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Review Article

Role of Gingival Crevicular Fluid as a Biomarker in Diabetes Mellitus Patients

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Abstract

Periodontal disease (PD) is a complication of diabetes mellitus (or diabetes mellitus). Various proinflammatory cytokines are expressed in the gingival crevicular fluid (GCF) of diabetic patients with PD. The aim of this study was to review the proinflammatory cytokinees that are expressed in the saliva, GCF and serum of diabetic patients with PD. The highlighted question which is addressed was "Which proinflammatory cytokines are expressed in the GCF of diabetic patients with PD?". Levels of interleukin (IL)-6 are higher in the GCF of diabetic patients with PD compared to healthy controls. IL-1β and tumor necrosis factor-alpha (TNF-α) are higher in the GCF of diabetic patients in PD compared to healthy controls. Weak evidence also suggested that resistin and visfatin are also dysregulated in diabetic patients with PD compared to controls. Raised levels of proinflammatory cytokines (including IL-1β, IL-6 and TNF-α) in the GCF of diabetic patients with PD may be a valuable tool in the early detection of PD. Elevated concentrations of proinflammatory cytokines in the GCF may also be indicative of "latent" diabetes mellitus in undiagnosed individuals.

Keywords: *Diabetes Mellitus; Periodontal Diseases; Gingival Crevicular Fluid; Saliva; Periodontitis; Proinflammatory Cytokines*

Introduction

Periodontal disease (PD) is a complication of diabetes mellitus (or diabetes mellitus). Various proinflammatory cytokines are expressed in the gingival crevicular fluid (GCF) of diabetic patients with PD. The aim of this study was to review the proinflammatory cytokinees that are expressed in the saliva, GCF and serum of diabetic patients with PD. The highlighted question addressed was "Which proinflammatory cytokines are expressed in the GCF of diabetic patients with PD?". Levels of interleukin (IL)-6 are higher in the GCF of diabetic patients with PD compared to healthy controls. IL-1β and tumor necrosis factor-alpha (TNF-α) are higher in the GCF of diabetic patients in PD compared to healthy controls.

Weak evidence also suggested that resistin and visfatin are also dysregulated in diabetic patients with PD compared to controls. Raised levels of proinflammatory cytokines (including IL-1β, IL-6 and TNF-α) in the GCF of diabetic patients with PD may be a valuable tool in the early detection of PD. Elevated concentrations of proinflammatory cytokines in the GCF may also be indicative of "latent" diabetes mellitus in undiagnosed individuals.

Inflammatory Mediators in GCF

GCF levels of IL-1β are known to be high in subjects with periodontitis [1-4], and even more so in subjects with diabetes mellitus [5-9]. The studies conducted by Salvi., *et al*. [5] showed comparison between the GCF levels of IL-1β, PGE2 and TNF-α in diabetics and systemically healthy subjects with varying degrees of periodontal disease severity and found that diabetics had significantly higher GCF levels of both PGE2 and IL-1β when compared to non-diabetic controls with similar periodontal status. In addition, GCF levels of IL-1β and PGE2 increased in diabetics as the severity of periodontal disease increased. Engebretson., *et al*. [7] investigated the effects of glycemic control on GCF levels of IL-1β in patients with chronic periodontitis and type 2 diabetes mellitus and found that clinical periodontal measures and measures of glycemic control (HbA1c, random glucose) were significantly correlated with GCF IL-1β. Patients with higher than 8% HbA1c showed significantly higher mean GCF IL-1β levels than patients with less than 8% HbA1c.

Andriankaja., *et al*. [9] compared the levels of serum IL-6 and GCF IL-1β and PGE2 in subjects with gingivitis and type 2 diabetes mellitus. GCF IL-1β was significantly elevated in the diabetic compared to the non-diabetic group but serum IL-6 and GCF PGE2 were not. GCF IL-1β and PGE2 levels were significantly elevated in subjects with gingivitis compared to subjects with gingival health regardless of diabetic status. However, levels of serum IL-6 was increased in subjects with gingivitis when compared to healthy subjects and was seen only among those subjects with diabetes mellitus. Kardeşler., *et al*. [10] investigated the relationship of periodontal disease in type 2 diabetics with GCF levels of PGE2 and IL-1β and in contrast to most studies, found lower IL-1β levels in the type 2 diabetic group, and similar levels of PGE2 in diabetic and non-diabetic periodontitis patients. In general, most studies report elevated levels of IL-1β in GCF from diabetic patients and increased expression of IL-1β as the severity of periodontal inflammation increases which is consistent with the hypothesis that hyperglycemia contributes to an heightened inflammatory response, and suggests a mechanism to account for the association between poor glycemic control and periodontal destruction.

Hyperglycemia-induced activation of the protein kinase C pathway leads to increased expression of vascular endothelial growth factor (VEGF) which can alter vascular permeability and angiogenesis. The increased concentration of VEGF in periodontitis [11,12] may be one of the reasons for the increased vascularization and permeability associated with periodontitis, and it may be regarded as a marker for disease severity. Prapulla., *et al*. [12] compared GCF VEGF levels in gingivitis and periodontitis patients and healthy controls and found that VEGF levels in GCF increased from health to periodontitis, and that periodontal treatment resulted in a reduction of GCF VEGF levels. The authors suggested that VEGF could act as a biomarker of periodontal disease progression.

Sakallioğlu., *et al*. [13] studied gingival tissue and GCF VEGF levels in diabetic periodontitis patients with good metabolic control compared to that of systemically healthy patients with periodontitis. This study found significantly higher VEGF levels in the gingival tissue supernatants of the diabetic group, but GCF VEGF levels were similar between the controlled diabetic and the systemically healthy subjects. Prostaglandin E2 (PGE2) is associated with periodontal disease progression and alveolar bone resorption [14]. Levels of GCF PGE2 are elevated in the presence of periodontitis and perhaps even more so in diabetic patients [5]. Offenbacher., *et al*. [15] reported significant increases in GCF PGE2 levels a few months prior to clinically evident progression of periodontal attachment loss and suggested that monitoring of GCF PGE2 levels could be of value in predicting episodes of periodontal disease progression enabling the administration of preventive therapy before the onset of tissue destruction. More recent studies of GCF PGE2 levels in diabetic patients have, however cast some doubt on the usefulness of this agent as biomarker of disease progression.

Kardesler., *et al*. [10] observed that GCF PGE2 levels in diabetics were higher than healthy controls when levels were expressed as total amount of PGE2. When GCF PGE2 levels were expressed as concentration of PGE2 was lower in GCF from diabetic subjects. These findings suggest that the differences in GCF PGE2 levels are more a function of increased volume of GCF in the diabetic rather than an increased expression of PGE2. Andriankaja., *et al*. [9] compared GCF PGE2 levels in diabetics and healthy controls during the development

of experimental gingivitis, and found that GCF PGE2 levels increased with the presence of gingivitis, but that the amount of GCF PGE2 was similar in diabetics and healthy controls.

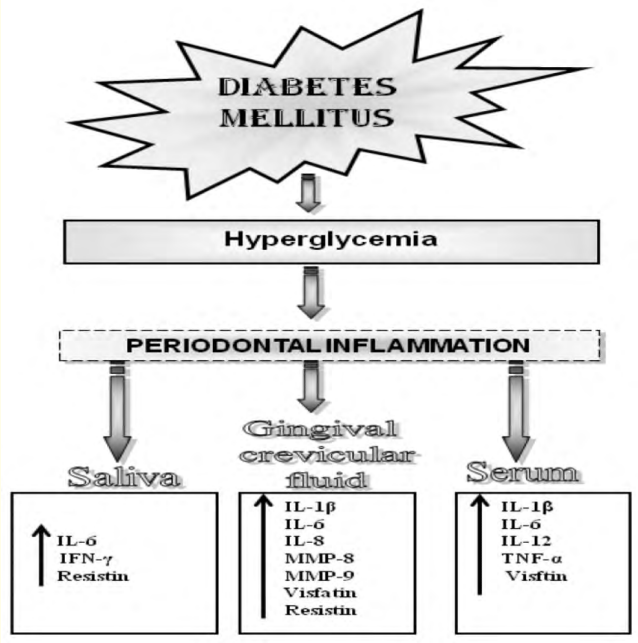

Figure 1: *Diagrammatic representation of the Cytokine Profile in the Saliva, Gingival.*

Crevicular Fluid and Serum of Diabetic Patients with Periodontal Disease

Hyperglycemia-induced activation of the protein kinase C pathway also results in increased expression of transforming growth factor (TGF)-β which leads to changes in collagen and fibronectin thereby promoting capillary occlusion. Gurkan., *et al*. [16] measured GCF TGF-β1 in several forms of periodontal disease and found that GCF levels of TGF-β1 were significantly elevated in subjects with periodontitis compared to healthy controls and that GCF TGF-β1 levels were correlated with all clinical periodontal parameters. Schierano., *et al*. [17] measured GCF levels of TNF-α, TGF-β2 and IL-1β before and after the onset of experimental gingivitis in non-diabetic subjects. Although the volume of the crevicular fluid and the GCF levels of IL- 1β increased significantly with the onset of gingivitis, TNF-α and TGF-β2 levels in GCF did not change significantly. The expression of transforming growth factor in GCF in diabetic periodontitis patients has not been reported.

Other inflammatory mediators which have been studied as potential biomarkers of periodontal disease include IL- 1α, IL-6, IL-8, IL-18, Interferon-α, and TNF-α. GCF levels of IL-1α have been shown to be increased in the presence of gingivitis and periodontitis [18-20] and to decrease following periodontal treatment [18,20]. No studies of GCF levels of IL-1α in diabetic subjects have been reported. Kurtis., *et al*. [21] compared levels of IL-6 in GCF in diabetics and healthy controls with and without periodontitis. The concentration of IL-6 in GCF was elevated in periodontitis than in healthy gingival sulci, and was elevated in diabetic patients than that of both healthy controls and non-diabetic patients with periodontitis. GCF levels of IL-8 [3,19,22], IL-18 [4] and Interferon-α [19] have also been shown to increase in the presence of gingivitis and periodontitis. In addition, the GCF levels of IL-8 have been shown to decrease following periodontal treatment [3].

However, no studies of GCF levels of IL-8, IL-18 or Interferon-α in diabetics have been reported. Studies have also investigated the potential of various components of saliva for diagnosing and evaluating the prognosis and evolution of diabetes mellitus and its oral manifestations. Borg Andersson., *et al*. [23] studied the glucose content of parotid saliva and found that salivary levels of glucose peaked at two hours following a glucose challenge and was significantly elevated in subjects with impaired glucose tolerance or diabetes mellitus, but not in healthy controls. Arana., *et al*. [24] compared markers of oxidative stress in saliva from patients with type 2 diabetes mellitus with that of healthy controls and found significantly higher glutathione peroxidase and glutathione reductase activity, and significantly lower reduced glutathione in diabetic subjects. More recently.

Gumus., *et al*. [25] also reported significantly lower reduced glutathione in diabetic subjects, but only in type 1 diabetics, and no other differences in the levels of other salivary antioxidants were observed. Possible explanations for the differences in the findings of these studies may include the fact that stimulated saliva samples were employed in one study [24], while unstimulated samples were evaluated in the other [25]. In addition, the prevalence and severity of periodontal disease differed somewhat between the two studies, as well as the methods used to diagnose and describe the degree of periodontal involvement.

Conclusion

Raised levels of proinflammatory cytokines (including IL-1β, IL-6 and TNF) in the saliva, serum and GCF of diabetic patients with PD may be a valuable tool in the early detection of PD. Elevated concentrations of proinflammatory cytokines in the saliva, serum and/or GCF may also be indicative of "latent" diabetes mellitus in undiagnosed individuals.

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