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Inflammatory Biomarkers in Chronic Periodontitis and Type 2 Diabetes Mellitus

[1]Gayathri.K, Post graduate student, Department of Periodontology SRM Dental College, Ramapuram, Chennai, Tamilnadu, India

[2]Deepa Ponnaiyan, Reader, Department of Periodontology, SRM Dental College, Ramapuram, Chennai, India

[3]Harinath Parthasarathy, Professor, Department of Periodontology, SRM Dental College, Ramapuram, Chennai, Tamilnadu, India

[4]Anupama Tadepalli, Reader, Department of Periodontology, SRM Dental College, Ramapuram, Chennai, Tamilnadu, India

Corresponding author: Gayathri.K, Post graduate student, Department of Periodontology SRM Dental College, Ramapuram, Chennai, Tamilnadu, India

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Abstract

Inflammatory mediators are considered as key players in initiating a cascade of events involved in periodontal disease. On the other hand, in systemic inflammatory diseases like Type 2, Diabetes inflammatory process leads to micro and macrovascular complications. The host-related inflammatory mediators and immune regulators were evaluated in several studies especially in chronic periodontitis and type 2 diabetes. Inflammatory biomarkers like TNF alpha, IL-1beta are most commonly related to both Diabetes and periodontitis as they possess a prominent pathogenic role in both the disease. Various adipokines are also suggested in recent studies as potential inflammatory markers. Thus, these mediators can be of great importance as reliable diagnostic prognostic markers and also as therapeutic targets. However certain recently evolved inflammatory markers may need further clarity on their specific role in periodontitis and diabetes to establish their diagnostic or prognostic potential.

Keywords: Biomarkers, type 2 diabetes, periodontitis

Introduction

Chronic periodontal disease was primarily considered as microbial origin but later, various studies focussed on the host immune aspects of the disease that paved the way for the understanding of the inflammatory process in the pathogenesis of the disease.[1] Disease pathogenesis can be netter understood by focussing on the abnormal host response to the subgingival plaque which is further influenced by the systemic inflammatory burden.[2] In that perceptive, the relationship between periodontal infection

and systemic inflammatory has a significant impact on the overall inflammatory status of an individual. Among systemic diseases, diabetes is one of the most common systemic illness and it is considered to be linked to periodontal disease by sharing common pathogenesis of increased inflammatory response.[3] Hence Periodontitis considered as the sixth complication of diabetes.[4] Persistent hyperglycaemia modulates periodontal tissue destruction by altering the function of polymorphonuclear (PMN) leukocytes, collagen and glycosaminoglycan synthesis, the formation of advanced glycation end products (AGEs), and deregulating cytokine production.[5] Similarly, Chronic periodontitis can lead to exacerbation of insulin resistance, with subsequent deterioration of glycaemic control. Thus, a complex two-way relationship has been suggested between diabetes and periodontitis with a vicious cycle that aggravates both conditions when present in the same patient.[6] Periodontal molecular research has advanced towards exploring a varied range of diagnostic biomarkers and also identifying periodontal and systemic risk factors determining the prognosis of a patient. inflammatory mediators formed due to exaggerated host response against microbial load, assumes a major role in the pathogenesis of the disease.[7] These biological mediators are used as biomarkers for diagnostic, prognostic purposes and also in the development of target therapies. To effectively implement these biomarkers in periodontal diagnosis, especially in the presence of systemic risk factors like diabetes, it is essential to understand their role in disease progression and effectiveness in modulating the biomarker levels through an intervention. Potential biomarkers in detecting the early risk of periodontitis in type 2 diabetes(T2DM) patient is still emerging and this review will provide a comprehensive insight on the recently identified biomarkers that play an important role in the pathogenesis of periodontitis and type2 diabetes mellitus.

Biomarkers

Biomarkers are defined as “A characteristic that can be measured and evaluated as an indicator of normal biological processes, pathological processes or pharmacologic responses to therapeutic interventions” (NIH Biomarkers Definitions Working Group, 1998). Most of these inflammatory mediators are expressed in the GCF and subsequently in the saliva also. Hence these markers can be studied in Salivary and GCF samples.

Gingival crevicular fluid (GCF): Gingival crevicular fluid is a physiological fluid as well as an inflammatory exudate originating from the gingival plexus of blood vessels in the gingival corium, subjacent to the epithelium lining of the dent gingival space (McCulloch 1994) As the fluid traverses from the microcirculation across inflamed periodontal tissues, it carries biological molecular markers gathered from the surrounding site. GCF is an attractive oral fluid due to its ease of collection and ability for the clinician to sample multiple sites within the oral cavity simultaneously.[8]

saliva: constituents derived from the salivary glands, gingival crevicular fluid, epithelial cells, bacterial proteins make up for the major composition whole saliva. In the presence of inflammation, exudative GCF and mucosal secretions. [9]

Biomarkers can be broadly grouped according to their sources.[10]

1.Inflammatory Mediators: Cytokines, Interleukins, Tumor necrosis factor-α, Interferon-α, Prostaglandin E2, matrix metalloproteinase, transferrin, C-reactive protein, etc

2. Host Derived: Aspartate Aminotransferase, Elastase, Cathepsin-G, b-glucuronidase, Alkaline phosphatase, Acid phosphatase, Myeloperoxidase

3. Lysozyme Connective Tissue Breakdown Products: Collagen-telopeptides, Osteocalcin, Proteoglycans, Breakdown products, Fibronectin fragments.

Inflammatory mediators as biomarkers in periodontitis and type 2 diabetes

Periodontal inflammation begins with an initial increase in the blood flow, enhanced vascular permeability and progresses to established stages due to the influx of inflammatory cells (neutrophils and monocytes-macrophages) from the peripheral blood to the gingival crevice. Subsequently, Bacteria induce tissue destruction indirectly by activating host defense cells, majorly T cells and B cells appear at the infection site and these cells produce a myriad of cytokines, which in turn release mediators that stimulate the effectors of connective tissue break down. These mediate the inflammatory process and acts as markers of inflammation. Literature evidence on different biological markers such as C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha), and prostaglandin (PGE2), that establishes a link between periodontal diseases and various systemic conditions have been extensively studied. Some of the established and recently discovered Inflammatory biomarkers related to diabetes and periodontitis are discussed below:

Tumour Necrosis Factor-alpha: In periodontal disease, microbial components like

lipopolysaccharide (LPS) can activate macrophages leading t to activation of tumor necrosis factor-alpha (TNF-alpha),interleukin-1 (IL-1) and, prostaglandins, especially PGE2.Type 2 diabetes is also an inflammatory conditioned, primarily due to the formation of AGE, prolonged interactions between AGEs and RAGE leads to elevated levels of TNF-alpha in subjects via an increase in NF-κB activation and TNF alpha is directly related to insulin resistance. [11,12]

Osteoprotegerin(OPG) belongs to tumor necrosis factor receptor superfamily also called Osteoclastogenesis Inhibitory Factor (OCIF) (Yamaguchi et al 1998). It is a glycoprotein that primarily regulates bone resorption by binding to RANKL (receptor activator of nuclear factor-kB ligand), a cytokine involved in osteoclast differentiation also binds TRAIL (TNF-related apoptosis-inducing ligand), which is involved in immune surveillance in type 2 diabetes, advanced glycation end products(AGE)-receptor for advanced glycation end products (RAGE) interaction in epithelial cells increase vascular damage, causing an increase in OPG expression mediating immune mechanism against different forms of vascular damage thus OPG acts as an important regulatory molecule in the vasculature.[13,14]

Interleukin-1 beta: IL-1beta is a pro-inflammatory released by monocytes and macrophages which are majorly involved in collagenase production, which in turn breaks down periodontal connective tissues leading to concomitant alveolar bone loss mediated by osteoclastic activation. AGEs have their receptors in immune cells like monocytes, macrophages, and endothelial cells. This AGE-RAGE binding may induce a hyperresponsive cellular state, further leading to the production of IL-1beta and other pro-inflammatory cytokines. [15]

Interleukin-6: IL-6 is one of the pro-inflammatory cytokines that contribute to periodontal bone loss by activation of the receptor activator of nuclear factor-kappa-B ligand (RANKL) or acts directly on osteoclast formation. As a result of pathogenic AGE formation, there is production of inflammatory mediators among them, IL-6 has a prominent role in imitating the transition of the immune response from acute to the chronic phase of inflammation by causing a shift in cellular nature i.e. from polymorphonuclear neutrophils to monocytes / macrophages, thus stimulating the T and B cells responses

and antibody formation thus leading to hyperinflammatory phase in diabetes.[16]

CRP: C-reactive protein is an acute-phase protein produced by activation of hepatic cells and the release of acute-phase proteins such as CRP into circulation is regulated by cytokines, including IL-6 and tumor necrosis factor-α. Literature evidence shows that elevated C-reactive protein level indicates an increased risk for developing cardiovascular disease, other chronic diseases such as diabetes mellitus and periodontitis.[17,18]

YKL-40 is a glycoprotein with a molecular weight of approximately 40 kDa and is named from three amino acids of tyrosine (Y), lysine (K), and leucine (L) at the N-terminal, it is one of the positive APP molecules that is produced by immune cells like neutrophils, macrophages and also by chondrocytes, osteoblastic cells, endothelial cells, etc during disease.it has a functional role in inflammation, cell proliferation, tissue remodeling, protection against apoptosis immune responses and remodeling of the extracellular matrix. Hence it has a common role in an inflammatory disease like periodontitis and diabetes.[19,20]

Macrophage Chemotactic Protein-1 is a major chemokine signal for chemotaxis of leukocytes macrophages and, eosinophils secreted by neutrophils especially in response to microbial pathogens thus plays a major role in chronic periodontal disease. MCP-1 increases in hyperglycaemic conditions due to the monocyte endothelial interaction.21

Matrix Metallo Proteinases are a group of proteolytic enzymes that mediate extracellular matrix degradation. The enzymes are present in latent form activated by disrupting Zn ion. In periodontal remodeling MMPs (MMP-1, -8, -13, and -14) which are considered as collagenolytic MMPs and MMPs (MMP-2 and -9) considered as the gelatinase MMP play a pivotal role. MMP-8, -13, and 9 are involved in periodontal tissue destruction. In oral fluids, they are strong biomarkers of severity, a progression of inflammatory diseases like periodontitis and diabetes. Reactive oxygen species are elevated in diabetes and they activate both MMP-2 and MMP-9 thus both 2,9 are involved in vascular mediated collagen degradation, delayed wound healing in diabetes [21,22]

Prostaglandins: bacterial endotoxins are involved in activating host defense cells, which leads to the release of pro-inflammatory mediators that stimulate connective tissue break down through PGE2 and MMP. prostaglandin e2 in one of the chemical mediators that has potent inflammatory action with a threefold increase in diseased tissues. in diabetic subjects elevated oxidative stress due to age binding with macrophages causes a further increase in PGE2. [23,24]

PAI-1 is a serine protease inhibitor that acts as a marker of fibrinolysis, secreted by fibroblasts, endothelial cell, hepatic and adipose tissue it is also one of the acute phase proteins activated in inflammatory conditions. cytokines also trigger the production and secretion of PAI-1 by hepatocytes leading to the formation of tissue plasminogen activator causing impaired fibrinolysis.24

Ghrelin is a peptide hormone regulating the neutrophil-mediated innate immune response. They are primarily secreted by cells of oral epithelium and fibroblasts. it has lipogenic action and involved in glucose regulation at low levels however elevated in chronic inflammatory diseases line T2DM, inflammatory bowel disease, and chronic periodontitis. [25,26]

Leptin is a hormone secreted by adipose tissues. It exerts an anti-diabetic effect by reducing insulin resistance by the dysregulation of adipose-insulin action. leptin a nonspecific local marker of periodontitis detected in GCF probably diffuses from the microvasculature to the gingival tissues, as there are no adipocytes within the

gingival tissue. it is noteworthy that the detection of high local leptin levels in T2DM patients with periodontal disease is regarded as one of the indicators of cardiovascular complications.[27]

Resistin is a molecule with the potential inhibitory role on the entry of glucose into cells, by inhibiting cell surface glucose. Resistin mRNA was strongly increased by TNF-alpha in human peripheral blood mononuclear cells hence associated with chronic periodontitis also.[28,29]

Visfatin is a 52 kDa molecule secreted by adipocyte, it is a human pre-B-cell colony enhancing factor it is involved in the synthesis of several cytokines inclusive of IL-6, TNF - α, and IL-1β and exerts its pro-inflammatory role on various organs. In diabetics it has a potential glucose-lowering effect increasing glucose uptake and enhancing triglyceride biosynthesis because it binds to the insulin receptor. Visfatin concentration was increased, severe periodontitis patients. [30,31]

Calprotectin is a major cytosolic protein secreted by leukocytes, neutrophils, monocytes and macrophages and epithelial cells. its expression is increased by inflammatory cytokines and endotoxins from porphyromonas gingivalis. It can interact with heparin and heparan sulfate glycosaminoglycans, the receptor for advanced glycation end products (RAGEs), the scavenger receptor CD36, and the toll-like receptor hence has a potential role in various inflammatory diseases like diabetes.[32]

Discussion

The biological relationship between DM and periodontal diseases has been well documented., the increased incidence of periodontitis in diabetic patients can be attributed to the defective host response reported in diabetic patients. Increased permeability of the basement membrane is often associated with diabetes leading to increased movement of proteins into secretions of the oral cavity. Thus, inflammatory status can be evaluated using saliva or GCF. The immune response is modified in response to AGEs leading to elevation of oxidative stress and cytokine production, which in turn terminates diabetic connective tissue degradation.

It was shown that DM was a risk factor for periodontal diseases, in type 2 diabetes associated with periodontitis, there are elevated levels of AGEs in the periodontal tissues, leading to severe periodontal destruction. Chronic hyperglycaemia also affects the phagocytic and chemotactic activity of mononuclear and PMN cells resulting in a shift in microbial sub-gingival flora to more pathogenic nature. This leads to the activation of immunoinflammatory pathways and elevates cytokine production.

Both diabetes and periodontitis are chronic inflammatory conditions, this leads to an exaggerated inflammatory response and proinflammatory cytokines production. These cytokines exert their function by stimulating the expression monocyte chemotactic protein 1 and macrophage inflammatory protein 1 which are chemokines that mediate the leukocytic migration into the vessel walls. T2DM and obesity are closely related characterized by free fatty acids (FFAs) release. Visceral fat consists of adipocytes and immune cells such as macrophages that are related to the synthesis of two major cytokines involved in insulin resistance namely IL-6 and TNF- alpha as they lead to elevated levels of adipokine release.IL-1β is related to vascular changes, collagen degradation, leading to periodontal breakdown and connective tissue destruction and loss of alveolar bone. All the pro-inflammatory cytokines are evaluated in various studies in the saliva, GCF or serum of diabetic patients with PD. Adipokines like visfatin and resistin are also evaluated in few studies however conclusive data on the reliability of these markers for diagnostic and

prognostic should be further studied. Recently studied biomarkers like ghrelin, YKL-40 should be further evaluated based on specificity towards diabetes and periodontal disease.

Conclusion

Elevated levels of inflammatory mediators in diabetic patients with PD may be a valuable tool in the early detection of Periodontitis. and diabetic levels in undiagnosed individuals. Inconsistencies in the literature have been found between various cytokines and inflammatory mediators as biomarkers, due to difference in their concentration in saliva, serum and GCF, variation among study subjects, methodology, other systemic illnesses, the effect of the periodontal intervention and hypoglycaemic drugs on the inflammatory status. Based on the data suggested in this review, estimation of these cytokines in DM and PD may have diagnostic and prognostic relevance as biomarkers in evaluating systemic inflammatory burden due to hyperglycaemia along with PD and may serve as future therapeutic targets with further studies. High-quality research designs specifically targeting sensitivity, specificity, and elimination of confounding factors, such as smoking and other systemic diseases should be addressed in upcoming studies biomarker research. This would help to improve the reliability and specificity of biomarkers which paves the way for development in target therapy and personalized periodontal approach according to each individual's inflammatory status.

References

1. Kinane, D, "Causation and pathogenesis of periodontal disease." Periodontology 2000, 25, 2001, 8-20.
2. Ellis, S, M Tucci, F Serio, & R Johnson, "Factors for progression of periodontal diseases.". Journal of Oral Pathology & Medicine, 2007, 27,101-105.
3. Pucher, J, & J Stewart, "Periodontal disease and diabetes mellitus.". Current Diabetes Reports, 2004, 4,46-50.
4. Loe, H, "Periodontal Disease: The sixth complication of diabetes mellitus.". Diabetes Care, 1993.16,329-334.
5. Schmidt, A, E Weidman, E Lalla, S Yan, O Hori, & R Cao et al., "Advanced glycation endproducts (AGEs) induce oxidant stress in the gingiva: a potential mechanism underlying accelerated periodontal disease associated with diabetes.". Journal of Periodontal Research, 1996, 31, 508-515.
6. Grossi, S, & R Genco, "Periodontal Disease and Diabetes Mellitus: A Two-Way Relationship.". Annals of Periodontology, 1998, 3, 51-61.
7. Chen, L, B Wei, J Li, F Liu, D Xuan, & B Xie et al., "Association of Periodontal Parameters with Metabolic Level and Systemic Inflammatory Markers in Patients with Type 2 Diabetes.". Journal of Periodontology, 2010, 81,364-371.
8. McCulloch, C, "Host enzymes in gingival crevicular fluid as diagnostic indicators of periodontitis.". Journal of Clinical Periodontology, 1994, 21, 497-506.
9. Kaufman, E, & I Lamster, "The Diagnostic Applications of Saliva— A Review.". Critical Reviews in Oral Biology & Medicine, 2002, 13,197-212.
10. Chen, L, B Wei, J Li, F Liu, D Xuan, & B Xie et al., "Association of Periodontal Parameters with Metabolic Level and Systemic Inflammatory Markers in Patients with Type 2 Diabetes.". Journal of Periodontology, 2010, 81,364-371.

11. Okada, H, & S Murakami, "Cytokine Expression in Periodontal Health and Disease.". Critical Reviews in Oral Biology & Medicine, 1998, 9,248-266
12. Singhal, S, A Pradeep, D Kanoriya, & V Garg, "Human soluble receptor for advanced glycation end products and tumor necrosis factor-α as gingival crevicular fluid and serum markers of inflammation in chronic periodontitis and type 2 diabetes.". Journal of Oral Science, 2016, 58,547-553.
13. Santos, V, J Lima, T Gonçalves, M Bastos, L Figueiredo, & J Shibli et al., "Receptor Activator of Nuclear Factor-Kappa B Ligand/Osteoprotegerin Ratio in Sites of Chronic Periodontitis of Subjects with Poorly and Well-Controlled Type 2 Diabetes.". Journal of Periodontology, 2010, 81, 1455-1465.
14. Vieira Ribeiro, F, A de Mendonça, V Santos, M Bastos, L Figueiredo, & P Duarte, "Cytokines and Bone-Related Factors in Systemically Healthy Patients with Chronic Periodontitis and Patients with Type 2 Diabetes and Chronic Periodontitis.".Journal of Periodontology, 2011, 82, 1187-1196.
15. Vieira Ribeiro, F, A de Mendonça, V Santos, M Bastos, L Figueiredo, & P Duarte, "Cytokines and Bone-Related Factors in Systemically Healthy Patients with Chronic Periodontitis and Patients with Type 2 Diabetes and Chronic Periodontitis.".Journal of Periodontology, 2011, 82, 1187-1196
16. Costa, P., Trevisan, G., Macedo, G., Palioto, D., Souza, S., Grisi, M., Novaes, A. and Taba, M.,. Salivary Interleukin-6, Matrix Metalloproteinase-8, and Osteoprotegerin in Patients with Periodontitis and Diabetes. Journal of Periodontology, 2010 81(3), pp.384-391.
17. Linden, G., McClean, K., Young, I., Evans, A. and Kee, F.,. Persistently raised C-reactive protein levels are associated with advanced periodontal disease. Journal of Clinical Periodontology, 2008, 35(9), pp.741-747.
18. Saito, T., Murakami, M., Shimazaki, Y., Oobayashi, K., Matsumoto, S. and Koga, T., 2003. Association Between Alveolar Bone Loss and Elevated Serum C-Reactive Protein in Japanese Men. Journal of Periodontology, 74(12), pp.1741-1746.
19. Polepalle, T, "Acute Phase Proteins and Their Role in Periodontitis: A Review.". in Journal of clinical and diagnostic research, 2015.
20. Kido, J, Y Bando, M Bando, Y Kajiura, Y Hiroshima, & Y Inagaki et al "YKL-40 level in gingival crevicular fluid from patients with periodontitis and type 2 diabetes.". in Oral Diseases, 21, 2015, 667-673.
21. Longo, P, H Artes, M Rabelo, D Kawamoto, A Foz, & G Romito et al., "Serum leveis of inflammatory markers in type 2 diabetes patients with chronic periodontitis.". in Journal of Applied Oral Science, 22, 2014, 103-108.
22. Panee, J, "Monocyte Chemoattractant Protein 1 (MCP-1) in obesity and diabetes.". Cytokine, 60, 2012, 1-12.
23. Zhong, Y, G Slade, J Beck, & S Offenbacher, "Gingival crevicular fluid interleukin-1beta, prostaglandin E2and periodontal status in a community population.".Journal of Clinical Periodontology, 2007, 34,285-293.
24. Kardeşler, L, N Buduneli, B Bıyıkoğlu, Ş Çetinkalp, & N Kütükçüler, "Gingival crevicular fluid PGE2, IL-1ß, t-PA, PAI-2 levels in type 2 diabetes and relationship with periodontal disease.". Clinical Biochemistry, 2008, 41, 863-868.
25. Yılmaz, G, F Kırzıoğlu, D Doğuç, H Koçak, & H Orhan, "Ghrelin levels in chronic periodontitis patients.". Odontology, 2013, 102,59-67.

26. Mohamed, H, S Idris, M Mustafa, M Ahmed, A Åstrøm, & K Mustafa et al., "Impact of Chronic Periodontitis on Levels of Glucoregulatory Biomarkers in Gingival Crevicular Fluid of Adults with and without Type 2 Diabetes.". PLOS ONE, 2015, 10
27. Kardeşler, L, N Buduneli, Ş Çetinkalp, & D Kinane, "Adipokines and Inflammatory Mediators After Initial Periodontal Treatment in Patients with Type 2 Diabetes and Chronic Periodontitis.". Journal of Periodontology, 2010, 81, 24-33
28. Devanoorkar, A, R Kathariya, N Guttiganur, D Gopalakrishnan, & P Bagchi, "Resistin: A Potential Biomarker for Periodontitis Influenced Diabetes Mellitus and Diabetes Induced Periodontitis.". Disease Markers, 2014,1-7.
29. Gokhale, N, A Acharya, V Patil, D Trivedi, S Setty, & S Thakur, "Resistin Levels in Gingival Crevicular Fluid of Patients With Chronic Periodontitis and Type 2 Diabetes Mellitus.". Journal of Periodontology, 2014, 85, 610-617.
30. Moschen, A, A Kaser, B Enrich, B Mosheimer, M Theurl, & H Niederegger et al., "Visfatin, an Adipocytokine with Proinflammatory and Immunomodulating Properties.". The Journal of Immunology, 2007, 178, 1748-1758.
31. Mishra, V., Interlinking Periodontitis and Type 2 Diabetes Mellitus by Assessment of Crevicular Visfatin Levels in Health and in Disease Before and After Initial Periodontal Therapy. Journal of clinical and diagnostic research. 2016.
32. Kajiura, Y, M Bando, Y Inagaki, T Nagata, & J Kido, "Glycated Albumin and Calprotectin Levels in Gingival Crevicular Fluid From Patients With Periodontitis and Type 2 Diabetes.". Journal of Periodontology, 2014, 85,1667-1675.