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VASCULAR ENDOTHELIAL GROWTH FACTOR, DIABETES MELLITUS AND PERIODONTAL DISEASE INTERRELATIONSHIPS - A REVIEW

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ABSTRACT

Vascular endothelial growth factor a 46 KD homodimeric glycoprotein is an endothelial – specific growth factor. Periodontitis is an infection of highly vascularised supporting tissues. Diabetes mellitus is often related to increased gingival inflammation as a response to plaque accumulation. There are many reports investigating the relationship between periodontitis and diabetes mellitus and Numerous cytokines and growth factors are involved in the regulation of angiogenesis, including members of Transforming growth factor α, and Transforming growth factor ß, Hepatocyte growth factor, Tumor necrosis factor, Interleukin 8. Of all, the most potent agent that acts specifically on vascular endothelium is vascular endothelial growth factor (VEGF). This article reviews the importance and the involvement of VEGF in periodontal disease and diabetes mellitus.

KEYWORDS: Vascular Endothelial Growth Factor, Angiogenesis, Periodontitis.

INTRODUCTION

Periodontal disease is a multifactorial disease that encompasses a range of pathological and inflammatory changes to the supporting structures of the tooth namely gingival, alveolar bone, cementum, the interposing periodontal ligament and junctional epithelium.[1] Generally this inflammatory disease induces periodontal connective tissue matrix destruction, loss of fibrous attachment, alveolar bone resorption and impaired new bone formation. The disease

expression involves intricate interactions of the biofilm with the host immunoinflammatory response and subsequent alterations in bone and connective tissue homeostasis. It is considered as crucible interaction of polymicrobial, polygenic, poly immunoinflammatory fators.[1]

Periodontitis is an infection of highly vascularised supporting tissues of teeth characterized by active and quiescent periods.[2] It has been shown that there is a significant increase in the numerical density of vascular profile in the connective tissue subjacent to the altered epithelial lining of the periodontal pocket due to marked variation in angiogenesis.

Angiogenesis occurs under pathological condition contributing to the degree of inflammation as a result of the ability of new blood vessels to transport proinflammatory cells to the lesion and supply oxygen and nutrients to the inflamed tissues.

Numerous cytokines and growth factors are involved in the regulation of angiogenesis, including members of Transforming growth factor α, and Transforming growth factor ß, Hepatocyte growth factor, Tumor necrosis factor, Interleukin 8. Of all, the most potent agent that acts specifically on vascular endothelium is vascular endothelial growth factor (VEGF).[3]

Vascular endothelial growth factor a 46 KD homodimeric glycoprotein is an endothelial – specific growth factor that potently increases microvascular permeability, stimulates endothelial cell proliferation, induces proteolytic enzyme expression and the migration of endothelial cells, monocytes all of which are essential for angiogenesis. Vascular endothelial growth factor stimulates interstitial collagenase production, Von williebrand Factor release, and enhanced procoagulant ativity.[3] It induces permeability of fluids and proteins. It is 50,000 times more potent than histamine. Vascular endothelial growth factor is detectable in periodontal tissues within endothelial cells, plasma cells, macrophages and in junctional, sulcular and gingival epithelium.

Diabetes mellitus is considered as a systemic risk factor for periodontal disease. Diabetes mellitus is often related to increased gingival inflammation as a response to plaque accumulation. There are many reports investigating the relationship between periodontitis and diabetes mellitus.[4] These investigations revealed the contribution of diabetes mellitus to periodontitis and to the severity of periodontitis via its effects on vasculature, inflammatory

and immune response, alterations in collagen synthesis and genetic predisposition. It has been demonstrated that diabetes mellitus results in increased expression of vascular endothelial growth factor in numerous tissues as a response to both hyperglycemia and tissue ischemia.[5]

The mechanism and molecular involvement in the pathogenesis of diabetic microvasculopathy have suggested that Vascular endothelial growth factor has a major role in microangiopathy and causes an increased angiogenic reaponse to diabetes mellitus. Therefore, the diabetic microvascualr complications that are related to vascular endothelial growth factor includes tissue ischemia, angiogenesis and permeability in many organs, and alterations in blood glucose levels.[6]

Diabetes Mellitus may have an inductive effect on vascular endothelial growth factor levels in periodontal disease which may be an important factor in the onset of gingivitis and in its progression to periodontiitis.

With the increasing number of diabetics in an aging population the determination of vascular endothelial growth factor levels in periodontally diseased tissues of diabetic patients may be beneficial.[7]

HISTORICAL BACKGROUND

In 1983 **Senger et al** described the partial purification of a protein that was able to introduce vascular leakage when injected in the guinea pig skin. This protein was named as vascular permeability factor (VPF) and was thought to be a specific regulator of the permeability of tumor blood vessels rather than a growth factor. In 1989 **Ferrara** and **Ploiet et al** independently reported the purification to homogeneity and NH2-terminal amino acid sequencing of an endothelial cell-specific mitogen, which they named as vascular endothelial growth factor (VEGF) and vasculotropin respectively. Cloning and expression of vascular endothelial growth factor and vascular permeability factor (VPF) revealed that the activities of vascular endothelial growth factor and VPF are embodied by the same molecule. The finding that vascular endothelial growth factor is potent, diffusible and specific for vascular endothelial cells led to the hypothesis that this molecule plays a unique role in the regulation of physiological and pathological growth of blood vessels.[3]

Over the past few years several members of the Vascular Endothelial Growth Factor gene family have been identified including placenta growth factor, vascular endothelial growth

factor-B, Vascular Endothelial Growth Factor– C, and Vascular Endothelial Growth Factor-D. The finding that the loss of even a single Vascular Endothelial Growth Factor allele result in embryonic lethality points to an irreplaceable role played by this factor in the development of the vascular system. There is strong evidence that Vascular Endothelial Growth Factor is also a key mediator of pathological angiogenensis.[8]

Biological Activities of Vascular Endothelial Growth Factor

Vascular Endothelial Growth Factor promotes expression of vascular cell adhesion molecule 1(VCAM) and intercellular adhesion molecule 1 (ICAM) in endothelial cells.[5] This induction results in the adhesion of activated natural killer cells to endothelial cells, mediated by specific interaction of endothelial vascular cell adhesion molecule 1 and intercellular adhesion molecule 1 with CD 18 and very late activation antigen 4 on the surface of natural killer cells.

A 46KD Vascular Endothelial Growth Factor (VEGF) promotes endothelial cell regeneration, stimulates the formation of collateral blood vessels, increases vascular permeability, inhibits the function of antigen presenting cells, and appears to play a role in the chemotaxis of monocytes, production of tissue factors, and lymphangiogenesis.[2] Vascular Endothelial Growth Factor expression is stimulated by many factors, including hypoxia, cytokines, growth factors, and ras oncogene [cell signaling molecule] activation.[3] Specific transmembrane tyrosine kinase receptor, Flt-1 [Fms-like tyrosine kinase] bind to Vascular Endothelila Growth Factor and mediate regulation of intracellular secondary messenger pathways.

Vascualar Endothelial Growth Factor And Periodontal Disease

Booth et al 1998 investigated the presence of Vascular Endothelial Growth Factor in human periodontal tissues and gingival crevicular fluid in periodontal health and disease. Vascular Endothelial Growth Factor in tissues was localized by immunohistochemistry, GCF and unstimulated saliva by enzyme linked immunosorbent assay. Vascular Endothelial Growth Factor was detected within vasculoendothelial cells, plasma cells, neutophils, junctional, pocket and gingival epithelium and higher concentration of Vascular Endothelial Growth Factor was found in healthy sites when compared with diseased sites of periodontitis patients and explained that thisfinding with two possible reasons.[8]

Vascular Remodelling In Chronic Inflammatory Periodontal Disease

chapple et al in his study used a confocal immunoflorescence microscopy and defined vascular remodeling in periodontitis. They investigated the distribution of major angiogenic growth factors using immunohistochemisty.

There was a marked regional variation in the intensity of immunostaining for Vascular Endothelial Growth Factor with a significant reduced staining of pocket epithelium. The changes in vascularity of the periodontal connective tissues in untreated periodontitis may be, in part, a consequence of altered expression of angiogenic activity by the epithelium.[2]

Human Neutrophils As A Source Of Vascular Endothelial Growth Factor

Norton et al 1996 suggested that neutrophils produce numerous vasoactive substances that induce a variety of reversible as well as irreversible alterations in endothelial cell functions. Neutrophil- derived elastase and other proteinases appear to indirectly influence inflammatory angiogenesis. By degrading vascular basement membranes and other subendothelial matrix components, these enzymes may facilitate endothelial cell migration into wounds. Activated human neutrophils may directly modulate endothelial cell proliferation by secreting vascular endothelial cell growth factor also referred to as vascular permeability factor.[11]

Diabetes—A Risk Factor for Periodontitis, Vascular Changes

The primary causal factor in the development of vascular changes in diabetes is prolonged exposure to hyperglycemia. The fundamental structural lesion in small blood vessels is thickening of basement membrane. The basement membrane components are collagen, laminin, heparin sulphate, and fibronectin. The structure and the function of the membrane are based on complex interactions between the membrane components.

When subjected to hyperglycemic conditions, basement membrane proteins undergo non-enzymatic glycosylation (spontaneous sugar-amino acid interaction) with subsequent changes in the physical properties of basement membrances. Extravasated plasma proteins are cross-linked or "trapped" on vessel wall proteins contributing to luminal narrowing over time.

Effects in Host Response

Defects in polymorphonuclear leckocyte (PMN) function have been considered a potential cause of bacterial infection in the diabetic individual. Several studies have demonstrated

decreased chemotaxis, adherence of peripheral blood leukocytes in diabetic patients. Diabetic patients with sever periodontitis have depressed chemotaxis of peripheral blood leukocytes when compared to non diabetic patients with mild periodontitis.

Pinson et al 1995 compared the periodontal status of 26 Type 1 diabetic patients and 24 control subjects of similar age, considering the probing pocket depth, clinical attachment loss, recession as clinical criteria. The diabetic status was evaluated with glycated hemoglobin to obtain a measure of diabetic control. Comparison based on site specific measurement showed the gingival index score and plaque index score to be some what higher among the diabetics. Rest of the clinical parameters was not significantly different between diabetic and non diabetic chronic periodontitis patients.[12]

Lucarini G, Zizzi A, et al 2009 investigated the relationship between expression of angiogenic and regeneration markers and periodontal disease in subjects with/ without diabetes mellitus. Immunohistochemical detection of vascular endothelial growth factor (VEGF), CD44 an integral membrane glycoprotein involved in cell differentiation, inflammatory cell accumulation and CD133 a marker a human haemotopoitic stem cells was done. The diseased gingival of patients with diabetic chronic periodontitis had greater clinical measures of periodontal disease than those with periodontitis alone. Vascular Endothelial Growth Factor expression was significantly enhanced in epithelial and endothelial cells from patients with diabetic periodontitis compared with controls ($p<0.05$). Epithelial CD44 expression was strong in both the groups, while CD44 was significantly enhanced ($p<0.05$) in connective tissue cells of diabetic group. Stromal CD 133 expression was significantly lower in patients with type II diabetes and periodontitis and was increased in periodontitis patients ($p<0.05$).[5]

CONCLUSION

The angiogenesis that occurs both in physiological and patho;ogical conditions involves the importance of growth factors and the involvement of vascular endothelial growth factor in diabetes mellitus and periodontal disease is generally high than other growth factors.

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