Bidirectional Dynamics between Hyperglycemia and Periodontal Infections

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Abstract

Hyperglycemia induces a higher rate of activation pathways responsible for inflammation which leads to microvascular and macrovascular complications, oxidative stress as well as apoptosis. In the pathological manifestation of hyperglycemic events, a raised level of inflammatory markers such as: IL6, TNF-α and C-reactive protein occurs which in turn promotes acute-phase of inflammation leading to signaling impairment of insulin function and insulin resistance. On the other hand, enhanced systemic inflammation due to periodontal diseases mediated by the release of IL-6 and TNF-α happens when associated with hyperglycemia. This review article deals with assessment on hyperglycemia and its correlation to dental pathologies with special reference to periodontitis and vice versa. Studies show that the paradigm shift in the oral microbiota due to hyperglycemic condition resulting in the increase in the pathogenicity of associated pathogenic microbes which results in increased inflammation and bone loss in periodontal pathologies.

The extensive studies about the association between inflammatory periodontal disease and diabetes show the cyclic relationship between the two. Diabetes predisposes the individual to periodontal infections and also the later exacerbates or worsens the glycemic control in diabetic patients. Routine periodontal examination provides an insight for the early diagnosis of diabetes in undiagnosed patients and may reduce the worsening of metabolic control thereby preventing serious complications. Also the oral health of diabetic patients may be improved and well maintained with proper management of blood glucose levels.

Although there are evidences in literature to establish correlation between Diabetes Mellitus associated with periodontitis and vice versa, still the outcomes are not conclusive. Therefore large-scale prospective epidemiological analysis are the only sought after approach to clearly bring in the connectivity between Diabetes and Periodontal disease

Keywords: *Hyperglycemia, Periodontitis, cytokines,IL6, HbA_{1C}, TNF-α, AGEs.*

Introduction

Hyperglycemia is a state of high blood sugar level in the body. Blood glucose levels shoots up in the body either due to decreased production of insulin in the body or when the body can't properly use the produced insulin. Several processes are involved in the development of the pathology of hyperglycemia that can lead to insulin deficiency or anomalies resulting to insulin resistance.[1] Hyperglycemic state is characterized by increased blood glucose levels ≥126mg/dl in fasting and in postprandial, blood glucose at 2 hr after intake of 75mg of oral glucose to be ≥200mg/dl, or HbA_{1C}≥6.5%[1]. Periodontitis is a process of resorption of periodontal ligament and alveolar bone, the structures that supports the teeth. The destruction of the collagen fibers leads to pocket

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formation in the periodontal zone, the space created in between the tooth & the gingiva. Further deepening of the pocket due to continuous loss of periodontal fibers and alveolar bone resorption culminates finally in attachment loss. Various studies indicate the existence of reciprocating relationship between glycemic control and healing of periapical lesions. The increased prevalence and severity of periapical lesions suggests that hyperglycemic state to be a disease modifying agent for the periapical dental pathologies.[2]

This review article is a detailed assessment of the literature on hyperglycemia and its correlation to dental pathologies with special reference to periodontitis and vice versa. Studies show that the paradigm shift in the oral microbiota due to hyperglycemic condition resulting in the increase in the pathogenicity of associated pathogenic microbes which results in increased inflammation and bone loss in periodontal pathologies. However such periodontal diseases are manifested at a higher rate (3-4 times) in immune-compromised condition of patients especially individuals with diabetes when compared with non-diabetics. Therefore there lies increased risk in diabetes patient with periodontal disorders and thus control of glycemic levels in them is inevitable.[2]

Mechanism behind effect of hyperglycemia on periodontal tissues: Hyperglycemic state affects many functions of the immune system and is associated with compromised immune response and delayed healing. The condition results in changes of immune cell function, thereby producing inflammatory immune cell phenotypes such as either upregulation of pro-inflammatory cytokines from monocytes or polymorpho-nuclear leukocytes or downregulation of growth factors from macrophages. This predisposes to chronic inflammation, progressive tissue breakdown and decreased capacity to tissue repair.[3,4] The resulting increased levels of inflammatory cytokines especially IL-17 acts as a signaling molecule for the immune response and inflammation which are associated with periodontal disease resulting in rapid bone loss.[2] In individuals with diabetic complications, the release and accumulation of AGEs (Advanced Glycation End products) has been observed in periodontal tissues. This leads to increased rate of periodontal inflammation. The receptors RAGE present in the cell binds with the released AGEs and induce the formation of IL-1β, TNF-α, IL-6 (inflammatory mediators). AGE formation results in the production of ROS (Reactive Oxygen Species), a natural byproduct of the normal metabolism of oxygen that plays important role in cell signaling and hemostasis and contribute to vascular injury, a common diabetic complication. Also AGEs have detrimental effects on bone metabolism leading to impaired repair and bone formation.[2]

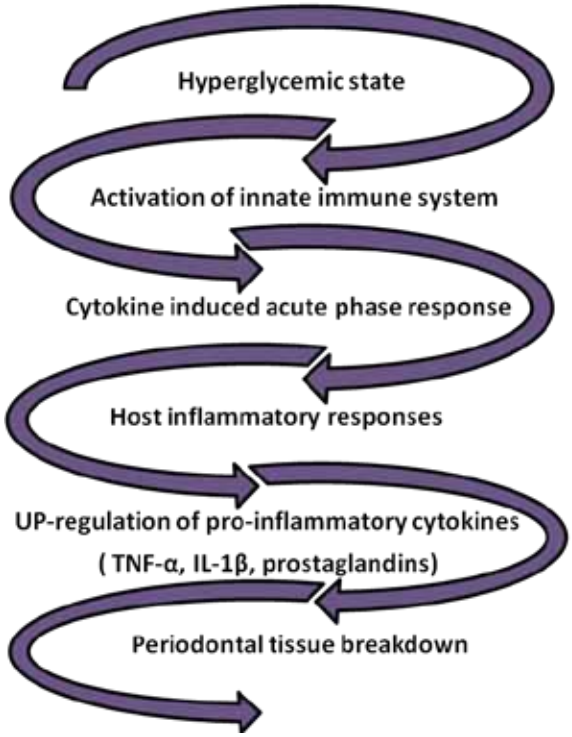

Fig 1: Series of events taking place in periodontal tissues breakdown due to hyperglycemia

Table 1: Animal studies illustrating correlation between hyperglycemic state and periodontal tissues:

Studies by	Model/subject	Analysis	Area of study/observation	Result
[5]	Animal study (rats) Streptozotocin induced diabetic rats.	Histologically & Histometrically	Pulpal and periapical tissue changes after pulp exposure in models	They observed that as compared to control group inflammatory changes in the apical PDL, root resorption and alveolar bone resorption in experimental group were more severe

Studies by	Model/subject	Analysis	Area of study/observation	Result
[6]	Female non obese diabetic mice	Histomorphometrically	They induced periapical lesions in 1st molars in experimental group and measured the size of the periapical lesion.	It was observed that the severity of the response in experimental group is more than the control group
[7]	Comparision between Goto-kakizaki rats with spontaneous non-insulin dependent DM and wistar rats as control group	Histologic analysis	Studied the development of periradicular lesions resulting from type 2 DM after exposing the pulp from occlusal surface in left mandibular 1st molars.	They observed the results after 4weeks. Alveolar bone loss and resorption and periapical lesions were severe in experimental GK diabetic rats.
[8]	Rats with steptozotocin induced hyperglycemia and control group injected with saline.	Histologic analysis	Studied the effect of hyperglycemia in exposed pulps over which MTA was placed.	Inhibition of dentin bridge formation and simultaneous increase in inflammatory cells in the exposed pulps. They observed an inverse relationship between dentin bridge formation and infiltration of inflammatory cells.

Table 2: Human studies illustrating correlation between hyperglycemic state and periodontal tissues:

Studies by	Analysis	Method and results
[9]	Radiographic analysis	They compared the outcome of healing of periapical lesions in poorly controlled DM and therapeutically controlled DM patients. The healing of the lesions of patients with DM under therapeutic control were similar to non-diabetics.
[10]	Radiographic analysis	Comparing the healing of periradicular lesion between low plasma glucose group and high plasma glucose group following root canal treatment, 30 weeks follow up shows 74% reduction in the lesion in low glucose levels where as only 48% reduction of lesion was observed in high glucose level groups.
[11]	Symptomatic analysis	Diabetic patients with abnormal glycemic levels showed a high rate of asymptomatic tooth infections.
[12]	Clinical and radiographic investigations	Diabetic patients of long duration showed greater prevalence of teeth with periapical lesions than other groups.
[13]	Clinical and radiographic investigations	Reported that Diabetic patients showed higher percentage of clinical symptoms relating to pulpal and periodontal infections thereby concluding that DM as a predisposing condition for endodontic infections.
[6]	Microbial analysis	Samples collected from root canals and necrotic pulp tissues of diabetic patients shows the association of *Porphyromonasgingivalis* and *Porphyromonasendodontalis*
[14]	Multivariate analysis, Endodontic diagnostic & treatment outcome	Diabetic patients following root canal treatment have more periodontal disease and also diabetic patients with pre-operative periradicular lesions exhibit lesser success rate of root canal treatment.
[15]	Radiographic analysis	Type 2 diabetic patients exhibited residual periradicular lesions in the radiographic periradicular radiolucencies.

Mechanism behind effects of periapical infection on glycemic control in diabetic patients: Over time the existence of periodontal diseases results in worsening of glycemic control in diabetic patients.[16] Chronic dental lesions or periodontal diseases exhibit similar characteristics as that of any other chronic infections of the body resulting in release of higher levels of pro-inflammatory mediators from harboring gram negative anaerobic microorganisms into the systemic circulation thereby predisposing to worsening of glycemic control in diabetic patients.[16] It has been proposed that the mechanism of insulin resistance developed in obesity induced diabetes and that in existence with periodontal disease are similar in manner i.e by enhancing activation

of the overall systemic immune response that are initiated by cytokines pro-inflammatory mediators.[17] Diabetes is a manifestation of host's inflammatory response resulting from cytokine induced acute phase response through the activation of innate immune system.[18]

The inflammatory manifestations due to periodontitis has been characterized to be mediated by uncontrolled secretion of IL-1β, IL-6, TNF-α, matrix metalloproteins (MMP-8, MMP-9, MMP-13), prostaglandin PGE2, cytokines, RANKL (Receptor Activator of Nuclear Factor Ligand). The periapical bone resorption has been observed due to enzymatic degradation of matrix and stimulated osteoclasts.[19]This could be due to TNF-α secretion in the cell that stimulates the fibroblasts resulting in above physiological and cytological changes. A correlation has been proposed that enhanced TNF-α level is the key factor in establishing the link between diabetic patients and their periodontal conditions.[20, 21]

Fig 2: Series of events taking place in periodontal tissues breakdown due to Periodontitis

Table 3 Animal and human studies supporting the association of periodontal disease and its treatment of Diabetes

Studied by	Results
[22],[23],[24]	Higher levels of HbA_{1c} & development of systemic complications of diabetes in periodontitis patients and also there is association of severe periodontitis and poorly controlled glycaemia.
[25]	It was observed that there is slight elevation in HbA_{1c} readings in non-diabetic patients with periodontitis and concluded that periodontitis may have the potential for the increase in the incidence of diabetes.
[26], [27]	The increase in resistance to insulin due to periodontal infections may impair the glycemic control. Also reducing the gingival inflammation by removing bacterial plaque accumulation can improve the glycemic levels
[26]	There is significant reduction in HbA_{1c} levels in type 2 Diabetic patients through non-surgical periodontal therapy.
[28]	Found that there is higher prevalence of IFG & lower homeostatic model assessment β in patients with chronic periodontitis than those with healthy periodontal tissues.
[29]	Tried to correlate between the albumin present in urine in diabetic patients with that of occurrence of periodontitis and found that the occurrence of periodontitis was relatively higher in albuminuria condition
[30]	Analyzed the risk involved in diabetic type 2 patients and correlated that there occurs severe periodontitis leading to alveolar loss in patients with uncontrolled glycemic condition to an extent of 6 times.
[31]	Suggested from a large scale study about reduction in the levels of HbA_{1c} in diabetic patients when subjected to periodontal treatment.
[32]	Interpreted the result of periodontal treatment in diabetes patients in terms of slight reduction of 0.29% in HbA_{1c} level leading to glycemic control. The study was conducted using Cochrane Database.
[33]	Found considerable improvement in glycemic control with reduction in HbA_{1c} to an extent of 0.46% when diabetic patients were subjected to effective periodontal treatment.
[34]	Showed decline in metabolism of glucose in ligature model (Zucker fatty rats) that are associated with periodontitis characterized by alveolar bone loss.
[35]	Marked higher production of cytokines (pro-inflammatory) in Diabetic patients with periodontitis and also observed a change in prevalence of macrophages as well as monocytes.

Inflammation: Central linking event between Periodontitis and hyperglycemic state: In hyperglycemic state, a higher rate of activation pathways responsible for inflammation has been observed which leads to microvascular and macrovascular complications, oxidative stress as well as apoptosis.[36] In the pathological manifestation of hyperglycemic events, a raised level of inflammatory markers such as: IL6, TNF-α and C-reactive protein has been reported which in turn induce acute-phase of inflammation leading to signaling impairment of insulin function and insulin resistance.[21,37,38] On the other hand, enhanced systemic inflammation due periodontal diseases mediated by the release of IL-6 and TNF-α has been also found to

be associated with enhancement of diabetic state. In addition, adipokines were known to regulate both the occurrence of periodontitis and diabetes.[39] Inflamed periodontal tissues of diabetes patients have higher level of prostaglandin E_2 and IL-1β when compared with the non-diabetics.[40] In another comparative study, a higher level of GCF(Gingival crevicular fluid) IL-1B was found in patients with higher percentage of HbA_{1c} (>8) and vice versa which establishes a correlation between the above two pathological state.[41]

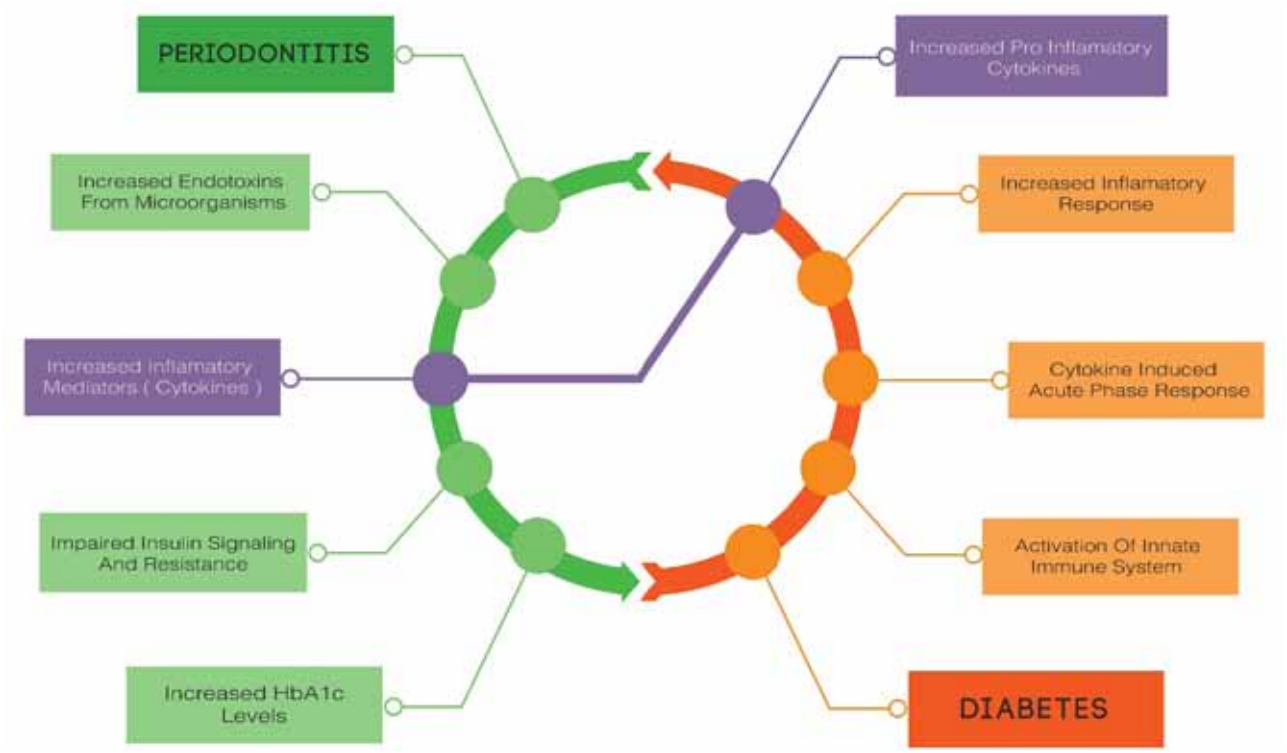

Fig 3: Central linking of events in the cyclic relationship between Periodontitis and Hyperglycemia

Conclusion

The extensive studies about the association between inflammatory periodontal disease and diabetes show the cyclic relationship between the two. One condition leads to the other and vice versa. Diabetes predisposes the individual to periodontal infections and also the later exacerbates or worsens the glycemic control in diabetic patients. Routine periodontal examination provides an insight for the early diagnosis of diabetes in undiagnosed patients and may reduce the worsening of metabolic control thereby preventing serious complications. Also the oral health of Diabetic patients may be improved and well maintained with proper management of blood glucose levels.

Although there are evidences in literature to establish correlation between Diabetes Mellitus associated with periodontitis and vice versa the outcomes are not conclusive. Therefore large-scale prospective epidemiological analysis are the only sought after approach to clearly bring in the connectivity between Diabetes and Periodontal disease

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