

The Bi-Directional Relationship between Diabetes Mellitus And Periodontal Disease A Structured Review And Contemporary Concepts

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Abstract

Objective: To review the relevant references and provide the updated knowledge about the relationship between diabetes and periodontal disease over last decade.

Methodology used: A structured review of articles and clinical research published in the authoritative and relevant journals of the last decade to make it convenient for the dental practitioner, to rapidly review the latest advances.

Conclusion: There is a confirmed bi-directional relationship between the worsening periodontal disease and the Diabetes mellitus aggravation; hence the role of dental surgeon in managing the diabetic patient is paramount.

Keywords: periodontitis, diabetes mellitus, complication of diabetes, bi-directional.

I. Introduction

Diabetes mellitus (DM) is one of the most common chronic systemic diseases in the world and particularly in the Arab world and considered one of most dangerous disease based on its complications. DM is a clinically and genetically non-homogeneous group of disturbances affecting the metabolism of carbohydrates, lipids, and proteins. ⁽¹⁾ The distinctive feature of the DM is an increase of the blood glucose above the normal range as result of the reduction or complete loss of insulin secretion from pancreatic Beta- cells or due to insulin resistance from the body. ⁽²⁾ Diabetic patients show classical triad of symptoms polydipsia, polyuria, and polyphagia. This often leads to chronic fatigue and Weight loss. Complications of DM include retinopathy, nephropathy, neuropathy, and cardiovascular disease. Most common oral disease related to diabetes mellitus is a periodontal disease. Periodontal disease (PD) is a chronic inflammatory disease that affects tooth surrounding periodontium. ⁽⁴⁾ Periodontitis is now considered as the sixth most common complication of the DM. ⁽⁵⁾ The common periodontal disease associated with DM are gingivitis which is (inflammation of the gingiva around the teeth) and periodontitis (inflammation and destruction of the periodontium {tooth supporting structures}).

The relationship between diabetes and periodontal disease has been investigated over past many years. Many clinical types of research showing a two-way relationship between diabetes mellitus and periodontal disease. ⁽⁹⁾ Therefore, as dental students and dentists, we have to be alert to the signs and symptoms of diabetes and periodontal disease and effects of both on each other. Here in this review, we will address to the recent knowledge about the relationship between DM and PD over last decade in many articles and clinical research published in the authoritative journals. This review highlights the need for further research to demonstrate the biological relationship between these chronic diseases.

II. Methods

A decade-long review of relevant literature has been attempted here. We wish to make it easier for the dental practitioners to make a rapid reading of different viewpoints within his economical time available. No statistical analysis was done and neither is this a structured meta-analysis. A qualitative review and summarization are done in this article. The review showing some of the epidemiological studies that demonstrate the relationship of both disease and showing possible mechanisms of interaction.

III. Discussion

The DM is classified into two main types; type1 diabetes, which considered as an autoimmune destruction of beta cells in the pancreas which in turn lead to total loss of the insulin secretion. ⁽²⁾ This type is commonly seen in children and adolescents, despite some studies showing 15% to 30% of all cases being discovered after 30 years of age. ⁽¹⁰⁾ Total loss of the insulin secretion often accompanied with ketoacidosis. The extreme cases of ketoacidosis can be fatal, thus it is necessary to use the exogenous source of insulin. The key to management of this type is with the regular blood glucose monitoring and insulin therapy.

Type II DM occurs due to a resistance of body tissues to endogenous insulin and its defective secretion.⁽¹⁾⁽²⁾ Today it is considered a lifestyle disorder. A 90-95% of all cases seen in clinic are type II DM. In this type, the quantity, responsiveness to the insulin, secretion is reduced, and autoimmune destruction of beta cells does not occur. The incidence of the ketoacidosis is comparatively low. The type II DM is not detected early because the hyperglycemia is gradually elevated and symptomless.⁽¹¹⁾ In early stages of the disease, the insulin secretion is increased as a response to insulin resistance. As the disease progresses the insulin secretion is decreased due to prolonged insulin secretion which results from the insulin resistance.⁽¹²⁾ Type II usually associated with lifestyle factors (LF) and genetics. The LF such as lack of exercises, being overweight, bad eating habits and stress are the modifiable and preventable risks. The fatty tissues have an important role in insulin resistance.⁽¹³⁾ Increase the free fatty acid level in the blood circulation will inhibit the glucose uptake, glycogen synthesis, glycolysis, and will increase hepatic glucose production.⁽¹⁴⁾ The management of the type II DM is associated with lifestyle modifications, weight loss, and oral drugs, and in extreme cases insulin injection. This type is commonly seen in adults, elderly patients, and recently increasing numbers of cases in younger age group.

Gestational diabetes mellitus [GDM] is the form of the DM that occurs during pregnancy. The children of mothers with gestational DM are at greater risk of experiencing obesity and diabetes as young adults.⁽¹⁵⁾ In addition, the mothers have a greater risk to develop type II DM in the future. The gestational DM typically start in the 3rd trimester of pregnancy. After parturition, generally, most of the women recover to normal status. The prevalence of GDM in Saudi women was determined by Al-Rubeaan et al (2015)⁽¹⁶⁾ to be 36.6%. Previously in [2000 and 2010], it was 12.5%.⁽¹⁷⁾⁽¹⁸⁾ Hence we see a significant increase over the 15 year period.

Criteria For Diagnosis Of Diabetes Mellitus

At the end of 19th Century, the WHO adopted the diagnostic criteria for DM by American diabetes association.⁽¹⁹⁾ Presently there are three ways to diagnose the DM. **1)** symptoms of DM such as polyuria, polydipsia, and sudden weight loss; plus casual plasma glucose concentration ≥ 200 mg/dl (≥ 11.1 mmol/l) which mean measuring of Blood glucose in any time a day. **2)** fasting blood glucose ≥ 126 mg/dl (≥ 7.0 mmol/l) defined as no caloric intake for at least 8 hrs. **3)** 2-hrs postload glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Table 1: 2005 American Diabetes Association Showing the Criteria for the Diagnosis of Diabetes Mellitus, IGT, and IFG.⁽²⁾

Table 1	Normal	Diabetes	IGT	IFG
Fasting Blood glucose (mg/dl)	<100	≥ 126		100 to 125
Casual plasma glucose (mg/dl)		≥ 200 plus symptoms of DM		
2-hrs PG (mg/dl)	<140	≥ 200	140-199	

The hemoglobin A 1 C test (Hb A 1C) is used to diagnose and observe diabetes and prediabetes in adults. The Hb A 1C test measures the glycolhemoglobin levels and provides an estimate of blood glucose level over a period of 4-12 weeks. The blood glucose and Hb A 1C levels exhibit a positive correlation.

Table 2: American Diabetes Association Recommendations for HbA1c Levels.⁽²⁾

Table 2	Interpretation
HbA1c <6	Normal value
HbA1c <7	Treatment objective for patient with diabetes; life style modifications should control glucose levels well enough to maintain HbA1c values <7%
HbA1c >8	Physician intervention is required to control the glucose levels

Table 3:Correlation between HbA1c Levels and Mean Glucose Levels.⁽²⁾

HbA1c (%)	Mean Glucose (mg/dl)
6	135
7	170
8	205
9	240
10	275
11	310
12	345

Periodontal Disease:

The periodontal disease is a microbial disease that affects supporting structures surrounded teeth (periodontium) due to bacteria and immune cells reaction.⁽²⁰⁾ The periodontal disease involves (1) Gingivitis, which is a reversible inflammation of the gingiva. It's usually related to plaque build-up around teeth. Dental plaque is a sticky biofilm build on the surface of the tooth containing colonies of the bacteria. Gingivitis resolve with regular using of oral hygiene methods. Untreated gingival inflammation may progress to (2) periodontitis, which is an advanced stage of inflammation, progressed to connective tissue and alveolar bone leading to a destruction of these tissues and pocket formation or recession or both, subsequently lead to tooth loss.

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Criteria For Diagnosis Of periodontal Disease

Estimating the prevalence of the periodontal disease is complex. Estimation usually based on the diagnostic criteria approved in each study. Many studies of periodontal disease prevalence utilize Loe and Silness gingival index.⁽²¹⁾ The severity of the periodontitis described by terms mild, moderate to severe. Because of the destruction of the supporting structures around the teeth, the periodontitis of the DM is a complex problem and it needs periodontitis to treat it effectively. Home oral hygiene by patient needs to be encouraged and plays an equally pertinent role.

Prevalence:

A study from Abha⁽²²⁾ found the periodontitis to be mild in 57.4%, moderate periodontitis in 36.6% and severe in 4.95% and aggressive in 0.89%. Those patients above the fourth decade of life showed a significantly higher value for a prevalence of PD. However in Riyadh El- Angbawi MF⁽²³⁾ mentioned that amongst the school children there was no difference in the periodontal status according to age and sex. This can be explained by the fact that the prevalence of PD becomes apparent only when patients reach an age of 40.

Diabetes Mellitus And Periodontal Diseases (Inter-Relationship)

The presence of the periodontal disease in diabetic people is commonly observed. Which mean the risk of periodontal disease increased in diabetic patients especially with uncontrolled patients. Belting et al⁽²⁴⁾ have registered the relationship of the DM and periodontal disease on the early 1960s. In the mid- nineties and after many research and epidemiological studies has been conducted the relationship of the DM and periodontal disease is confirmed. Moreover, the periodontal disease becomes the sixth complication of the DM.⁽⁵⁾

The DM As Risk Factor For The Periodontal Disease:

According to many authors, DM is at the present, considered as a high-risk factor for periodontal disease and contribute to increasing the severity and progression of the periodontitis.⁽²⁵⁾⁽²⁶⁾ The possible mechanisms of this relationship of both diseases have similar common features in addition to the classic complication of DM include retinopathy, nephropathy, and neuropathy. These mechanisms are currently under study and are still controversial. We will discuss some of the mechanisms briefly proposed to this relationship.

Despite the periodontal disease require bacterial flora develop there is little differences in gingival bacteria between diabetic patients and non-diabetic patients with periodontitis. Some early research reported a high proportion of the of Capnocytophaga species in those with diabetes.⁽²⁷⁾ Most later cultural studies reported no significant difference in the sub-gingival bacterial flora in diabetic and non-diabetic periodontal disease patients.⁽²⁸⁾⁽²⁹⁾ Therefore lacking differences of the pathogenic bacteria causing periodontal disease in both diabetic and non-diabetic patients guided authors and researcher to concentrate on the immune response of

diabetic and controls patients, to these microorganisms. In the diabetic patient the immune cells response as neutrophils, monocytes, and macrophages, are changed and the chemotaxis, phagocytosis, and adherence of the neutrophils are impaired.⁽³⁰⁾ Thus their ability to attack the bacteria is reduced which lead to increase in periodontal loss. Although the neutrophils in diabetic patients numerically decline, other inflammatory immune cells response such as monocytes and macrophages may display up-regulation in the secretion of proinflammatory cytokines and mediators such as tumor necrosis factor (TNF α) and interleukin-1 β (IL-1 β), prostaglandins in response to tissue damage. The increase in the (TNF α) can be measured from blood serum and crevicular fluid. In the study conducted by the Engebretson and colleagues⁽³¹⁾ between the diabetic and controls people in measuring the (IL-1 β) in the clavicular fluid, they found that the patients with HbA1C greater than 8% they had almost twice high in (IL-1 β) compared to the patients with Hb1AC less than 8%. The ability of tissue healing in diabetic people decreased consequently the periodontal tissue healing response to the chronic bacterial infection is impaired which lead to increase periodontal inflammation, Attachment loss, and bone loss. Thus, controlling of blood glucose level play an important role in the progression of periodontal disease.^{(9) (32)(33)}

The Periodontal Disease As Risk Factors For DM:

As the DM has a role in developing periodontal disease, a chronic periodontitis have a significant impact on the glucose levels in diabetic patients. On the longitudinal trial study among diabetic patients, one group with severe periodontitis and another group without periodontitis. The diabetics with periodontitis had six folds increased the risk for worsening of the glucose level compared to those without periodontitis as well as the periodontal disease have a role in developing complications of diabetes. In the longitudinal case-control study, between diabetics, one group with severe periodontitis and another group without periodontitis 82% of diabetics with severe periodontitis depicted one or more of the major cardiovascular, peripheral vascular or cerebrovascular disease compared to 21% of these without periodontitis.^{(34) (35)}

Chronic periodontitis is considered as chronic inflammation that affects the glycemic control, which in turn lead to deterioration of cell-mediated immunity like neutrophil chemotaxis and macrophage function,⁽³⁶⁾⁽³⁷⁾ besides cytokines such as transforming growth factor (TGF)- α and IL-10 which have role in control hormonal responses and IL-2 and interferon (IFN) gamma, which control the cellular response. These changes will affect the secretion of the insulin from β - cells of the pancreas, which in turn affect the glycemic control.

The mechanism by which the periodontal disease affects the glycemic control has been demonstrated recently. Both periodontal diseases and DM especially type 2 diabetes, have main inflammatory components. Bacterial and viral systemic infections result in increased systemic inflammation, which in turn increases insulin resistance and makes it difficult for patients to control blood glucose levels. Chronic periodontal diseases also have likely to increase insulin resistance and worsen glycemic control. The serum levels of proinflammatory cytokines in the patients with the chronic periodontal disease are increased.⁽³⁹⁾ Similarly in the diabetics which in turn increase the insulin resistance and complicate the glycemic control.⁽⁴⁰⁾ A study reported that periodontal treatment may improve the glycemic control of diabetics.⁽⁴¹⁾ Iwamoto et al.⁽⁴²⁾ conduct study on the patient with type II diabetes and severe periodontitis they reported that the periodontal treatment have significant role in decreasing the serum levels of TNF- α was accompanied by a significant decrease in mean HbA1c values (from 8.0 to 7.1 percent). This proposes that treatment of periodontal disease will reduce the inflammatory mediators and cytokines in the serum and which in turn will reduce the insulin resistance.

The Role of Dental Professional:

In the year 2007, World Health Organization (WHO) had linked oral health and overall health.⁽⁴³⁾ They propose that the oral health care should be included in the routine health care programs by which cause it is considered the neglected area in most of the global health. Dental professionals have the open door and the duty to identify, assessment and management of their patients who are susceptible to the risk of developing diabetes. It is their duty to raise the awareness of society about the oral health and oral complications associated with the systemic disease as diabetes, prevention, management of these complications and oral health education. It is important that the patients be referred to primary health care practitioners. Guidelines recommended for dental professionals to utilize with the treatment of diabetics in dental practice.⁽⁴⁴⁾

- Instruct patients with diabetes of the increased risk of periodontal diseases, which may make glycemic control more troublesome, and educating people that they are at higher risk of diabetic complications.
- A detailed oral examination of people with type 1, type 2 and gestational diabetes.
- A periodontal examination for all recently determined people to have type 1 and type 2 diabetes (with annual follow-up) as a major part of their continuous management of diabetes.
- Immediate periodontal evaluation for diabetic patients presenting with signs and symptoms of periodontitis such as increased mobility, a spacing of teeth and/or gingival recession.

- All diabetic patients require dedicated health education. An increased risk of oral fungal infections and experience delayed wound healing is observed characteristically, and oral symptoms (such as dry mouth and burning mouth) are noticed.
- Regular yearly oral screening in schools will help in the early diagnosis of juvenile diabetes.

IV. Conclusion

As stated in this review the DM and the periodontal disease have the strong bilateral association as diabetes increase the risk to develop the periodontal disease and periodontal disease worsening the glycemic control. Controlling of the DM have a significant impact on reducing the periodontal inflammations likewise, treatment of periodontal disease have the clear impact on the glycemic control. Further research needs to be done on these relationships and clarifying the exact mechanism for this two-way relationships. We as dental professionals we have to contribute in raise the awareness of the community and particularly diabetic patients about the oral complications of DM by establishing awareness campaigns in the schools and malls using social media, radio, and television.

References

- [1]. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. *Periodontol* 2000 2007; 44 :127-153.
- [2]. Position statement of American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2005;29(Suppl. 1):S37-S42.
- [3]. Soskolne WA, Klinger A. The relationship between periodontal diseases and diabetes: an overview. *Ann Periodontol* 2001; 6: 91-8.
- [4]. Pihlstrom, B.L., Michalowicz, B.S. and Johnson, N.W. (2005) Periodontal Diseases. *The Lancet*, 366, 1809-1820. [http://dx.doi.org/10.1016/S0140-6736\(05\)67728-8](http://dx.doi.org/10.1016/S0140-6736(05)67728-8)
- [5]. Loe H. Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* 1993; 16: 329-34.
- [6]. Mealey BL. Periodontal implications: medically compromised patients. *Ann Periodontol* 1996;1:256-321.
- [7]. Papapanou PN. Periodontal disease: epidemiology. *Ann Periodontol* 1996;1:1-36.
- [8]. Mealey BL, Oates TW; American Academy of Periodontology. Diabetes mellitus and periodontal diseases. *J Periodontol*. 2006;77:1289-303.
- [9]. Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. *J Periodontol* 2006; 77:1289–1303. This is a broad and detailed review commissioned by the American Academy of Periodontology. It covers scope of bilateral interrelationships between diabetes and inflammatory periodontal diseases
- [10]. Laakso M, Pyorala K. Age at onset and type of diabetes. *Diabetes Care* 1985;8:114-117.
- [11]. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;14:173-194.
- [12]. Rhodes CJ. Type 2 diabetes – A matter of b-cell life and death? *Science* 2005;307:380-384.
- [13]. Festa A, D’Agostino R Jr., Howard G, Mykkanen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000;102:42-47.
- [14]. Bergman RN, Ader M. Free fatty acids and pathogenesis of type 2 diabetes mellitus. *Trends Endocrinol Metab* 2000;11:351-356.
- [15]. Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, and others. 1998 clinical practice guidelines for the management of diabetes in Canada. Canadian Diabetes Association. *CMAJ* 1998; 159 (Suppl 8):S1-29.
- [16]. Al-Rubeaan K, Al-Manaa HA, Khoja TA, Youssef AM, Al-Sharqawi AH, Siddiqui K, et al. A community-based survey for different abnormal glucose metabolism among pregnant women in a random household study (SAUDIDM). *BMJ Open*. 2014;4(8). doi: 10.1136/bmjopen-2014-005906.
- [17]. Al-Rowaily M, Abolfotouh M. Predictors of gestational diabetes mellitus in a high-parity community in Saudi Arabia. *EMHJ*. 2010;16(6).
- [18]. Ardawi M, Nasrat HA, Jamal HS, Al-Sagaaf HM, Mustafa BE. Screening for gestational diabetes mellitus in pregnant females. *Saudi medical journal*. 2000;21(2):155.
- [19]. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.
- [20]. Graves D (2008) Cytokines that promote periodontal tissue destruction. *J Periodontol* 79(8Suppl): 1585S–1591S
- [21]. Loe, H. (1967) The Gingival Index, the Plaque Index and the Retention Index Systems. *Journal of Periodontology*, 38,610-616.
- [22]. Hossain MZ, Fageeh HN, Elagib MF: (Abha, KSA) :Prevalence of the periodontal disease among patients attending the out patient department atCity dent coll J vol 10 no 1, 9-12. January 2013.
- [23]. El-Angbawi MF, Younes SA. Periodontal disease prevalence and dental needs among schoolchildren in Saudi Arabia. *Community Dent Oral Epidemiol*. 1982 Apr;10(2):98-9.
- [24]. Belting, C.M., Hiniker, J.J. and Dummett, C.O. (1964) Influence of Diabetes Mellitus on the Severity of Periodontal Disease. *Journal of Periodontology*, 8, 34-39. <http://dx.doi.org/10.1902/jop.1964.35.6.476>
- [25]. Salvi, G.E., Carollo-Bittel, B. and Lang, N.P. (2008) Effects of Diabetes Mellitus on Periodontal and Peri-Implant Conditions: Update on Associations and Risks. *Journal of Clinical Periodontology*, 35, 398-409. <http://dx.doi.org/10.1111/j.1600-051X.2008.01282.x>
- [26]. Khader, Y.S., Dauod, A.S., El-Qaderi, S.S., Alkafajei, A. and Batayha, W.Q. (2006) Periodontal Status of Diabetics Compared with Nondiabetics: A Meta-Analysis. *Journal of Diabetes and Its Complications*, 20, 59-68. <http://dx.doi.org/10.1016/j.jdiacomp.2005.05.006>
- [27]. American Academy of Periodontology. Diabetes and periodontal diseases (position paper). *J Periodontol* 1999;70:935-949.
- [28]. Sastrowijoto S, Hillemans P, van Steenberghe T, Abraham-Inpijn L, de Graaff J. Periodontal condition and microbiology of healthy and diseased periodontal pockets in type 1 diabetes mellitus patients. *J Clin Periodontol* 1989;16:316-322.
- [29]. Zambon JJ, Reynolds H, Fisher JG, Shlossman M, Dunford R, Genco RJ. Microbiological and immunological studies of adult periodontitis in patients with non-insulin dependent diabetes mellitus. *J Periodontol* 1988;59:23-31.
- [30]. Manoucher-Pour M, Spagnuolo PJ, Rodman HM, Bissada NF. Comparison of neutrophil chemotactic response in diabetic patients with mild and severe periodontal disease. *J Periodontol* 1981;52(8):410-5.

- [31]. Engebretson SP, Hey-Hadavi J, Ehrhardt FJ, et al. Gingival crevicular fluid levels of interleukin-1 β and glycemic control in patients with chronic periodontitis and type 2 diabetes. *J Periodontol* 2004;75(9):1203-8.
- [32]. Lalla E, Cheng B, Lal S, et al. Periodontal changes in children and adolescents with diabetes. *Diabetes Care* 2006; 29:295–299.
- [33]. Mealey BL. Periodontal disease and diabetes: A two-way street. *J Am Dent Assoc* 2006; 137 (10 suppl):26s–31s.
- [34]. Taylor GW, Burt BA, Becker MP, et al. Severe periodontitis and risk for poor glycemic control in patients with noninsulin-dependent diabetes mellitus. *J Periodontol* 1996; 67:1085–1093.
- [35]. Thorstensson H, Kuylensteirna J, Hugoson A; Medical status and complications in relation to periodontal disease experience in insulin-independent diabetics. *J ClinPeriodontol.*, 1996; 23: 194-202.
- [36]. Kornman KS. Mapping the pathogenesis of periodontitis: a new look. *J Periodontol* 2008; 79: 1560-8.
- [37]. Alonso N, Martínez-Arconada MJ, Granada ML, Soldevila B, Cantón A, Mate JL, et al. Regulatory T cells in type 1 diabetic patients with autoimmune chronic atrophic gastritis. *Endocrine* 2009; 35: 420-8.
- [38]. Yki-Jarvinen H, Sammalkorpi K, Koivisto VA, Nikkila EA. Severity, duration and mechanisms of insulin resistance during acute infections. *J ClinEndocrinolMetab* 1989;69(2):317-23.
- [39]. Loos BG, Craandijj J, Hoek FJ, Wertheim-van Dillen PME, van der Velden U. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontal patients. *J Periodontol* 2000;71(10):1528-34.
- [40]. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes and periodontal infections. *J Periodontol* 2005; 76: 2075-84.
- [41]. Loesche WJ, Grossman NS. Periodontal disease as a specific, albeit chronic, infection: diagnosis and treatment. *ClinMicrobiol Reviews* 2001; 14: 727-52.
- [42]. Iwamoto Y, Nishimura F, Nakagawa M, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor α and glycosylated hemoglobin level in patients with type 2 diabetes. *J Periodontol* 2001;72(6):774-8.
- [43]. World Health Organisation. Oral health: action plan for promotion and integrated disease prevention (EB120/10). 120th Session, 22-30 January. Geneva:
- [44]. Chapple IL, Genco R (2013) Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J ClinPeriodontol* 40(Suppl 14): S106–12.