Review Article

Association between Diabetes Mellitus and Periodontal Diseases

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Abstract: Objective: Diabetes mellitus (DM) is a serious health burden and its frequency is increasing worldwide. Several complications are related with diabetes mellitus and now periodontal disease (PD) is also considered as DM-related problem. A 2-way association between DM and PDs has been reported. The purpose of this article is to deliver the knowledge relating to the association between DM and PDs. Several researches have been published over the past 50 years in this regard yet more research is obligatory so as to elucidate the two-way relationship trait between DM and PDs.

Keywords: Diabetes mellitus, Periodontal disease, Diabetes mellitus related complications, Hyperglycemia, Fibroblast, Collagen.

INTRODUCTION

Diabetes Mellitus (DM) is described by hyperglycemia which is instigated by a lack of insulin, insulin resistance, or both. DM is related with the progression of secondary complications thereby causing much comorbidity [1]. Mostly, people suffering from DM have one comorbid chronic ailment at least with augmented risks of cardiovascular complications, hypertension, and end-stage renal disease [2, 3].

A major complication of DM is periodontal disease. There can be increased destruction of periodontal tissues in the diabetics which can be due to an atypical immune response, changed fibroblast role and levels of collagen, and also the microvascular effects of advanced glycosylation end products (AGE). The AGE buildup in the periodontium is connected with a rise in the inflammatory mediators' levels that are linked with damage of the tissue. In the diabetic patients with periodontal disease (PD), these inflammatory mediators can make tissue destruction more severe. The augmented frequency of periodontal disease in diabetic patients exhibits oral-systemic relationship and this relationship can be two-dimensional also. It is stated that the diabetic patients with active periodontal disease have a tendency for unsatisfactory glycemic control in comparison to patients devoid of periodontitis [1].

The connection between these two enduring ailments has been examined and published in over 200 articles in the past 50 years. The data explanation is every so often confounded by variable descriptions of DM and periodontitis as well as diverse clinical measures used for extent, prevalence, and severity of PD, glycemic control levels and diabetes impairments [4]. After intensive studies, a two way association has been established between the glycemic level changes and periodontal alterations of a patient. Inflammation can coordinate both the DM and PD pathogenesis and impediments. On the other hand, PD can be extremely harmful for the metabolic control of specific diabetic patients. The management of PD and decrease in the oral inflammatory signs can lead towards favorable result on the diabetic condition of a patient [1]. The underlying mechanisms for this relationship are quite unclear despite of availability of abundant literature in this direction; it is very probable that periodontal diseases aid as originators of insulin resistance, thus aggravating the glycemic control [5, 6]. Several studies strongly advocate the diabetics have higher prevalence, severity and progression of Periodontal Diseases [7-9].

This article tends to provide useful information about the correlation between PD and DM through an extensive overview of major outcomes from published studies from over past approximately 20 years. This article counts on original data analyses and interpretation of author only and does not seek out for statistical analyses of any data from the articles reviewed. Numerous references are referred to from available literature and they are not intended to be encompassing all or a considerable portion of medical literature accessible on subjects of DM or PD [1].

REVIEW

Diabetes Mellitus

DM covers a group of heterogeneous metabolic disorders (clinically and genetically) which is described by hyperglyce-

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mia, resulting from a flawed insulin secretion and/or activity [7, 10]. Type 1 DM (T1DM) results due to complete deficiency of insulin; the etiologies can be different but this usually arises as a result of auto-immunological damage of pancreatic β cells producing insulin. In type 2 DM (T2DM), various cells i.e. muscles and fats cells etc. become resistant to insulin actions. Due to this, a compensatory mechanism is activated by which β cells secrete more insulin. So in T2DM, the compensatory surge in insulin is deficient to sustain blood glucose levels in a usual physiological level [7, 11, 12].

The major type of diabetes in early life is T1DM, with >85% of cases in youth < 20 years of age globally; overall the disease denotes 5%–10% of total diabetes cases globally [7, 13, 14]. Both male and female genders are influenced by T1DM in the same way in youth on an average. The deterioration of insulin-secreting pancreatic beta cells is characteristic of T1DM and is a polygenic autoimmune disorder. It occurs typically due to failure in immune regulation, causing auto-reactive CD4+ and CD8+ T cells expansion and auto-antibody-producing B lymphocytes and innate immune system activation; this pools up in devastation of insulin-producing beta cells [15]. T1DM is also thought to be activated by genetic susceptibility and environmental factors [7].

Worldwide, T2DM represents 90% of diabetes cases and has become much common recently in young adults, adolescents and infrequently, in children [16]. Altered lipid metabolism and hyperglycemia in T2DM begin by the incapacity of β cells in secretion of sufficient insulin in reaction to fluctuating levels of insulin resistance that can be produced by inactivity, obesity or over-nutrition. The incapacity of β cells for compensation of elevated levels of glucose related to extra food intake, amplified secretion of glucagon and decreased response of incretin, impaired enlargement of subcutaneous adipose tissue, hypo-adiponectinaemia, adipose tissue inflammation, augmented production of endogenous glucose and the advancement of peripheral insulin resistance are the metabolic defects that add to the evolution of T2DM [17]. Chronic excess of calories is the key pathogenic incident that initiates T2DM development in genetically and epigenetically susceptible persons [18, 19].

Both T1DM and T2DM have several potential enduring impediments. It is indicated by the epidemiological research that the severity of diabetic impairments is proportional to volume of hyperglycemia in general [20, 21].

There is a greater prevalence of DM in the developed countries in comparison to the developing countries. Females are more affected than males DM and T2DM institutes 90% cases. The adult prevalence of DM worldwide in 1995 was assessed to be around 4.0% and it was predicted to rise by the year 2025 up to 5.4%; mostly this increase would ensue in the developing regions of the world. So, it is probable that by 2025, 75% diabetic individuals will be in the developing countries, ageing between 45-64 years however in the developed regions, most of diabetic individuals will be > 65 years of age. DM will be progressively arising in urban zones [22]. In America, DM affects ~21 million people, together with over 9% of the adult populace [10]. Nearly 6 million of these persons remain undiagnosed despite of having the disease [23]. Around 85% to 90% of diabetics have T2DM, while 5% to 10% of patients have T1DM.

Micro-vascular and macro-vascular problems are often experienced by the individuals having DM and with chronically meager metabolic control. This problem embraces direct charges of medical care and indirect charges, such as productivity loss, resulting from diabetes-linked ill health and premature death [5, 24]. There are consistent defects demonstrated clearly in neutrophil chemotactic, phagocytic, and microbicidal activities, through clinical investigations in the diabetics [25-27]. Due to reduced functional activity of neutrophils, DM escalates the susceptibility to, and severity of, infections and thus contributes to delay wound healing. DM can cause several ailments and chronic systemic impediments if left untreated, mostly produced by hyperglycemia-induced oxidative stress and also cellular and molecular defect in neural and vascular structure and function [25, 28]. DM-induced complications can result in the irregular function of cells, tissue, and organ systems, consequently demise [25].

Chronic hyperglycemia influences the nervous and circulatory systems ensuing in irreversible chronic problems e.g. diabetic nephropathy, neuropathy, retinopathy, cardiovascular illnesses, peripheral vascular maladies, and PDs. Since the 1960s, relationship has been reported in the literature between DM and PD and PD had been advocated as a 6th long-term diabetic impairment [29].

Periodontal Disease [PD]

It is a chronic and infectious disease. Gram-negative microbes cause PD which are found in bacterial plaque adhering to the teeth [30]. It has been reported that dental microbial plaque can be formed due to about 500 various bacterial entities and different human viruses [7, 31].

Recently, destructive PD has been associated with some herpes viruses, i.e. Epstein-Barr virus (EBV-1) and the human cytomegalovirus (HCMV). Many situations like smoking, dyslipidemia, obesity, genetics, estrogen deficiency and estrogen excess can enable and/or affect the incidence of PD [7, 32- 37].

PD is a very widespread ailment. It has been reported that in the USA, majority population with >18 years age have PD in

its primary phases, rising to about 75% after 35 years of age. Approximately 30% to 50% individuals exhibit mild to moderate disease while the severe generalized phase exists in 5% to 15% of the adult general populace [38]. PD has an extensive universal variation, much greater prevalence in minority groups, poor and developing states [39].

To determine gingival tissue injury, disparity between a localized infection and an exaggerated host inflammatory response shows a fundamental part. The effects of PD might have systemic consequences too apart from the oral cavity as PD has been related with a low-grade systemic inflammation also, though the processes behind this relationship are still vague. The augmented danger of impeding metabolic control in diabetes-linked impairments and the undesirable effects of DM on periodontal condition could be described by this relationship [40].

It has been established since long that due to the existence of Gram-negative anaerobic bacteria, a local inflammatory reaction initiates which then advances and gets chronic. The bacteria can bring about an early infiltrate of inflammatory cells, like macrophages, lymphocytes and polymorph nuclear leukocytes (PMNs). An abundant variety and quantity of pro-inflammatory molecules, i.e. cytokines interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), prostaglandins (especially prostaglandin E2 (PGE2) and specific further enzymes can be synthesized and secreted by macrophages that are activated by certain microbial components, particularly lipopolysaccharide (LPS) [41].

T lymphocytes can be activated too by the bacterial toxins to yield IL-1 and Lymphotoxin (LT), which has the features alike to those of TNF-α. These cytokines exhibit strong catabolic and pro-inflammatory actions, and have significant part in periodontal tissue devastation produced by collagenolytic enzymes like Metalloproteinase (MMPs). The reactive oxygen species activate the collagenolytic enzymes thereby elevating interstitial collagenase levels in swollen gingival tissue [41, 42]. The attachment failure excavates the sulcus, generating a periodontal port that has heaps of bacterial cells. This phase is the evolution between gingivitis and periodontitis, in general, the PDs [43, 44].

It is known that several situations can affect and/or enable the existence of PD i.e. smoking, genetics, estrogen deficiency, estrogen excess, dyslipidemia and obesity. Obesity epidemic is too related with an augmented incidence of obesity-related illnesses such as hypertension, cardiovascular diseases, metabolic syndrome and DM that are associated with PD too [7, 25, 33-37, 45].

This is established that there is a two-way association between DM and PD [46]. The severity of periodontal inflammation affects glycemic control negatively while diabetes escalates the risk of PD [47]. A report shows that the risk of periodontitis is augmented almost 3-folds in diabetics in comparison to non-diabetic patients [1, 25] and poor glycemic control increases the risk [24]; the severity of PD has an adverse influence on glycemic control [48-50]. Periodontal therapy has improved glycemic regulation for at least 3 months in type 2 diabetics [51].

Several studies have discovered that majority of the diabetics did not have adequate information regarding adverse effects of diabetes on their oral fitness [52-54] although they have more information about the systemic consequences of DM [25]. It has been reported that around 70% of diabetics had never received any instruction from the dental specialists about oral health care associated with DM [25, 52]. It was also stated that the health care professionals managing DM in patients were not instructing them about their oral health care mostly due to inadequate awareness and limited time in dealing with oral complications related to DM [55].

Influence of Diabetes Mellitus on Periodontal Disease

DM and chronic periodontitis are long-term ailments that are linked biologically since long [56, 57]. DM is one of the principal risk elements for PD [21, 58]. The risk of periodontitis has been identified to be about 3-4 times more in diabetics than in non-diabetics through cross-sectional and longitudinal studies [21]. A research among African Americans exhibited that 70.6% of T2DM patients suffered from moderate periodontitis and 28.5% suffered with a severe level. This was considerably greater than the prevalence of 10.6% amid control group devoid of DM [59]. A direct correlation amid the degree of glucose control and periodontitis severity was established [60, 61].

DM and PD both are widespread diseases. The WHO report of 2014 mentioned that worldwide 8.5% of adults of 18 years and above age had DM while 10–15% of the global populace had severe periodontitis [62, 63]. A considerably greater prevalence of PD in T2 DM patients was seen as compared to non-DM control group (50% versus 36%) in another study [64]. Apart from this, the severity and advancement of PD is also affected by DM [1]. The patients with uncontrolled DM can have greater risk of developing severe PD as compared to non-DM control group [65]. It was established that in meagerly regulated DM patients, there is more progressive alveolar bone loss [66, 67] and periodontal deterioration [68], poorer consequence after periodontal therapy [69], further recurring periodontal infection and unfavorable long term prognosis [70]. PD was thus considered to be the sixth DM complication [71]. The bidirectional relation between DM and PD has been supported by many researches [72, 73].

As described extensively in previous studies [1, 67], 27 in 29

studies were reported to have substantial confirmation of the adverse effects of DM on periodontal condition by Carlos *et al.* [7].

One study suggested that gingivitis appeared to be widespread much more in females with Gestational DM when related with healthy pregnant females; the plaque buildup seemed to be the leading source of gingival swelling [74] Reports from one more research showed that all kinds of DM escalate PD risk, inclusive of Gestational DM [7]. Data from more than 4,000 females with a history of GDM was collected in two studies in the USA concluding a strong association between GDM and PD [75]. Analysis of existing statistics exposes substantial indication that DM is a risk factor for gingivitis and periodontitis, with degree of glycemic regulation as a significant element in this connection [76].

In children with T1DM, gingivitis prevalence was found to be more than in non-diabetics with same levels of plaque [77]. Two times as many locations had gingival swelling in diabetic children as matched to non-diabetic controls with same levels of plaque [78]. Gingival swelling was also higher in T2DM adults than in control group, with the utmost swelling in patients with meager glycemic control [1]. A more speedy and marked progression of gingival swelling in reasonably well-controlled mature T1 diabetics was observed than in non-diabetic controls in a longitudinal gingivitis research [79], despite of same buildup of plaque levels and comparable bacterial plaque composition, signifying a hyper-inflammatory gingival reaction in diabetes.

Such researches put forward that increased gingival inflammation is often connected with the presence of DM. Furthermore, glycemic control level in diabetics may play its part in the gingival reaction to bacterial plaque. DM has been linked with a greater risk of periodontitis at a young age also. Periodontitis was not observed under the age of 12 years in a group of 263 T1 diabetics in comparison to 59 non-diabetic relatives and 149 non-diabetic non-relative controls [1]. But, 13.6% of the diabetics had periodontitis aged between 13 and 18 years, and the prevalence amplified to 39% among ages from 19 to 32 years; by evaluation, the prevalence in non-diabetic control group was less than 3%.

Epidemiologic researches in diabetic adults have frequently exposed an escalation in degree and severity of periodontitis. The prevalence and severity of attachment damage and bone loss was larger between diabetics than non-diabetic controls in all age groups in the Pima Indians of Arizona who have the maximum occurrence of T2DM globally. The diabetic persons were seen to have 2.8- to 3.4-fold enlarged odds of having periodontitis in a multivariate risk analysis as compared to non-diabetics, after adjusting confounders like gender, age and oral hygiene procedures; a larger risk of attachment failure and bone loss in adult diabetics is generally exhibited via smaller studies. The incidence and prevalence of PD were assessed in 2,273 Pima Indians aged 15 years or more. The prevalence of periodontitis was found to be 60% in diabetics and 36% in non- diabetics. The incidence in a subset of 701 15 to 54 years old subjects at baseline had negligible or no evidence of periodontitis. After an average of more than 2.5 years, the incidence of periodontitis was observed to be 2.6-fold greater in diabetics than in non-diabetics. Later, poorly controlled adult diabetics showed a 2.9-fold amplified risk of having periodontitis as compared to non-diabetics in a large US based epidemiologic research. On the other hand, well-controlled diabetics showed no substantial rise in the risk of periodontitis. T1DM subjects with a mean period of > 16 years, with meager glycemic regulation exhibited more interproximal attachment damage and bone loss in a cross sectional study. Other studies also revealed similar results displaying increased calculation of profound periodontal pockets and the prevalence of severe detachment with worsened glycemic regulation [1, 80-82].

The bacterial microflora at spots with PD in diabetics is found to be same like the microflora at same ailing locations in non-diabetics as reported by culture studies. The role of immune cells, together with monocytes, macrophages, and neutrophils, is changed in DM. Neutrophil attachment, chemotaxis, and phagocytosis are every so often compromised, which can deter bacterial slaying in the periodontal pocket thereby considerably increasing destruction of periodontal tissues. Even if the role of neutrophils is generally reduced in DM, the monocyte/macrophage cell line can display up regulation in reaction to bacterial antigens. Due to monocytes/macrophages hyper-responsiveness, there is noteworthy rise in the creation of pro-inflammatory cytokines and mediators. The higher degree of periodontal attachment and bone loss in diabetics could be linked with variations in connective tissue metabolism which detach the resorptive and formative reactions. Several studies have demonstrated compromised osseous healing and bone turnover in relationship with hyperglycemia. The resultant of hyperglycemic condition embraces restriction of Osteoblastic cell proliferation and collagen manufacture, leading to diminished bone development and weakened mechanical features of the freshly formed bone [1, 83, 84].

Microvascular modifications are a symbol of a lot of diabetic impairments. The structural modifications that illustrate diabetic angiopathy comprise of uncharacteristic growth and compromised vessels redevelopment. The alterations observed in the microvasculature of the retina, glomerulus, and other end organs in diabetic impairments also ensue in the periodontium. Due to persistent hyperglycemia, proteins are irreversibly glycated to make advanced glycation end products (AGEs) which are stable carbohydrate-containing proteins. These AGEs have numerous effects on cell-to-cell and cell-to-matrix interactions and are generally believed to be the main connection between different diabetic impair-

ments. The development of AGEs also takes place in the periodontium, and greater periodontal AGE buildup is seen in the diabetic patients than in non-diabetics. AGEs are frequently formed on collagen, with growing collagen cross-linking and ensuing in the development of very firm collagen macromolecules. The macromolecules gather in tissues as they are resistant to normal enzymatic degradation and tissue turnover. AGE-modified collagen collects in the walls of bigger blood vessels, hence condensing the vessel wall and constricting the lumen. Moreover, AGE-modified vascular collagen has an affinity for low-density lipoprotein (LDL); it leads to LDL buildup in the vessel wall, supporting atherosclerotic modifications specific to macrovascular DM impairments. The basement membranes of endothelial cells store AGE-modified collagen macromolecules too, which may lead to the increased thickness of basement membrane in the microvasculature, changing normal homeostatic transport through membrane. Such a growth in thickness of basement membrane is observed in periodontium blood vessels of diabetic patients. AGE development is also connected with amplified creation of vascular endothelial growth factor (VEGF) which is a multifunctional cytokine which persuades neovascularization and has a chief part in microvascular DM impairments [1, 85]. Raised VEGF levels have been noticed in serum of diabetics and also in main tissues influenced by diabetic vasculopathies.

The common alterations in synthesis of collagen, maturation, and homeostatic turnover in DM can add to the pathogenesis of PDs and to changes in curing of wound as collagen is the chief fundamental protein in the periodontium. Human gingival fibroblasts yield reduced quantities of collagen and glycosaminoglycans in hyperglycemic situations. A diminished rate of collagen production is seen in diabetic animals that can be reinstated by insulin administration to regularize levels of plasma glucose. Newly synthesized collagen, along with its diminished synthesis, is vulnerable to deterioration by MMPs like collagenase, which is raised in diabetic tissues together with periodontium [1].

The clinical and epidemiological proof established in the literature delivers the notion that DM affects adversely on PD, PD deteriorates corresponding to glycemic regulation and lastly PD is connected with an escalation in the risk for diabetes-linked impairments.

CONCLUSION

The scientific evidence reviewed supports that PDs and DM are correlated and are vastly prevalent chronic ailments with numerous resemblances in pathobiology. As DM has an adversative effect on periodontal wellbeing similarly, PD also has an adversative effect on glycemic regulation and on complication linked with diabetes. Additional studies are required in order to explain these associations and the mechanisms through which this occurs. The influence of PDs on glycemic regulation of DM and the processes through which this proceed are less clear. Associated antecedent situations together with obesity and insulin resistance due to inflammatory PDs may play an important role on the effect of PDs on glycemic regulation of DM. Inflammation plays a perilous part in the relationship, and its significance is now being revealed. Bigger, prospective, controlled trials with varied ethnic populaces are necessary to institute that by treatment of PD there can be a positively influenced glycemic regulation and this probably can decrease the problem of diabetes-related problems.

CONFLICT OF INTEREST

Declared none.

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