Periodontitis and Diabetes: Complication or Predictor

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Recent studies indicate that periodontal health influences systemic health and that this has also been considered as a bidirectional relationship for several systemic conditions. This is particularly evident for the inter-relationship between periodontal disease and diabetes mellitus (DM). This relationship between the health of periodontium and DM provides an example of a viz. association. Whereby, there is always possibility that a systemic disease predisposes the individual to oral infections, and, once the oral infection is established, it exacerbates the systemic disease through its pathogenesis and its disease cycle incorporating other organs as oral cavity is also a part of a human body. There are also associations between periodontal disease and systemic conditions such as cardiovascular problems, osteoporosis, obesity, and pancreatic disease. Hence, emphasis should now be placed on treating chronic periodontal diseases as a means of deteriorating systemic diseases. Nowadays periodontitis has been considered as the sixth complication of DM.

Keywords: Diabetes mellitus, Glycemic control, Inflammatory markers, Periodontitis

INTRODUCTION

Diabetes mellitus (DM) is a highly prevalent metabolic disease, in the most of these people, disease remains undiagnosed. More importantly, the prevalence of DM has increased three-fold since 1970. This is a significant finding for dental professionals, as evidence from clinical research showing a strong relationship between diabetes and periodontal disease. In fact, periodontitis is often referred to as the sixth complication of diabetes. Ongoing research suggests that control of periodontal disease may play a key role in the control of blood glucose level in diabetes. Thus, dentists must be aware of the signs and symptoms of diabetes, and understand the importance of maintaining periodontal health for individual with diabetes at the same time it is also important to monitor persistent periodontal infection which can modify systemic conditions. DM is a metabolic disorder characterized by hyperglycemias due to a defect in secretion or activity of insulin. It may lead to further complications such as poor regulation of protein and lipid metabolism.

ACCORDING TO AMERICAN DIABETES ASSOCIATION MODIFIED IN 2003

Type 1 DM is normally a result of autoimmune destruction of the β-cells in the islets of Langerhans of the pancreas of the affected individual. This condition often leads to an absolute deficiency of insulin. It is believed that the tendency to develop the abnormal antibodies in Type 1 DM is, in part, which may be genetically inherited, though the mechanism is not fully understood. Exposure to certain viral infections such as mumps and Coxsackie viruses or other environmental toxins may lead to trigger abnormal antibody responses that damage these β-cells.

With Type 2 diabetes, patients can still produce insulin but do so relatively inadequately. In many cases, the pancreas produces larger than normal quantities of insulin. A major feature of Type 2 diabetes is a lack of sensitivity to insulin by the cells of the body, particularly in fat and muscle cells. These larger quantities of insulin are produced as an attempt to get these cells to recognize that insulin is present. In this condition, the problem is with an increase in insulin resistance, the release of insulin by the pancreas may also be defective, and occur late in response to increased glucose levels. Finally, the liver in these patients continues to produce glucose despite elevated glucose levels.

This bidirectional relationship between periodontal disease and DM provides an example of a systemic association. Periodontal disease is defined as an inflammatory disease characterized by inflamed gingiva, alveolar bone...
loss, and attachment loss. The inflammatory response in the periodontal tissues in response to oral biofilm is a network of cytokines functioning in synergy. The inflammatory response is characterized by the production of the inflammatory markers such as cytokines and matrix metalloproteinases. These increased secretions of inflammatory cytokines contribute to bone loss in periodontitis.

DM AS A RISK FACTOR FOR PERIODONTITIS

Diabetes has been identified as an important risk factor in periodontal diseases in epidemiological studies. Initiation and progression of periodontal inflammation take place by Gram-negative bacterial infection inside the periodontal pocket, whereas diabetic complications are mainly result of the presence of hyperglycemia. It is suggested that both the clinical entity a share common pathogenic processes and both are thought to be up-regulated responses of the immune system to environmental stress. The effects of hyperglycemia on oral health can be attributed by three mechanisms.

First, the hyperglycemia leads to increased levels of gingival crevicular fluid that reflects the elevated blood glucose levels. This correlation may influence the microbial flora in the oral biofilm and planktonic bacteria as well. Second, there is increased expression of advanced glycation end-products due to hyperglycemia. Advanced glycation end-products affect normal protein function; these advanced glycated products have the potential to create molecular complexes, reducing the solubility of the target protein-like collagens. They alter the synthesis and remodeling of several important matrix molecules such as Type 1 collagen and laminin. Third, matrix metalloproteinases are the major players in collagen breakdown during periodontal tissue destruction. DM is associated with altered collagen metabolism and increases the response of the periodontal tissue to bacterial infection, thereby increasing the severity of periodontal destruction.

Evidence suggests that changes in periodontium are the first clinical manifestation of diabetes. Studies have shown that patients with diabetes exhibited greater periodontal breakdown in response to the bacterial challenge, however, this actually depends on the degree of glycemic control. The highest prevalence of gingivitis were seen in diabetic patients with poor glycemic control. Studies have proven that individuals diabetes carries a three-fold increased risk of periodontitis compared to non-diabetic individuals. In addition, Loe described periodontitis as the 6th complication of diabetes. In research, it has been found a higher gingival index and gingival recession in patients with uncontrolled DM compared to healthy controls. In similar studies, comparison of Type 2 diabetes individuals with non-diabetic subjects and reported a higher gingival index and attachment loss positively associated with hemoglobin A1c (HbA1c) levels in diabetic patients. In a recent study, Lim et al. evaluated the relationship between biomarkers of metabolic control and the severity of existence of the periodontal disease in subjects with Type 2 DM. They reported positive correlations between HbA1c and the prevalence of periodontal diseases providing further evidence for the importance of glycemic control.

PERIODONTITIS AS A RISK FACTOR FOR DM

Oral infections result in a series of events that include increased cytokine production, acute-phase protein synthesis, and insulin resistance, which produces pathogenic changes resulting in Type 2 diabetes. Chronic periodontal infection leads to an increase in various inflammatory markers such as serum tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, and C-reactive proteins. The increase in these markers can increase insulin resistance by interfering with glucose and lipid metabolism as well as antagonizing insulin action. The increased insulin resistance will ultimately lead to an increase in the risk for Type 2 diabetes. Due to bacterial stimulation host cells release pro-inflammatory cytokines (e.g. IL-1α, IL-1β, and TNF-α) as part of the immune response. These cytokines production further leads to recruitment and stimulate polymorphonuclear leukocytes, which in turn produce reactive oxygen species. This imbalance between the production of reactive oxygen species and antioxidant defense leads to increased oxidative stress. This increased oxidative stress in turn mediates activation of the polyol pathway, the hexosamine pathway, protein kinase C, and the formation of advanced glycation end-products. This whole cascade of event against inflammatory response induces advanced glycation end-products which subsequently contributes to the systemic degradation of connective tissue in diabetic subjects, thus increasing the risk of diabetic complications.

A 10-year cohort study found that the increase in mean pocket depth was more closely related with the development of glucose intolerance. Other studies have also suggested that the presence of periodontal infection may be linked to poor metabolic control of diabetes. Studies showed that the extent of periodontal infection was associated with glycemic control (P < 0.001). It has been reported that diabetics with severe periodontal disease are 6 times more likely to have poor glycemic control. Lalla et al. investigated the outcome of the periodontal treatment in diabetes patients. They revealed significant suppression of serum C-reactive protein, production of pro-inflammatory cytokine TNF-α and the number of circulating monocytes, all these have
identified for the inflammatory complications of diabetes, e.g. atherosclerosis.26

Correa et al. demonstrated a tendency toward a decrease in inflammatory biomarkers, particularly TNF-α and fibrinogen, at 3 months after periodontal treatment. The periodontal treatment regime also causes a reduction in the levels of high-sensitivity C-reactive proteins and HbA1c.27 Reducing the levels of these mediators retards the process of insulin resistance.

**THE EFFECT OF PERIODONTAL HEALTH ON THE COURSE OF DIABETES**

The basic mechanism for insulin resistance in periodontitis: Pro-inflammatory cytokine TNF-α does downregulation of the insulin signaling mechanisms by blocking the phosphorylation of insulin receptor substrates, Hampers the glucose transporter four translocation for the glucose molecule across the plasma membrane of the host cell and Resulting in insulin resistance and decreased insulin action. Grossi et al. 1997, in their study they attempted to demonstrate that if there is any correlation present between periodontal inflammation which influences the control of HbA1c and they have documented that periodontal therapy may improve metabolic status of diabetic individuals.28

Periodontitis is a destructive disease of supporting structure of teeth which is the result of a complex interplay of bacterial infection and host responses, and is often modified by various systemic conditions such as DM. Such diseases are capable of affecting the periodontium as well as the treatment outcome of the periodontal disease.29 However, recent researches have changed our concept of how periodontal disease should be treated. The researchers present several concerns which are directed toward the periodontal therapy of patients with DM based on various studies. When treating periodontitis patients who have DM, it is important to consider the type of diabetes as well as the overall health status of that individual. Patients with non-insulin dependent DM can be further classified according to the degree of insulin resistance since recent epidemiological studies have suggested that successful anti-microbial therapy might result in improved insulin resistance in highly insulin resistant patients. Because it has been currently considered that the major contributing factor for insulin resistance is the release of a pro-inflammatory cytokine, TNF-α due to periodontal inflammation and because periodontal surgery may cause transient bacteremia which may lead to up-regulate the serum TNF-α level, which in turn suppresses insulin action. Hence, patients should be strictly treated with non-surgical periodontal therapy and their serum TNF-α level should be periodically monitored. On the other hand, diabetic patient’s positive for serum anti-glutamate decarboxylase autoantibody should be examined for the source of this antibody, since:

1. Gingival and periodontal ligament fibroblasts were found to express glutamate decarboxylase, in diseased condition
2. Some otherwise healthy periodontitis patients develop anti-glutamate decarboxylase antibody.

Thus, chronic periodontitis may influence the level of this antibody which is widely used as a predictive marker for slowly progressive insulin dependent DM. Periodontal consideration is of utmost important because not only is periodontal disease thereby affected by systemic diseases, but carefully managed periodontal therapy may also have a positive effect on the general health of patients with systemic diseases.

DM is a systemic disease with several major complications affecting both the quality as well as the length of life. One of these complications is the periodontal disease (periodontitis). Periodontitis is much more than a localized oral infection. Data from recent studies have indicated that periodontitis may cause changes in systemic physiology conditions. The inter-relationships between periodontitis and diabetes provide an example of systemic disease predisposing to oral infection, and once that oral infection is established, the oral infection exacerbates that systemic disease.30 In this case, it may also be possible for the oral infection to predispose to systemic disease. To understand the cellular and molecular mechanisms responsible for such a bidirectional association, one must identify common physiological changes associated with diabetes and periodontitis together that produce a negative impact on individual’s health when the conditions coexist. There is a potential mechanistic link which involves the broad axis of inflammation, specifically immune cell phenotype, serum lipid levels, and also tissue homeostasis. Diabetes-induced changes in immune cell function produce an inflammatory immune cell phenotype which leads to the up-regulation of pro-inflammatory cytokines from monocytes or polymorph nuclear leukocytes and down-regulation of growth factors from macrophages. This predisposes to chronic inflammation, progressive tissue destruction, and diminished normal tissue repair capacity. Periodontal tissues frequently manifest these changes because they are constantly exposed to the external environment and wounded by substances emanating from bacterial biofilms. Diabetic patients are more prone to elevated low-density lipoprotein cholesterol and triglycerides (LDL/TRG) even when their blood glucose levels are well controlled. This finding is significant, because as recent studies demonstrate that hyperlipidemia may be one of the factors which are associated with diabetes and can induce immune cell alterations. Recent human studies have established that
there is a relationship between high serum lipid levels and periodontitis. Some evidence now suggests that periodontitis itself may lead to elevated LDL/TRG. As periodontitis can also induced bacteremia or endotoxemia, it has been shown to cause elevations in serum pro-inflammatory cytokines such as IL-1β and TNF-α, which have been demonstrated to produce alterations in lipid metabolism leading to hyperlipidemia. Within this context, periodontitis may contribute to elevated levels of the pro-inflammatory cytokines and serum lipids and potentially to systemic disease arising from chronic hyperlipidemia and/or increased inflammatory mediators. These cytokines can further produce an insulin resistance syndrome similar to that observed in diabetes and initiate destruction of pancreatic β-cells leading to the development of diabetes. Thus, there is potential for periodontitis to exacerbate diabetes-induced hyperlipidemia, immune cell alterations, and diminished tissue repair capacity. Still ongoing researches have hypothesized that it may also be possible for chronic periodontitis to induce diabetes.

Evidences point out to an increased cytokine response in Type 2 diabetes, especially the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. Various parameters such as genetics, age, and nutrition are important signals for this increased response and as reported more recently, infections and inflammation. Persistent elevation of IL-1β, IL-6, and TNF-α in the diabetic state have an effect on the other body organelles like liver, stimulate the release of acute-phase proteins, produce the characteristic dysregulation of lipid metabolism associated with Type 2 diabetes, and have effects on pancreatic β-cells as well. In addition, TNF-α is found to be a potent inhibitor of the tyrosine kinase activity of the insulin receptor, so it has been implicated as an etiologic factor for insulin resistance. Collectively, the evidence supports a role for cytokine elevation in the pathophysiology and other metabolic abnormalities associated with diabetes. Epidemiological studies have revealed that periodontitis is an infection that is twice as prevalent in diabetic individuals compared to non-diabetics.

Porphyromonas gingivalis, one of the microorganisms which are responsible for this infection, is able to invade endothelial cells and act as a potent signal for monocyte and macrophage activation. Thus, once established in the diabetic host, this chronic infection complicates diabetes control and increases the occurrence and severity of microvascular and macrovascular complications by causing the destruction of the periodontal ligament. Unlike treatment of acute infections, modalities of treatment for chronic infections are a matter of debate. Some studies have also revealed that mechanical removal of subgingival infection does not result in complete elimination of periodontal infection, and thus consequently there is no effect on diabetes control measured as a reduction in HbA1c. On the other hand, studies incorporating systemic antibiotics as an adjunct to mechanical debridement result in a reduction of P. gingivalis up to non-detectable levels and a concomitant reduction in HbA1c, independent of the treatment like hypoglycemic effects of diabetes drugs or insulin. The evidence supports the notion that treatment of chronic periodontal infection is an essential protocol that has to be followed in the diabetic patients. Assessment of infection status in diabetic patients is fundamental for appropriate treatment decisions, as well as its outcome.

A cohort over a 10-year period, subjects included people with normal glucose tolerance, impaired glucose tolerance and no glucose tolerance (diabetics).

He found an increase in mean pocket depth was more closely associated with the development of glucose intolerance from normal status than the past glucose tolerance status itself. One-third of the subjects with impaired glucose tolerance or diabetes at the beginning of the 10 years study improved their glucose status to normal. In addition, the proportion with normal glucose tolerance was higher in subjects with shallower pocket depths than in those with deeper pockets.22

Serum IL-1β in Insulin Secretion in Type II Diabetic

This study has two important findings:

1. The first one is that the levels of IL-1β as inflammatory cytokines in patients with diabetes are far higher than those with non-diabetic counterparts
2. Secondly the serum levels of this inflammatory cytokine are significantly correlated with β-cell function.

Thus, the inverse relationship between serum levels of IL-1β and β-cell function somehow supports the role of increased IL-1β in pancreatic β-cell dysfunction and further corroborates the hypothesis that increased secretion of this cytokine reduces the amount of secretion of insulin from β-cells.

CONCLUSION

It has been well established until the date that there is a bidirectional relationship is evident for diabetes and periodontal disease. Early diagnosis and screening are utmost protocol for the better outcome of treatment of periodontitis as well as control of the glycemic level.

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