported that certain anti-inflammatory cytokines

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play a role in the inhibition of ET-1 expression. The study by Lester et al revealed a negative correlation of angiopoietin-1 with ET-1 and gingival inflammation. [9] A study by McCarter et al suggested that the anti-inflammatory action of angiopoietin-1 was played a key role in the inhibition of ET-1 secretion, which dampened the proinflammatory cytokine synthesis. [14]

Another anti-inflammatory cytokine which can play a role in the expression of ET-1 is nitric oxide (NO). In blood dynamics, the balance between NO and endothelin system is an important factor. Nitric oxide has biologic function to inhibit endothelin levels. During periodontitis, it is seen that nitric oxide is relevantly increased, but due to development of reiterative infection, the levels are much lower than endothelin levels, and this leads to pathological changes. In the study by Chen et al, it was found that the expression of ET-1 was increased significantly in the gingiva of chronic periodontitis compared with healthy gingiva. This could be due to continuous relapsing inflammation which could stimulate endothelial cells to synthesize and release endothelin, causing a vessel constriction and injuring endothelial cells, causing a further increase in release of endothelin. This suggests the role endothelin plays in amplifying inflammation in chronic periodontitis. [10]

Another factor which influences the expression of ET-1 is mechanical strain. In the study by Fen Guo et al, mechanical strain was able to upregulate ET-1 expression in gingival fibroblasts which increased its proliferative capacity. He further assessed the synthesis of ET-1 between dermal and gingival fibroblasts. He concluded that the ET-1 synthesis was much lowering in gingival compared to dermal fibroblasts, which explains the absence of scar formation in the oral cavity. [15]

Only one study showed no detection of ET-1 in gingival crevicular fluid samples in healthy, gingivitis and chronic periodontitis groups. The inability to detect ET-1 could be due to the rapid degradation by microbial and host derived proteases, short plasma half life of 1.5 min and a heterogeneous study population. Other reason was the absence of free form in the gingival crevicular fluid due to the binding of ET-1 to its receptors in the gingival tissues. [16]

It is found that two studies estimated the influence of ET-1 on inflammatory mediators and other cytokines. A study conducted by Tetsuya et al demonstrated that the ET-1 in human periodontal ligament fibroblasts and human oral epithelial cell lines stimulated the IL-1β mRNA expression and protein release in a dose dependent manner. [8] Chronic periodontitis reflects an underlying constant inflammatory condition which is established by an ET-1-IL-1β inflammatory loop which is independent of the original stimulus. A similar model was suggested by Mullol J et al in nasal sinusitis, where an inflammatory loop was established, by interplay of ET-1 and IL-1B. [17] Another study by Li Liang et al, demonstrated that ET-1 induced proinflammatory cytokine such as TNF-α, IL-1β and IL-6 expression acted via mitogen activated protein kinase (MAPK) pathway. [14] Extracellular signal-regulated protein kinase (ERK) 1/2 inhibitor showed the pronounced reducing effects on TNF-α, IL-1B, and IL-6 expression, c-Jun N-terminal kinase (JNK) inhibitor demonstrated the decreasing effect on TNF-α and IL-1β expression, whereas p38 inhibitor showed the reducing effects on IL-1β and IL-6 expression. He collectively concluded that each cytokine acted via a specific variant of MAPK pathway. [18]

A total of eight studies estimated the cells which express ET-1 in the periodontium. ET-1 expression on fibroblasts was most studied, with six studies showing increased expression by gingival and periodontal fibroblasts. [6, 8, 15, 19, 20, 23] Other cells which express ET-1 include periodontal ligament cells as shown in two studies, [8,18] epithelial cells as shown in two studies, [7,9] vascular endothelial cells as shown in one study, [10] and human gingival keratinocytes as shown in one study. [8] Among the various cells which express ET-1, human gingival keratinocytes showed the strongest expression compared to fibroblasts and other periodontal ligament cells. [8]

One study assessed the influence of treatment on secretion of ET-1. Thomas Beiker et al, found that following periodontal therapy the proinflammatory cytokine profile fell within a normal healthy range, which led to a decreased expression of ET-1. [23]

**Endothelin-1 in Drug-Induced gingival overgrowth:**
Gingival overgrowth is seen as one of the side effects observed in patients receiving, cyclosporine, phenytoin and nifedipine. It has been found that these drugs also play a role in elevating ET-1 levels during the pathogenesis of drug-induced gingival overgrowth. [19, 20, 21, 22]

The effects of phenytoin and nifedipine have been studied in the in-vitro study by Nozomi et al. [21] It has been found that above drugs can induce angiotensin-II (ANG-II) and ET-1 secretion in cultured porcine gingival fibroblasts. Phenytoin and nifedipine prevent calcium accumulation in juxtaglomerular cells which in turn increase renin secretion. Renin mediates the conversion of angiotensinogen to ANG-I which in turn is converted to ANG-II by the action of angiotensin converting enzyme. ANG-II acts as a potent hypertrophic agent and is known to stimulate ET-1 secretion from endothelial cells. [24,25] This mechanism was substantiated by the results of latter part of Nozomi’s study where they found an increased cell proliferation in fibroblast cultures when treated with ANG-II and ET-1. It has been
shown by Yangisawa et al that cyclosporine indirectly stimulated renin-angiotensin and thereby leads to an increase in ET-1 levels.\[1\] It is also found that cyclosporine can indirectly induce the ET-1 stimulation by inducing the synthesis of ANG-II. This could be the direct mechanism by which ET-1 play a role in the pathogenesis of drug-induced gingival overgrowth.

Second possible mechanism is through mast cell chymase as suggested by Toyoda M et al.\[26\] Mast cell chymase are elevated in drug induced gingival overgrowth and tends to replace endothelin-converting enzyme which converts big endothelin to ET-1.

An indirect mechanism by which ET-1 is expressed in drug-induced gingival overgrowth is by the upregulation of proinflammatory cytokines as a result of P.gingivalis infection.

In the study by Chin YT et al, it was suggested that the mRNA expression of ET-1 presented a biphasic nature where increasing concentrations of cyclosporine, induced increased ET-1 expression up to a point after which it started to decrease.\[19\] However, a clear reasoning for this effect has not been discussed.

Limitations and Future Implications:
The available literature on ET-1 in periodontal disease is limited to in vitro and cross sectional studies which are of lower levels of evidence. More number of long term association and interventional studies are required to establish it as a diagnostic and prognostic marker for periodontal disease (Table 1).

Table1: Present state and future considerations of ET-1

<table>
<thead>
<tr>
<th>Present state</th>
<th>Future consideration</th>
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<tbody>
<tr>
<td>1. In vitro, experimental animal studies, cross-sectional studies are mainly present.</td>
<td>More number of long term association studies is required to establish it as the diagnostic and prognostic marker. Intervventional studies incorporating ET-antagonists in periodontal therapy can be done.</td>
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<td>2. Heterogeneous population was studied.</td>
<td>A homogenous population should be selected.</td>
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<td>3. Baseline values of ET-1 were not estimated.</td>
<td>A baseline value for each disease state should be estimated.</td>
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<td>4. Techniques and samples used for measurement varied.</td>
<td>A common standard and sensitive technique and sample should be developed for assessment.</td>
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CONCLUSION:
From this review, we can conclude that, ET-1 plays a role in the pathogenesis of chronic periodontitis and drug induced gingival overgrowth. But, to use ET-1 as a marker needs to be proved by further longitudinal and interventional studies. Further studies can be done to incorporate ET-antagonists in periodontal therapy.

Conflict of Interest:
The authors declare no conflict of interest.

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