Association between Diabetes Mellitus and Periodontal Diseases

Sahar Abdelkhalik Elsheikh[1], Khalid Mahmood Uddin[2], Shamail Zia*,[3], Syeda Alveera Batool[4], Fahmeeda Khatoon Junejo[3]

[1]Department of Medicine, Tanta University, Tanta, Egypt.

[2]Department of Neurology, Henry Ford Hospital, Detroit, USA.

[3]Department of Pathology, Jinnah Sindh Medical University, Karachi, Pakistan.

[4]Department of Medicine, Jinnah Post Graduate Medical Center, Karachi, Pakistan.

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-

*Address correspondence to this author at the Department of Pathology, Jinnah Sindh Medical University, Karachi, Pakistan.
Email: drshamailzia@gmail.com

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.

REFERENCES

[1] Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. J Periodontol 2006; 77(8): 1289-303. DOI: 10.1902/-jop.2006.050459

[2] Mealey BL, Ocampo GL. Diabetes mellitus. Periodontal 2000 2007; 44: 127-53. DOI: 10.1111/j.1600-0757.2006.00193.x

[3] Diagnosis and classification of diabetes mellitus: Position statement. Diabetes Care 2005; 29(Suppl 1): S37-S42. DOI: 10.2337/diacare.28.suppl_1.S37

[4] Mokdad AH, Ford ES, Bowman BA, *et al*. The continuing increase of diabetes in the U.S. Diabetes Care 2001; 24: 412. DOI: 10.2337/diacare.24.2.412

[5] National Center for Health Statistics, United States. Chart book on Trends in the health of Americans, Table 55. Hyattsville, MD: National Center for Health Statistics 2005.

[6] Centers for Disease Control and Prevention. National Diabetes Fact sheet. Available at: http://www.cdc.gov/diabetes/-pubs/estimates.html. [Accessed December 27, 2005].

[7] Negrato CA, Tarzia O, Jovanovic L, Montenegro LE. Periodontal disease and diabetes mellitus. J Appl Oral Sci 2013; 21(1): 1-12. DOI: 10.1590/1678-7757201302106

[8] Taylor GW, Borgnakke WS. Periodontal disease: Associations with diabetes, glycemic control and complications. Oral Dis 2008; 14: 191-203. DOI: 10.1111/j.1601-0825.2008.01442.x

[9] Teeuw WJ, Gerdes VE, Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: A systematic review and meta-analysis. Diabetes Care 2010; 33(2): 421-7. DOI: 10.2337/dc09-1378

[10] Skyler J, Oddo C. Diabetes trends in the USA. Diabetes Metab Res Ver 2002; 18: S21-6. DOI: 10.1002/dmrr.289

[11] Kahn SE. Clinical review 135: The importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 2001; 86(9): 4047-58. DOI: 10.1210/jcem.86.9.7713

[12] Cavaghan MK, Ehrmann DA, Polonsky KS. Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. J Clin Invest 2000; 106 (3): 329-33. DOI: 10.1172/JCI10761

[13] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2009; 32(Suppl 1): S62-7. DOI: 10.2337/dc09-S062

[14] SEARCH for Diabetes in Youth Study Group, Liese AD, D′Agostino RB, Jr, *et al*. The burden of diabetes mellitus among US youth: Prevalence estimates from the SEARCH for Diabetes in Youth Study. Pediatrics 2006; 118(4): 1510-8. DOI: 10.1542/peds.2006-0690

[15] Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature 2010; 464(7293): 1293-300. DOI: 10.1038/nature08933

[16] Pinhas-Hamiel O, Zeitler P. The global spread of type 2 diabetes mellitus in children and adolescents. J Pediatr 2005; 146(5): 693-700. DOI: 10.1016/j.jpeds.2004.12.042

[17] Nolan CJ, Damm P, Prentki M. Type 2 diabetes across generations: From pathophysiology to prevention and management. Lancet 2011; 378(9786): 169-81. DOI: 10.1016/S0140-6736(11)60614-4

[18] Prentki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006; 116 (7): 1802-12. DOI: 10.1172/JCI29103

[19] Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009; 58 (4): 773-95. DOI: 10.2337/db09-9028

[20] Wu YY, Xiao E, Graves D. Diabetes mellitus related bone metabolism and periodontal disease. Int J Oral Sci 2015; 7: 63-72. DOI: 10.1038/ijos.2015.2

[21] Tandon N, Ali MK, Narayan KM. Pharmacologic prevention of microvascular and macrovascular complications in diabetes mellitus: Implications of the results of recent clinical trials in type 2 diabetes. Am J Cardiovasc Drugs 2012; 12(1): 7-22. DOI: 10.2165/11594650-000000000-00000

[22] King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: Prevalence, numerical estimates, and projections. Diabetes Care 1998; 21(9): 1414-31. DOI: 10.2337/diacare.21.9.1414

[23] Centers for Disease Control and Prevention. National Diabetes Fact Sheet. Available at: http://www.cdc.gov/diabetes/-pubs/estimates.htm. [Accessed December 27, 2005].

[24] Rhodes CJ. Type 2 diabetes- A matter of β cell life and death?

Science 2005; 307: 380-84. DOI: 10.1126/science.1104345

[25] AlShwaimi E, Idrees M, Berri Z, El-Sakka H, Kujan O. Association between diabetes mellitus and periodontal diseases: A survey of the opinions of dental professionals. Med Princ Pract 2019; 28: 141-9. DOI: 10.1159/000495881

[26] Yano H, Kinoshita M, Fujino K, *et al.* Insulin treatment directly restores neutrophil phagocytosis and bactericidal activity in diabetic mice and thereby improves surgical site Staphylococcus aureus infection. Infect Immun 2012; 80(12): 4409-16. DOI: 10.1128/IAI.00787-12

[27] Lecube A, Pachón G, Petriz J, Hernández C, Simó R. Phagocytic activity is impaired in type 2 diabetes mellitus and increases after metabolic improvement. PLoS One 2011; 6(8): e23366. DOI: 10.1371/journal.pone.0023366

[28] Leite RS, Marlow NM, Fernandes JK, Hermayer K. Oral health and type 2 diabetes. Am J Med Sci 2013; 345(4): 271-3. DOI: 10.1097/MAJ.0b013e31828bdedf

[29] Sima C, Glogauer M. Diabetes mellitus and periodontal diseases. Curr Diab Rep 2013; 13: 445-52. DOI: 10.1007/s11892-013-0367-y

[30] Negrato CA, Tarzia O. Buccal alterations in diabetes mellitus. Diabetol Metab Syndr 2010; 2: 3. DOI: 10.1186/1758-5996-2-3

[31] Amar S, Han X. The impact of periodontal infection on systemic diseases. Med Sci Monit 2003; 9: RA291-RA9.

[32] Slots J, Kamma JJ, Sugar C. The herpesvirus-Porphyromonas gingivalis-periodontitis axis. J Periodontal Res 2003; 38: 312-23. DOI: 10.1034/j.1600-0765.2003.00659.x

[33] Lösche W, Marshal GJ, Apatzidou DA, Krause S, Kocher T, Kinane DF. Lipoprotein-associated phospholipase A2 and plasma lipids in patients with destructive periodontal disease. J Clin Periodontal 2005; 32: 640-4. DOI: 10.1111/j.1600-051X.2005.00725.x

[34] Morita M, Horiuchi M, Kinoshita Y, Yamamoto T, Watanabe T. Relationship between blood triglyceride levels and periodontal status. Community Dent Health 2004; 21: 32-6.

[35] Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. J Periodontal 2005; 76(Suppl 11): 2075-84. DOI: 10.1902/jop.2005.76.11-S.2075

[36] Burt B, Research, Science and Therapy Committee of the American Academy of Periodontology. Position paper: Epidemiology of periodontal diseases. J Periodontal 2005; 76: 1406-19. DOI: 10.1902/jop.2005.76.8.1406

[37] Haytaç MC, Cetin T, Seydaoglu G. The effects of ovulation induction during infertility treatment on gingival inflammation. J Periodontal 2004; 75(6): 805-10. DOI: 10.1902/jop.2004.75.6.805

[38] Friedewald VE, Kornman KS, Beck JD, *et al*. The American Journal of Cardiology and Journal of Periodontology editor's consensus: Periodontitis and atherosclerotic cardiovascular disease. J Periodontal 2009; 80: 1021-32. DOI: 10.1902/jop-.2009.097001

[39] Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet 2005; 366: 1809-20. DOI: 10.1016/S0140-6736(05)67728-8

[40] D'Aiuto F, Graziani F, Tetè S, Gabriele M, Tonetti MS. Periodontitis: From local infection to systemic diseases. Int J Immunopathol Pharmacol 2005; 18(Suppl 3): 1-11.

[41] Sorsa T, Ingman T, Suomalainen K, *et al*. Identification of proteases from periodontopathogenic bacteria as activators of latent human neutrophils and fibroblast-type interstitial collagenases. Infect Immun 1992; 60: 4491-5. DOI: 10.1128/i-ai.60.11.4491-4495.1992

[42] Lee W, Aitken S, Sodek J, McCulloch CA. Evidence of a direct relationship between neutrophil collagenase activity and periodontal tissue destruction *in vivo*: Role of active enzyme in human periodontitis. J Periodontal Res 1995; 30: 23-33. DOI: 10.1111/j.1600-0765.1995.tb01249.x

[43] Kornman KS, Page RC, Tonetti MS. The host response to the microbial challenge in periodontitis: assembling the players. Periodontal 2000 1997; 14: 33-53. DOI: 10.1111/j.1600-0757.1997.tb00191.x

[44] Geerts SO, Legrand V, Charpentier J, Albert A, Rompen EH. Further evidence of the association between periodontal conditions and coronary artery disease. J Periodontal 2004; 75: 1274-80. DOI: 10.1902/jop.2004.75.9.1274

[45] Al-Zahrani MS, Bissada NF, Borawskit EA. Obesity and periodontal disease in young, middle-aged, and older adults. J Periodontal 2003; 74: 610-5. DOI: 10.1902/jop.2003.74.5.610

[46] Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. J Periodontal 2005; 76(Suppl 11): 2075-84. DOI: 10.1902/jop.2005.76.11-S.2075

[47] Preshaw PM, Alba AL, Herrera D, *et al*. Periodontitis and diabetes: A two-way relationship. Diabetologia 2012; 55(1): 21-31. DOI: 10.1007/s00125-011-2342-y

[48] Lamster IB, DePaola DP, Oppermann RV, Papapanou PN, Wilder RS. The relationship of periodontal disease to diseases and disorders at distant sites: Communication to health care professionals and patients. J Am Dent Assoc 2008; 139(10): 1389-97. DOI: 10.14219/jada.archive.2008.0051

[49] Arora N, Papapanou PN, Rosenbaum M, Jacobs DR Jr, Desvarieux M, Demmer RT. Periodontal infection, impaired fasting glucose and impaired glucose tolerance: Results from the Continuous National Health and Nutrition Examination Survey 2009-2010. J Clin Periodontol 2014; 41(7): 643-52.

DOI: 10.1111/jcpe.12258

[50] Shultis WA, Weil EJ, Looker HC, *et al*. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. Diabetes Care 2007; 30(2): 306-11. DOI: 10.2337/dc06-1184

[51] Teeuw WJ, Gerdes VE, Loos BG. Effect of periodontal treatment on glycemic control of diabetic patients: A systematic review and meta-analysis. Diabetes Care 2010; 33(2): 421-7. DOI: 10.2337/dc09-1378

[52] Bowyer V, Sutcliffe P, Ireland R, Lindenmeyer A, Gadsby R, Graveney M, *et al*. Oral health awareness in adult patients with diabetes: A questionnaire study. Br Dent J 2011; 211(6): E12. DOI: 10.1038/sj.bdj.2011.769

[53] Faden AA, Alsalhani AB, Idrees MM, Alshehri MA, Nassani MZ, Kujan OB. Knowledge, attitudes, and practice behavior of dental hygienists regarding the impact of systemic diseases on oral health. Saudi Med J 2018; 39(11): 1139-47. DOI: 10.15537/smj.2018.11.23267

[54] Eldarrat AH. Awareness and attitude of diabetic patients about their increased risk for oral diseases. Oral Health Prev Dent 2011; 9(3): 235-41.

[55] Poudel P, Griffiths R, Wong VW, Arora A, George A. Knowledge and practices of diabetes care providers in oral health care and their potential role in oral health promotion: A scoping review. Diabetes Res Clin Pract 2017; 130: 266-77. DOI: 10.1016/j.diabres.2017.06.004

[56] Bullon P, Newman HN, Battino M. Obesity, diabetes mellitus, atherosclerosis and chronic periodontitis: A shared pathology via oxidative stress and mitochondrial dysfunction? Periodontol 2000 2014; 64(1): 139-53. DOI: 10.1111/j.1600-0757.2012.00455.x

[57] Sai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Community Dent Oral Epidemiol 2002; 30(3): 182-92. DOI: 10.1034/j.1600-0528.2002.300304.x

[58] Preshaw PM, Bissett SM. Periodontitis: Oral complication of diabetes. Endocrinol Metab Clin North Am 2013; 42(4): 849-67. DOI: 10.1016/j.ecl.2013.05.012

[59] Fernandes JK, Wiegand RE, Salinas CF, *et al*. Periodontal disease status in gullah african americans with type 2 diabetes living in South Carolina. J Periodontol 2009; 80(7): 1062-8. DOI: 10.1902/jop.2009.080486

[60] Popławska-Kita A, Siewko K, Szpak P, *et al*. Association between type 1 diabetes and periodontal health. Adv Med Sci 2014; 59(1): 126-31. DOI: 10.1016/j.advms.2014.01.002

[61] Al-Khabbaz AK. Type 2 diabetes mellitus and periodontal disease severity. Oral Health Prev Dent 2014; 12(1): 77-82. DOI: 10.1902/jop.2005.76.12.2187

[62] WHO. Global report on diabetes. 2016; Available at: https://www.who.int/publications/i/item/9789241565257

[63] Petersen PE, Ogawa H. Strengthening the prevention of periodontal disease: The WHO approach. J Periodontol 2005; 76(12): 2187-93. DOI: 10.1902/jop.2005.76.12.2187

[64] Leung WK, Siu SC, Chu FC, *et al*. Oral health status of low-income, middle-aged to elderly Hong Kong Chinese with type 2 diabetes mellitus. Oral Health Prev Dent 2008; 6(2): 105-18.

[65] Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. Commun Dent Oral Epidemiol 2002; 30(3): 182-92. DOI: 10.1034/j.1600-0528.2002.300304.x

[66] Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M. Glycemic control and alveolar bone loss progression in type 2 diabetes. Ann Periodontol 1998; 3(1): 30-9. DOI: 10.1902/annals.1998.3.1.30

[67] Taylor GW, Burt BA, Becker MP, *et al*. Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years. J Periodontol 1998; 69(1): 76-83. DOI: 10.1902/jop.1998.69.1.76

[68] Salvi GE, Carollo-Bittel B, Lang NP. Effects of diabetes mellitus on periodontal and peri-implant conditions: update on associations and risks. J Clin Periodontol 2008; 35(8 Suppl): 398-409. DOI: 10.1111/j.1600-051X.2008.01282.x

[69] Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. J Am Dent Assoc 2008; 139Suppl: 19S-24S. DOI: 10.14219/jada.archive.2008.0363

[70] Tervonen T, Karjalainen K. Periodontal disease related to diabetic status. A pilot study of the response to periodontal therapy in type 1 diabetes. J Clin Periodontol 1997; 24(7): 505-10. DOI: 10.1111/j.1600-051X.1997.tb00219.x

[71] Loe H. Periodontal disease: The sixth complication of diabetes mellitus. Diabetes Care 1993; 16(1): 329-34. DOI: 10.2337/diacare.16.1.329

[72] Chee B, Park B, Bartold PM. Periodontitis and type II diabetes: A two-way relationship. Int J Evid Based Healthc 2013; 11(4): 317-29. DOI: 10.1111/1744-1609.12038

[73] Mealey BL. Periodontal disease and diabetes. A two-way street. J Am Dent Assoc 2006; 137Suppl: 26S-31S. DOI: 10.14219/jada.archive.2006.0404

[74] Mittas E, Erevnidou K, Koumantakis E, Papavasileiou S, Helidonis E. Gingival conditions of women with gestational diabetes on a Greek island. Spec Care Dentist 2006; 26: 214-9. DOI: 10.1111/j.1754-4505.2006.tb01441.x

[75] Xiong X, Buekens P, Vastardis S, Pridjian G. Periodontal disease and gestational diabetes mellitus. Am J Obstet Gynecol 2006; 195: 1086-9. DOI: 10.1016/j.ajog.2006.06.035

[76] Mealey BL, Moritz AJ. Hormonal influences: Effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. Periodontol 2000 2003; 32: 59-81. DOI: 10.1046/j.0906-6713.2002.03206.x

[77] Cianciola L, Park B, Bruck E, Mosovich L, Genco R. Prevalence of periodontal disease in insulin-dependent diabetes mellitus (juvenile diabetes). J Am Dent Assoc 1982; 104: 653-60. DOI: 10.14219/jada.archive.1982.0240

[78] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Position statement. Diabetes Care 2005; 29(Suppl 1): S37-S42. DOI: 10.2337/diacare.28.suppl_1.S37

[79] Salvi GE, Kandylaki M, Troendle A, Persson GR, Lang NP. Experimental gingivitis in type 1 diabetics: A controlled clinical and microbiological study. J Clin Periodontol 2005; 32: 310-6. DOI: 10.1111/j.1600-051X.2005.00691.x

[80] Campus G, Salem A, Uzzau S, Baldoni E, Tonolo G. Diabetes and periodontal disease: A case-control study. J Periodontal 2005; 76: 418-25. DOI: 10.1902/jop.2005.76.3.418

[81] Tsai C, Hayes C, Taylor GW. Glycemic control of type 2 diabetes and severe periodontal disease in the U.S. adult population. Community Dent Oral Epidemiol 2002; 30: 182-92. DOI: 10.1034/j.1600-0528.2002.300304.x

[82] Guzman S, Karima M, Wang H-Y, Van Dyke TE. Association between interleukin-1 genotype and periodontal disease in a diabetic population. J Periodontol 2003; 74: 1183-190. DOI: 10.1902/jop.2003.74.8.1183

[83] Beam A, Parsons JR, Lin SS. The effects of blood glucose control upon fracture healing in the BB Wistar rat with diabetes mellitus. J Orthop Res 2002; 20: 1210-16. DOI: 10.1016/S0736-0266(02)00066-9

[84] Amir G, Rosenmann E, Sherman Y, Greenfeld Z, Ne'eman Z, Cohen AM. Osteoporosis in the Cohen diabetic rat: Correlation between histomorphometric changes in bone and microangiopathy. Lab Invest 2002; 82: 1399-405. DOI: 10.1097/01.LAB.0000032378.19165.E2

[85] Chiarelli F, Santilli F, Mohn A. Role of growth factors in the development of diabetic complications. Horm Res 2000; 53: 53-67. DOI: 10.1159/000023515