Bidirectional relationship between diabetes and periodontal disease: Review of Evidence
Bilal Abdul Qayum Mirza, Ayma Syed, Faisal Izhar, Ayyaz Ali Khan
Department of Oral Health Sciences, Sheikh Zayed Postgraduate Medical Institute, Lahore.

Abstract
Presently there are 170 million diabetic patients worldwide. Pakistan ranks sixth in the world with approximately 6.2 million in the 20-79 year age affected by the diabetes. 6-10% of the 35-44 year old diabetic patients have been reported to be affected by moderate form of periodontal disease in Pakistan. Periodontal disease is referred to as sixth complication of diabetes. The association between diabetes and periodontal disease has been reported for more than 40 years but reverse has not been the focus of researchers until recently. Studies have suggested a bi-directional relationship between periodontal disease and glycaemic control with each disease having a potential impact on the other.

Introduction
Diabetes mellitus, a metabolic disorder characterized by hyperglycaemia due to the defective secretion or activity of insulin, affects an estimated 171 million people currently worldwide. Prevalence is same for both genders. Pakistan ranks sixth in the world with approximately 6.2 million in the 20-79 year age affected by the condition.1-4

Diabetics present with the classical triad of symptoms polydypsia, polyuria and polyphagia. This is often accompanied by chronic fatigue and loss of weight. Complications of diabetes mellitus include retinopathy, nephropathy, neuropathy, and cardiovascular disease.5,6 Periodontitis is now referred to as the sixth most common complication of diabetes.7

Clinical studies have demonstrated a higher prevalence of periodontitis in diabetic patients.8-10

Periodontal disease and diabetes have a number of common pathways in their pathogenesis; both diseases are polygenic disorders with some degree of immunoregulatory dysfunction.5 The association between diabetes and periodontal disease has been reported for more than 40 years but reverse has not been the focus of researchers until recently.11 Studies have suggested a bi-directional relationship between periodontal disease and glycaemic control with each disease having a potential impact on the other.12,13

This review attempts to correlate bidirectional relationship between diabetes and periodontal disease.

The effect of diabetes on periodontal disease:

Years of research have established a number of mechanisms by which diabetes can influence the periodontium. Many of these mechanisms share common characteristics with those involved in the classic complications of diabetes, such as retinopathy, nephropathy, neuropathy, macrovascular diseases and altered wound healing. Periodontal diseases are infectious diseases, research initially focused on possible differences in the subgingival microbial flora of patients with and without diabetes. Although some early studies reported higher proportions of certain bacteria in the periodontal pockets of patients with diabetes, later studies involving cultures revealed few differences in periodontally diseased sites of subjects with diabetes and those of subjects without diabetes.14 Therefore, researchers have now focused attention on potential differences in the immunoinflammatory response to bacteria between diabetics and non diabetics.

The immunoinflammatory response is altered due to alteration in the function of inflammatory cells involved (macrophages, neutrophils and monocytes). These cells are the first line of host defense and inhibition of their function may prevent destruction of bacteria in the periodontal pocket, thereby increasing periodontal destruction. Immunoinflammatory responses are unregulated in people with diabetes. For example, chemotaxis, phagocytosis and adherence, of neutrophils are often impaired.15 Macrophages and monocytes often exhibit elevated production of proinflammatory cytokines and mediators such as tumour necrosis factor α (TNF-α) in response to periodontal pathogens, which may increase host tissue destruction. Elevated TNF-α levels are found in the blood and gingival crevicular fluid, suggesting both a local and systemic hyper responsiveness of this immune cell line. Glycaemic control has been reported to be an important determinant of this response.15

In a study of subjects with diabetes and periodontitis, Engebretson and colleagues found that crevicular fluid levels of interleukin 1β (IL-1β) were almost twice as high in subjects with HbA1c levels greater than 8 percent compared to those whose HbA1c levels were up to 8 percent.15
Altered wound healing is another common problem in people with diabetes. The primary reparative cell in the periodontium, the fibroblast, does not function properly in high-glucose environments. Furthermore, the collagen that is produced by these fibroblasts is susceptible to rapid degradation by matrix metalloproteinase enzymes. The production of this enzyme is elevated in diabetes. Thus, periodontal wound healing responses to chronic microbial insult may be altered in those with sustained hyperglycaemia. The result an increased bone loss and attachment loss.

One of the major characteristics of diabetic complications is a change in microvascular integrity, which underlies end-organ damage, such as that responsible for retinopathy and nephropathy. People with diabetes, especially those with poor glycaemic control, accumulate high levels of irreversibly glycated proteins called advanced glycation end products (AGEs) in the tissues, including the periodontium. AGEs are a primary link between numerous diabetic complications, because they induce marked changes in cells and extracellular matrix components. These changes, including abnormal endothelial cell function, capillary growth and vessel proliferation, also occur in the periodontium of some people with diabetes. The accumulation of AGEs in patients with diabetes also increases the intensity of the immunoinflammatory response to periodontal pathogens, because inflammatory cells such as monocytes and macrophages have receptors for AGEs. Interactions between AGEs and their receptors on inflammatory cells result in the increased production of proinflammatory cytokines such as IL-1β and TNF-α. This interaction may be the cause of the marked elevation in gingival crevicular fluid levels of IL-1β and TNF-α seen in subjects with diabetes compared with those without diabetes. Thus it may contribute to the increased prevalence and severity of periodontal diseases found in numerous studies of populations of people with diabetes.

Diabetes has been observed to increase the risk of experiencing continued periodontal destruction over time up to 5 folds. Studies have been done which suggest that poorly controlled diabetics respond less successfully to periodontal therapy compared to well-controlled and non-diabetics. Bridges and others found that diabetes affected all periodontal parameters, including bleeding scores, probing depths, and loss of attachment and missing teeth. In fact, one study has shown that diabetic patients are five times more likely to be partially edentulous than non diabetic subjects.

Saito followed a cohort over a 10-year period. Subjects included people with normal glucose tolerance, impaired glucose tolerance and manifest diabetics. He found that an increase in mean pocket depth was more closely associated with the development of glucose intolerance from normal status. One-third of the subjects with impaired glucose tolerance at the beginning of the 10-year 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.

Increase in glycaemic level increases the pocket depth and leads to periodontal disease.

The effect of periodontal disease on diabetes:

All chronic infections affect the glycaemic control in diabetics. Chronic inflammation leads to impairment in cell-mediated immunity such as neutrophil (polymorphonucleocyte) chemotaxis and macrophage function and vascular disease. Cytokines such as IL-10 and transforming growth factor (TGF)-q, which control humoral responses, and IL-2 and interferon (IFN) gamma, which control the cellular response are produced. These changes in cellular and hormonal response affect the release of insulin and affect glycaemic control.

Periodontal disease is one such chronic infection which affects the glycaemic control in a similar manner. A two year longitudinal trial indicated a six fold increase in risk of worsening glycaemic control in diabetic patients having severe periodontitis compared with subjects with diabetics having no periodontitis.

Studies have attempted to determine the influence of periodontal diseases on the control of diabetes and reported that periodontal therapy may improve metabolic control of diabetes. The study observed that mechanical periodontal treatment alone not only improves periodontal health it also has a positive effect on the level of glycosylated haemoglobin. However, the magnitude and duration of the improvement may not be clinically significant.

There is weak evidence from clinical trials that diabetics require more thorough and aggressive periodontal therapy than non-diabetics with periodontal disease.

The mechanisms by which periodontal diseases may affect the diabetic state have been elucidated only recently. Both periodontal diseases and diabetes, especially type 2 diabetes, have major inflammatory components. Chronic periodontal diseases also have the potential to exacerbate insulin resistance and worsen glycaemic control, while periodontal treatment that decreases inflammation may help diminish insulin resistance.

Patients with inflammatory periodontal diseases often have elevated serum levels of proinflammatory cytokines. These levels are exacerbated in diabetics. This has the potential to increase insulin resistance and make it more difficult for the patient to control his or her diabetes. Research shows improvement in glycaemic control after periodontal therapy in diabetic patients. In a recent study of
subjects with type 2 diabetes and periodontitis, Iwamoto and colleagues found that periodontal treatment to have a significant correlation with reduction in serum levels of TNF-α. This reduction in the TNF-α levels was accompanied by a significant reduction in mean HbA1c values (from 8.0 to 7.1 percent). This suggests that a reduction in periodontal inflammation helps decrease inflammatory mediators in the serum that are associated with insulin resistance, thereby improving glycaemic control.

**Bidirectional relationship model:**

Diabetes is a risk factor for severe periodontal disease. Severe periodontal disease often coexists with severe diabetes mellitus. A model is presented whereby severe periodontal disease increases the severity of diabetes mellitus and complicates metabolic control. It was proposed that an infection-mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from lipopolysaccharide (LPS) and products of periodontopathic organisms may amplify the magnitude of the advanced glycation end product (AGE)-mediated cytokine response operative in diabetes mellitus. In this model, the combination of these 2 pathways, infection and AGE-mediated cytokine up regulation, helps explain the increase in tissue destruction seen in diabetic periodontitis. It shows how periodontal infection may complicate the severity of diabetes and the degree of metabolic control, resulting in a 2-way relationship between diabetes mellitus and periodontal disease/infection. This proposed dual pathway of tissue destruction suggests that control of chronic periodontal infection is essential for achieving long-term control of diabetes mellitus.

**References**