Review Article

Gingival crevicular fluid level of interleukin 1 in chronic periodontitis with diabetes mellitus

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ABSTRACT

The aim is to review the gingival crevicular fluid (GCF) level of interleukin 1 (IL-1) in chronic periodontitis with diabetes mellitus. Diabetes and periodontal illnesses show a bidirectional relationship focused on an improved provocative reaction that shows both locally and fundamentally. Periodontitis may occur in patients with and without Type 2 diabetes. GCF is an exudate that can be collected from the sulcus or periodontal pocket. Different pro-inflammatory cytokines are communicated in the GCF of diabetic patients with PD. It may be hypothesized that the GCF cytokine profile in patients with periodontitis with poorly controlled Type 2 diabetes may differ from the GCF cytokine profile in medically healthy individuals with periodontitis. IL-1β is a potent stimulator of bone resorption and has been implicated in the pathogenesis of periodontal destruction. From various studies, it was found that GCF IL-1 levels were elevated and also it was found to be a potential biomarker in patients with chronic periodontitis and diabetes mellitus.

KEY WORDS: Biomarker, Diabetes, Gingival crevicular fluid, Interleukin 1, Periodontal disease

INTRODUCTION

Chronic periodontitis, also known as adult periodontitis, is an infectious inflammatory disease caused by the bacteria of the dental plaque, resulting in the progressive destruction of the tissues that support the teeth, i.e., the gingival, the periodontal ligament, cementum, and the alveolar bone.[1] The clinical features of periodontitis include clinical attachment level, alveolar bone loss, periodontal pockets, and gingival inflammation.[2] Periodontal inflammation has a significant impact on various systemic diseases with high prevalence, incidence, morbidity, and mortality, for example, diabetes mellitus (DM) and cardiovascular diseases.[3] Diabetes is a multifactorial, hazardous perpetual illness described by a dysregulation of the endocrine and metabolic pathways associated with the control of blood glucose levels bringing about hyperglycemia.[4] In Type 1 diabetes, loss of β-cell mass in pancreatic islets of Langerhans leads to insufficient insulin release and hyperglycemia.

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DM is an important systemic predisposing factor in the etiology of inflammatory periodontal disease.[5] Periodontal disease and DM are both inflammatory diseases. Periodontal diseases along with DM induce a variety of cells including endothelial cells, fibroblasts, adipocytes, monocytes, and macrophages to release a cascade of peptides called cytokines.[6] Levels of important cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and prostaglandin E2 (PGE2) in serum, gingival crevicular fluid (GCF), and periodontal or adipose tissues have all been shown to correlate with increasing diseased states. β-cells producing IL-1β have been observed in pancreatic secretions obtained from type 2 diabetes (T2D) patients.[7] This may explain the strong two-way relationship between the diseases. Severe periodontal disease can lead to poor glycemic control; poorly controlled diabetes can increase the severity of alveolar bone loss.[8]

IL-1 is present in two active forms, IL-1α and IL-1β. IL-1 is produced by macrophage and marrow stromal cells. IL-1α is a unique member in the cytokine family which is synthesized as a 31 kDa precursor protein, ProIL-1α.[9] IL-1β is a pro-inflammatory multifunctional cytokine that is produced in large amounts by

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macrophage monocytes and may play a significant role in periodontal disease.[10] In the periodontal lesion, IL-1β has many important effects. The redness in periodontal disease is due to the capillary wall permeability that occurs in response to this cytokine. IL-1β stimulates collagenase production, which, in turn, breaks down periodontal connective tissues.[11]

Gingival crevicular liquid (GCF) is a provocative exudate that saturates the gingival hole or periodontal pockets around teeth with excited gingiva. It is a source of biomolecular sampling to investigate the condition of periodontal tissues. Thus, the detection of these biomarkers can provide current information about tissue destruction in periodontitis.[12] GCF is composed of many components that have been described as markers for periodontal disease development. These comprise host-derived enzymes, host response modifiers, and tissue breakdown products.[13] Glycemic status in Type 2 DM patients appears to adjust osteoinvulnerable incendiary mediators.[14] GCF composition may be altered by DM since it comprises the sum of components produced locally in the gingival tissues and those of other sources brought with the plasma. Thus, comparison of GCF composition analysis may provide information not only on the gingival inflammatory status but also on the systemic inflammatory response.[15]

GCF - as a Diagnostic Marker

Gingival crevicular liquid (GCF) was found in the 19th century, and its organization and oral barrier component were shown by Brill and Björn, in 1959. GCF is a physiological liquid that is delegated incendiary exudate by numerous specialists, and some propose it is an adjusted tissue transudate in an ordinary solid state. Initially, they begin from the gingival plexus of veins in the gingival corium and are subjacent to the epithelium coating of the dentogingival space.[16] It is made out of serum and privately created materials, for example, tissue breakdown items, fiery middle people, and antibodies coordinated against dental plaque microscopic organisms. The piece of the GCF is the consequence of the transaction between the bacterial biofilm follower to the tooth surfaces and the cells of the periodontal tissues. The accumulation of GCF is a negligibly intrusive system, and the examination of particular constituents in the GCF gives a quantitative biochemical marker to the assessment of the nearby cell digestion that mirrors a man's periodontal well-being status.[17]

Over 65 GCF components have been preliminarily examined as possible markers for the progression of periodontitis. These components fall into three general categories:[18]

- Host-derived enzymes and their inhibitors
- Tissue breakdown products
- Inflammatory mediators and host response modifiers.

GCF levels of IL-1β are known to be high in subjects with periodontitis and even more so in subjects with DM.[19] The studies conducted by Salvi *et al*. 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.[20] In addition, GCF levels of IL-1β and PGE2 increased in diabetics as the severity of periodontal disease increased. Engebretson *et al*. investigated the effects of glycemic control on GCF levels of IL-1β in patients with chronic periodontitis and Type 2 DM and found that clinical periodontal measures and measures of glycemic control (HbA1c, random glucose) were significantly correlated with GCF.[21]

Diabetes as a Risk Factor for Periodontal Disease

For diabetes to be acknowledged as a risk factor, it must meet the risk analysis criteria:[16]

1. Biological plausibility that the factor can cause a given disease by a known action mechanism and
2. Demonstration in prospective studies that the factor chronologically precedes the disease.

Mandell *et al*. studied the microorganisms associated with diseased sites in a group of poorly controlled diabetics and found bacterial patterns in the diseased sites of diabetics similar to those of healthy adults with periodontal disease. These sites commonly harbored *Porphyromonas gingivalis* and *Prevotella intermedia* in similar proportions to those in non-diabetic adult periodontitis patients.[17] The proportion of *P. gingivalis* was reported to be higher in non-insulin-dependent DM patients with periodontitis. It is possible that, in the diabetic patient, the abnormal host defense mechanisms in addition to hyperglycemic state can lead to the growth of particular fastidious organisms.[18] Defects in chemotaxis, phagocytosis, and killing have all been reported in diabetics. Engebreston *et al*. studied neutrophil chemotaxis in individuals with advanced periodontal disease and a genetic predisposition to diabetes.[19] Diabetes is also associated with a marked decrease in collagen production and impairments in collagen degradation. 20 poor wound healing has been repeatedly reported in diabetics and is characterized by a decrease in the amount of wound collagen and lowered tensile strength.[20]

Periodontal Disease as a Risk Factor for Diabetes

In addition to the substantial evidence demonstrating diabetes as a risk factor for poor periodontal health, there is a growing body of evidence supporting periodontal infection adversely affecting glycemic control in diabetes and contributing to increased risk

for the pathogenesis of diabetes complications.[21] The cell wall structures of Gram-negative bacteria are of major importance in the pathogenesis of periodontal disease. In light of the prevalence of Gram-negative anaerobic microscopic organisms in periodontal disease, the ulcerated pocket epithelium is thought to constitute an incessant wellspring of fundamental test from microbes, bacterial items, and privately delivered provocative middle people.[22] Periodontal small-scale living beings, specifically *P. gingivalis* and *Tannerella forsythia*, were found to build matrix metalloproteinase-9 (MMP-9) in gingival crevicular liquid and serum. The periodontal infection may build the officially lifted cytokine levels in diabetic patients and in this manner add to fundamental aggravation. Extreme arrangement and collection of AGEs in tissues are the most widely recognized reason for diabetic intricacies.[23]

GCF Levels of IL-1 IL-1 in Chronic Periodontitis with DM

Many studies have been performed to define biomarkers in GCF associated to periodontal diseases. IL-1β levels are usually higher in the CGF of patients with periodontitis.[24]

Studies by Takeda and Lamster have reported that advanced glycation end products can interact with specific receptors on gingival cells, thereby stimulating the production of pro-inflammatory proteins such as IL-6, IL-1b, and MMP. This suggests that patients with Type 2 diabetes and periodontitis have two chronic inflammatory conditions, each of which may affect the other.[25] GCF volume is normally high in periodontitis locales and tends to diminish after the periodontal treatment. Since periodontitis is related with diabetes, it is sensible to expect higher GCF volume in diabetes than in the foundationally well-being subjects, as detailed by Mootha *et al*.[26]

A study by ofenbacher, showed that GCF concentrations of IL-1α and IL-1β were similar in patients with periodontitis with and without T2D.[27] GCF concentrations of IL-1β were similar in patients with periodontitis with and without T2D in a study done by Janket *et al*., 1999.[28] The levels of IL-1β increased in accordance with progression of periodontal disease are reported by Serrano *et al.,* 2011.[29]

A study reported by Trombelli *et al*., 2001, found that IL-1α levels were higher in patients with periodontitis with T2D compared to medically healthy individuals with periodontitis.[30] The results of the study by Takeda *et al*. indicated that concentrations of GCF increased progressively from healthy to periodontitis sites, these markers reflect chronic inflammation. As the periodontal disease advances from healthy to chronic periodontitis and their levels are much in chronic periodontitis.[31] Another study by Pradeep AR *et al*. reported that GCF levels of IL-1α to be significantly higher in patients with periodontitis with Type 2 DM compared to medically healthy individuals with periodontitis.[32]

Bulut et al has reported that there was an upregulation of monocytic IL-1b in diabetic patients. Upregulation of IL-1β synthesis may be related to metabolic abnormalities of the diabetic condition. Such a change may lead to excessive production of pro-inflammatory cytokines by macrophages, thus increasing the rate and degree of tissue destruction.[33]

A study by Cutler *et al*. showed a significant reduction in GCF levels of IL-1β after periodontal treatment.[34] Similarly, another study by Navarro-Sanchez *et al*., 2007, showed a significant reduction in GCF levels of IL-1β after periodontal treatment.[35]

CONCLUSION

From various studies, it was found that GCF IL-1 profile in patients with T2D seems to be governed by the intensity of periodontal inflammation and the role of T2D, in this regard, is rather secondary. Previous studies have concluded that GCF IL-1 levels were elevated in diabetic patients with chronic periodontitis. Hence, GCF IL-1 level was found to be a potential biomarker in patients with chronic periodontitis and DM.

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