Relationship between type 2 diabetes and periodontal disease

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ABSTRACT

Purpose: To assess periodontal status in type 2 diabetes (T2D) to compare the findings between diabetic and non-diabetic individuals using Community Periodontal Index (CPI) and Oral Hygiene Index (OHI). Associations between glycemic control and inflammatory biomarkers were analyzed among T2D patients in comparison with controls.

Materials and methods: A total of 135 patients with T2DM (F64/ M71) and 40 healthy controls (CG) (F21/M19) individuals were assessed. Periodontal status was assessed using CPI, OHI and tooth number. Blood samples were analyzed for glycemic control markers (FPG and HbA1c), inflammatory mediators (CRP, TNF-α, Il-1) and lipids (TG, TC, HDL, LDL). Study participants with T2D were classified into 2 groups according to their level of HbA1c: good metabolic control group (GMC) had HbA1c below 7.0% and poor metabolic control group (PMC) had HbA1c above 7.0%.

Results: The prevalence of periodontitis in all patients with T2D was 83.5%, 82.7% in GMC group, and 86.4% in PMC group as compared to CG 57.7%. The number of sextants with CPI codes of 3 was higher in PMC T2D as compared to controls. We observed significant positive correlation between OHI and: age (R=0,566, $p<0.001$), creatinine concentrations (R=0.377, $p<0.01$), tooth number (R=0.841, $p<.001$), CPI3 (R=0.518, $p<0.01$) and CPI4 (R=0.498; $p<0.001$). Negative correlation (R=-0.388; $p<0.01$) between OHI and IL-1 concentrations and number of sextants with CPI1 was found.

Conclusion: The study indicated that type 2 diabetic subjects should improve their oral hygiene practices and that the control of blood glucose levels ought to be emphasized.

Key words: Type 2 diabetes, hyperglycemia, periodontitis, Community Periodontal Index, Oral Hygiene Index

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INTRODUCTION

The main complications of diabetes mellitus (DM) affect organs and tissues rich in capillary vessels and are secondary to the development of angiopathy. Similar changes in small vessels can be found in the oral tissues [1]. Thus, many researchers assert that periodontal disease is the sixth complication of DM [2-6]. Periodontal disease can occur in most age groups but is more common in adults and elders worldwide [7,8]. Periodontal diseases include gingivitis (in which the inflammation is confined to the gingiva and is reversible with good oral hygiene) and periodontitis (in which the inflammation extends and results in tissue destruction and alveolar bone resorption). Periodontitis is a major chronic inflammatory disease associated with increased production of numerous proinflammatory cytokines leading to the destruction of the periodontal tissue and ultimately to loss of teeth. Tissue destruction in periodontitis results in the breakdown of the collagen fibres of the periodontal ligament, resulting in the formation of a periodontal pocket between the gingiva and the tooth [9].

Diabetes and periodontal disease are two pathological entities that destructively emphasize each other. There is emerging evidence to support the existence of a two-way relationship between diabetes and periodontitis, with diabetes increasing the risk of periodontitis, and periodontal inflammation negatively affecting glycemic control [2, 3, 7, 8].

Studies suggest that diabetes is a risk factor for periodontal disease, pointing out that the prevalence, incidence and severity of periodontal disease are higher among patients with DM in comparison to healthy individuals [9-12]. The mechanisms by which diabetes influences periodontal disease include vascular abnormalities, neutrophil dysfunction, abnormalities in collagen synthesis and genetic predisposition [13]. There are two hypotheses for determining the relationship between periodontitis and diabetes. First of all, the basement membrane protein undergoes non-enzymatic glycation when subjected to hyperglycemic condition. Because of the high vascularity of the inflamed periodontium, this inflamed tissue may serve as an endocrine-like source for tumor necrosis factor alpha (TNF-α) and other inflammatory mediators [14]. Therefore, it was hypothesized that diabetes-induced exaggeration of host immune responses played a crucial role in periodontal pathogenesis, as glucose-mediated advanced glycation end products can increase the production of proinflammatory cytokines and mediators, which could contribute to periodontal destruction [14]. According to the second proposed hypothesis, a fortuitous combination of genes (gene sets) combined with the influence of a variety of environmental stressors could lead to the development of either periodontitis or diabetes, or both [15]. On the other hand, a different prospective study has proved that periodontal disease can increase the risk of difficult metabolisation of carbohydrates, which causes the occurrence of DM, and that periodontopathies in patients with diabetes are associated with a poorer metabolic control of diabetes and with a greater number of chronic diabetic complications [16]. In contrary, certain findings indicate no apparent association between periodontitis and incident diabetes [17].

This bidirectional relation between periodontal disease and diabetes is of a major importance for dentists in making certain therapeutic decisions connected with diabetic patients. For this reason, the aim of this study was to determine the periodontal status in type 2 diabetic patients (T2D) compared with normal healthy individuals using Community Periodontal Index (CPI) and Oral Hygiene Index (OHI). We evaluated the associations between glycemic control, serum inflammatory biomarkers and periodontal disease among T2D patients in comparison with age- and gender-matched non-diabetic controls.

MATERIAL AND METHODS

The study included 135 patients with T2D (F64/ M71) and 40 healthy controls (CG) (F21/M19) of similar age and gender distribution who were treated in our outpatient clinic. Inclusion criteria were: type-2 diabetes diagnosed by a diabetologist more than one year before, having 6 or more teeth and lack of other general health problems such as cardiovascular, liver and kidney diseases, or other systemic conditions, including immunologic or psychiatric disorders. All the patients and controls gave informed consent to participate in the study before the enrollment. The protocol was approved by the local ethics committee.

All the subjects underwent a comprehensive assessment, including documentation of medical history, physical examination and measurement of laboratory parameters. Physical examination encompassed systolic and diastolic blood pressure. Blood pressure was recorded three times, in accordance with the recommended standard. Prior to each measurement, the participants were asked to remain resting for at least 5 min.

Complete clinical periodontal examinations included the assessment of OHI and Community Periodontal Index (CPI 0, CPI1, CPI 2, CPI 3, CPI 4). The mouth was divided into six sections, with index teeth 11, 16, 17, 26, 27, 31, 36,

37, 46, and 47 representing each section. Typically, testing results of index teeth represented the periodontal health for each section. CPI is recommended as an epidemiological tool by the World Health Organization and has been widely used. The highest CPI code was recorded in each segment (code 0: no signs of periodontal disease, code 1: gingival bleeding after gentle probing, code 2: supragingival or subgingival calculus, code 3: 4 to 5 mm deep pathologic pockets, code 4: 6 mm or deeper pathologic pockets). In our study, a community periodontal index (CPI) of 3 to 4 and a CPI value of 0 to 2 were classified as periodontitis and non-periodontitis, respectively. All the examinations were performed by an experienced dental specialist.

The oral hygiene condition was visually evaluated by examining all present teeth without using the disclosing solution as follows: 1) good, plaque covering less than one-third of tooth surfaces; 2) fair, plaque covering more than one-third but less than two-thirds of tooth surfaces; and, 3) poor, plaque covering more than two-thirds of tooth surfaces. The worst score was recorded as the representative for that subject.

The blood samples were collected from an antecubital vein without the use of a tourniquet, between 7:30 and 8:30h, after an overnight fast to avoid the differences of diurnal variation. Blood samples were clotted for 30 minutes and next centrifuged for 10 minutes at 1000 g. Serum aliquots were frozen at –80°C. Venous blood samples were taken from each patient and analyzed for glycemic control markers: fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), inflammatory mediators: high-sensitivity C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-1 (Il-1) and lipids: triglycerides (TG), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL) and high-density lipoprotein-cholesterol (HDL). The mean percentage of HbA1c measurement was used to indicate the long-term control of diabetes. HbA1c was measured by HPLC (high-performance liquid performance liquid chromatography, Bio-Rad VARIANT), external and internal quality controls were positioned within the allowed ranges. Serum TNF-α was measured by commercial ELISA kit (Bender MedSystems, Vienna, Austria). The measurements were carried out according to the manufacturer's directions. CRP was measured by Sandwich Enzyme Immunoassay (DSL-10-42100 Active, DSL, Webster, Texas, USA).

Participants with T2D were classified into 2 groups according to the level of HbA1c: good metabolic control group (GMC) had HbA1c below 7% (33 patients, 21F/12M), and poor metabolic control group (PMC) had HbA1c over 7% (102 patients; 43F/59M).

The data were analyzed by the STATISTICA 10.0 for Windows Software (StatSoft. Inc., Tulsa, USA). Prior to the analysis, the data were tested for normality of distribution using the Shapiro-Wilk test. The differences between the groups were compared by Student t-test or Mann-Whitney U test, as appropriate, and the relationships between variables were tested by Spearman's rank correlations. P value less than 0.05 was regarded as statistically significant.

RESULTS

The clinical biochemical characteristics and mean values of periodontal variables depending on metabolic control in the studied groups are presented in Table 1. We noticed no statistically significant differences between mean scores of weight, age and blood pressure in both examined and the control group. The mean HbA1c score for the GMC in T2D values was 6.2±1.2% and for the PMC group values, it was 10.5±0.8%, and the difference was statistically significant ($p<0.01$) (Table 1).

We observed significant differences in the HDL values between CG and both GMC: T2D and PMC T2D ($p<0.05$, $p<0.01$; respectively), LDL values between CG and GMC T2D ($p<0.001$) also between GMC T2D and PMC T2D ($p<0.01$) (Table 1). TG was statistically significantly higher in PMC T2D as compared to GMC T2D and CG ($p<0.01$; $p<0.01$). In T2D, both GMC and PMC group, statistically significantly higher concentrations of serum inflammatory biomarkers were observed: TNF-α ($p<0.001$; $p<0.01$, respectively) and Il-1 β ($p<0.01$; $p<0.001$, respectively). We observed significant differences in the microalbuminuria values between PMC T2D and both GMC T2D and the control group ($p<0.05$, $p<0.05$; respectively) (Table 1).

There were no differences in the number of teeth between diabetic patients and control group. The values of OHI were higher in diabetic patients, both GMC and PMC compared to CG, and the differences were statistically significant ($p<0.05$, $p<0.001$, respectively) (Table 1).

Using the standard definition of periodontitis, the prevalence of periodontitis in all the patients with T2D was 83.5%, 82.7% in GMC group, and 86.4% in PMC group as compared to CG 57.7%. The number of sextants with CPI codes of 0 was statistically significantly higher in control group as compared to GMC T2D ($p<0.05$). The number of sextants with CPI codes of 2 was statistically significantly higher in GMC T2D as compared to controls ($p<0.001$) and the number of sextants with CPI codes of 3 was statistically significantly higher in PMC T2D as compared to CG ($p<0.05$) (Table 1).

The percentage of sextants with Community Periodontal Index (CPI 0, CPI 1, CPI

2, CPI 3, CPI 4) in the diabetic patients and the control group is presented in Table 2.

Spearman's correlation coefficients in the patients with T2D are presented in Table 3. We observed a significant positive correlation between OHI and age (R=0.566, p<0.001), creatine concentrations (R=0.377, p<0.01), tooth number (R=0.841, p<0.001), CPI3 (R=0.518, p<0.01) and CPI4 (R=0.498; p<0.001). We also found a negative correlation between OHI and: IL-1 β concentrations (R=-0.388; p<0.01) and the number of sextants with CPI codes of 3 and 4 (Table 3).

Table 1. The clinical, biochemical characteristics and mean values of periodontal variables depending on metabolic control in the studied groups.

Parameters **Mean ± SD**	**T2D** **Good metabolic control** **HbA1c ≤ 7.0%** n=33(F21/M12)	**T2D** **Poor metabolic control** **HbA1c > 7.0%** n=102 (F43/M59)	**Control group** n =40 (F21/M19)
Age (years)	63.9 ± 12.6	58.5 ± 10.7	61.7 ± 7.6
Weight (kg)	86.6 ± 18.8	88.4 ± 21.5	71.3 ± 16.0
Systolic pressure (mmHg)	140.2 ± 12.3	143.0± 26.5	137.0 ± 27.3
Diastolic pressure (mmHg)	87.8 ±18.8	88.4 ± 21.5	85.3 ±12.8
HbA1C (%)	6.2 ± 1.2	10.5 ±0.8**	Ne
Fasting glucose (mg%)	128.2 ± 28.4	165.6 ± 58.7**	92.4 ± 12.8[2b]
Total Cholesterol(mg/dl)	171.7 ± 59.3	202.2 ± 60.3	196.6 ± 47.9
HDL (mg/dl)	41.5 ± 12.2	49.9 ± 26.1	51.7 ± 19.8[1b]
LDL(mg/dl)	88.2± 31.3	117.5± 37.7**	120.5 ± 36.3[3]
TG(mg/dl)	172.6 ± 149.2	218.0 ± 230.8**	107.1 ± 41.6[b]
Microalbuminuria	14.8±23.0	113.2±177.1*	24.0±20.1
Creatinine	1.0±0.3	1.0±0.4	0.8±0.2
CRP(ng/ml)	8.6 ± 6.9	8.0 ± 6.6	5.6 ± 1.3
Il-1 β (ng/ml)	0.5± 0.2	0.7 ± 0.9	0.4 ± 0.6[bc]
TNF-α (pg/ml)	2,8 ± 2.4	1.6 ± 1.7	1.2 ± 1.0[3b]
Number of tooth	10.9 ± 10.9	12.9± 10.1	11.9 ± 9.7
OHI	2.0 ± 0.6	2.0 ± 0.7	1.5 ± 0.7[1b]
CPI 0	0.0 ± 0.0	0.2 ± 0.6	0.3 ± 0.71[1]
CPI 1	1.1 ± 1.4	1.2± 1.4	1.5 ± 1.7
CPI 2	1.6 ± 1.5	1.2 ± 1.2	0.9 ± 1.4[2]
CPI 3	1.1 ± 0.9	1.5 ±1.4	1.0 ± 1.3[a]
CPI 4	0.5 ± 0.9	0.5 ±0.9	0.5 ± 1.0

Data are shown as means ± SD

Differences between GMC diabetic patients with control group at [1]p<0.05, [2]p<0.01, [3]p<0.001

Differences between PMC diabetic patients with control group at [a]p<0.05, [b]p<0.01, [c]p<0.001

Differences between diabetic patients with GMC and PMC at [*]p<0.05, [**]p<0.01, [***]p<0.001

Table 2. The percentage of sextants with Community Periodontal Index (CPI 0, CPI 1, CPI 2, CPI 3, CPI 4) in the diabetic patients and the control group.

	T2D **Good metabolic control** n=33(F21/M12)	**T2D** **Poor metabolic control** n=102 (F43/M59)	**Control group** n =40 (F21/M19)
CPI 0	0%	4.84%	7.5%
CPI 1	25.5%	20.0%	36.4%
CPI 2	38.3%	29.0%	21.5%
CPI3	25.5%	34.2%	23.4%
CPI4	10.6%	12.1%	11.2%

Table 3. Spearman's correlation coefficients in the patients with type 2 diabetes mellitus.

Variable	**R**	**P value**
OHI /age	0.566	<0.0001
OHI / creatinine	0.377	<0.01
OHI / Il-1 β	-0.388	<0.01
OHI / tooth number	0.841	<0.0001
tooth number / age	0.417	<0.01
tooth number / Il-1 β	-0.392	<0.01
CPI 1/tooth number	0.408	<0.001
CPI 1 /OHI	-0.451	<0.001
CPI 2 / OHI	0.336	<0.001
CPI 3/ TNFα	0.348	<0.01
CPI 3/ fasting glucose	0.217	<0.05
CPI 3/ tooth number	-0.282	<0.01
CPI 3/ OHI	0.518	<0.01
CPI4/ tooth number	-0.456	<0.001
CPI 4 /OHI	0.498	<0.001

DISCUSSION

Periodontitis is a slowly progressing disease but the tissue destruction that occurs is largely irreversible. Periodontitis is therefore a highly prevalent, but largely hidden, chronic inflammatory disease [9]. In non-diabetic patients the prevalence of mild, moderate and severe periodontitis was 28.9%, 10.2% and 8.0%, respectively [18]. In the present study, the subjects with CPI codes of 0, 1 and 2 were regarded as healthy while those with CPI codes of 3 and 4 were regarded as suffering from periodontitis. The prevalence of periodontitis observed in patients with T2D was 83.5%, 82.7% in GMC group and 86.4% in PMC group as compared to control group (57.7%). These results indicate a poorer periodontal health in type 2 diabetic patients than in control subjects. In the study by Mealey [19], the risk of periodontitis is increased by approximately threefold in diabetic individuals. *Chuang et al*. [20] reported no significant difference in the CPI index between diabetic and non-diabetic groups. These conflicting results may have been caused by the differences in the types of subjects (i.e., race, gender, and age) and the type of diabetes.

The level of glycemic control is of a key importance in determining the increased risk of periodontitis. For example, according to the US National Health and Nutrition Examination Survey (NHANES) III, adults with HbA1c level of >9% had a significantly higher prevalence of severe periodontitis than those without diabetes after controlling for age, ethnicity, education, gender and smoking [21]. In our study, periodontal health of this group of individuals with type-2 diabetes was poorer in the group with HbA1c over 7%. In this group, we observed a higher number of sextants with CPI codes of 3 in T2D with PMC (HbA1c >7.0%) (34.2%) than in GMC patients (25.5%) and controls (23.4%). Similarly, to our results, in the study by *Hodge et al*. the prevalence of severe periodontitis was higher in all T1D (24.1%) and poorly controlled patients (27.2%) than in controls (20.5%) [22].

Our findings are in accordance with the results of the studies conducted by Grossi *et al*.[23] and Bridges *et al*.[24] which indicate that diabetes significantly affects all the measured clinical parameters of periodontal status. We observed a statistically significant positive correlation OHI and a negative correlation tooth number in both groups: with shallow pockets (CPI 3) and with advanced periodontitis (CPI 4). The results obtained in this study strongly indicate the need of maintaining a good oral hygiene as well as the show that prevention and control of periodontal disease should be a mandatory part of diabetes control.

Many investigators have suggested the possibility of a bidirectional relationship between the two diseases, proposing that not only does the diabetes increase periodontal disease but also the presence of periodontal disease raises the risk of developing diabetes by inducing insulin resistance, impedes glycemic control and thus is responsible for other complications of diabetes [19,25]. FPG concentrations showed a significant relationship with CPI 3, which is coincident with preceding studies [26,27]. However, FPG levels reflect the metabolic control at one time point and one moment of the day, whereas HbA1c reflects glucose metabolism over the 3 preceding months. However, in the present study, no correlation was demonstrated between periodontal disease and HbA1c. This was in accordance with the results obtained in the study conducted by Alpagot et al. [28] who also found no correlation between glycated hemoglobin levels and clinical measurements of periodontitis.

In type 2 diabetes, hyperglycemia is often accompanied by hyperlipidemia. In our study, we observed marked elevations of low-density lipoprotein and triglycerides in T2D patients as compared to controls. These serum lipid abnormalities resulted from the disruption of fatty acid metabolism and accumulation of omega-6 polyunsaturated fatty acids that contribute to the formation of LDL [29]. There is substantial evidence that periodontal diseases are associated with elevated systemic cholesterol concentrations. Presumably, the association between periodontitis and lipid levels is the consequence of systemic effects of inflammatory stimulation [28]. In the present study, we observed no correlation between lipids concentrations, periodontitis index and inflammatory parameters. According to another study, dyslipidemia was also unrelated to periodontal disease [30,31].

The effect of serum lipids on immune cell phenotype/function leads to chronic localized infections. There occurs to be more than a regular relationship between serum lipid levels and diabetes susceptibility to periodontitis, and serum levels of pro-inflammatory cytokines. The relationship between periodontal status, proinflammatory mediators and metabolic parameters have been studied by numerous authors [25, 28, 32]. Periodontitis can easily turn periodontal tissue into a proinflammatory environment through increased levels of inflammatory mediators. The accumulated proinflammatory mediators play a pivotal role in reducing the sensitivity of insulin signaling and glucose metabolism [29, 32]. In this study, TNF-α concentrations were statistically significantly higher in diabetic patients with GMC and PMC as compared to controls. Increased serum concentrations of CRP have been observed in diabetic patients with both PMC and GMC, but the differences were not statistically significant. However, serum concentrations of CRP and TNF- α

were higher in patients with good metabolic control, yet the differences between PMC and GMC groups were not statistically significant. Our findings suggest that the presence of type 2 diabetes but not glycemic control is associated with inflammatory progression.

TNF-α, but also IL-1 β, have been shown to have important effects on glucose and lipid metabolism, particularly following an acute infectious challenge or a trauma [33]. It is believed, that IL-1β recruits inflammatory cells, facilitates polymorphonuclear leukocyte preparing/ degranulation, increases the synthesis of infla-mmatory mediators (prostaglandins)/matrix metalloproteinases (MMP), inhibits collagen synthesis and activates both T and B lymphocytes [29, 30]. In our study, we observed significant differences in serum concentration of Il-1 β in PMC T2D, as compared to the controls and negative correlations of IL-1β concentrations with the number of teeth. Therefore, our findings confirm the hypothesis that elevated levels of lL-1β are thought to play a role in the oral health.

Loss of teeth is associated with periodontitis. The presence of diabetes is a well known risk factor for tooth loss in subjects with periodontal disease [30]. There is also good evidence that inadequate metabolic control is the key factor leading to this complication and that the number of teeth decreases with increasing HbA1c values [34, 35]. In an earlier study, diabetic adults had, on average, approximately one more missing tooth compared to non-diabetics (31). In the present study, we observed no statistically significant decrease of tooth number in diabetic patients as compared to controls. However, the number of teeth positively correlated with OHI and age. These findings suggest that good oral hygiene might protect T2D patients from the progression of periodontal disease and loss of teeth.

CONCLUSIONS

The incidence of periodontitis was higher among type 2 diabetic patients with both good and poor metabolic control as compared to non-diabetic controls. This study indicated that type 2 diabetic subjects should improve their oral hygiene practices and that the control of blood glucose levels ought to be emphasize.

Conflicts of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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REFERENCES

1. Frantzis TG, Reeve CM, Brown A, Jr. The ultrastructure of capillary basement membranes in the attached gingiva of diabetics and nondiabetics patients with periodontal disease. J Periodontol. 1971 Jul;42(7):406-11.
2. Camen GC, Caraivan O, Olteanu M, Camen A, Bunget A, Popescu FC, Predescu A. Inflammatory reaction in chronic periodontopathies in patients with diabetes mellitus. Histological and immunohistochemical study. Rom J Morphol Embryol. 2012;53(1):55-60.
3. Löe H, Periodontal disease. The sixth complication of diabetes mellitus. Diabetes Care. 1993 Jan;16(1):329-34.
4. Lalla E, Lamster IB, Feit M, Huang L, Spessot A, Qu W, Kislinger T, Lu Y, Stern DM, Schmidt AM. Blockade of RAGE suppresses periodontitis-associated bone loss in diabetic mice. J Clin Invest. 2000 Apr;105(8):1117-24.
5. Pontes Andersen CC, Flyvbjerg A, Buschard K, Holmstrup P. Relationship between periodontitis and diabetes: lessons from rodent studies. J Periodontol. 2007 Jul;78(7):1264-75.
6. Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. Oral Dis. 2008; 14(3):191–203.
7. Chavarry NGM, Vettore MV, Sansone C, Sheiham A. The relationship between diabetes mellitus and destructive periodontal disease: a meta-analysis. Oral Health Prev Dent. 2009; 7(2):107-27.
8. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, et al. Assessment of risk for periodontal disease I Risk indicators for attachment loss J Periodontol. 1994 Mar; 65(3):260-7.
9. O'Dowd LK, Durham J, McCracken GI, Preshaw PM. Patients' experiences of the impact of periodontal disease. J Clin Periodontol. 2010 Apr; 37 (4): 334-9.
10. 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 Sep; 35(8 Suppl): 398-409.
11. Kasaj A, Zafiropoulos GG, Tekyatan H, Pistorius A, Willershausen B. Periodontal disease status of pregnant women with diabetes mellitus. Coll Antropol. 2008 Mar;32(1):115-8.
12. Pradhan S, Goel K. Interrelationship between diabetes and periodontitis: a review. J Nepal Med Assoc. 2011;51(183):144-53.
13. Oliver RC, Tervonen T. Diabetes—a risk factor for periodontitis in adults? J Periodontol. 1994 May; 65(5 Suppl):530-8.
14. Kiran M, Arpak N. The effect of improved periodontal health on metabolic control in type

2 diabetes mellitus. J Clin Periodontol. 2005 Mar;32(3):266-72.
15. Nishimura F, Iwamoto Y, Soga Y. The periodontal host response with diabetes. Periodontol 2000 2007;43:245-53.
16. Thorstensson H, Kuylenstierna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. J Clin Periodontol. 1996 Mar;23(3 Pt 1):194-202.
17. Ide R, Hoshuyama T, Wilson D, Takahashi K, Higashi T. Periodontal disease and incident diabetes: a seven-year study. J Dent Res. 2011 Jan;90(1):41-6.
18. Gulinuer A, Kurexi Y, Linlin L, Halmurat U, Jun R. Epidemiological Survey on the Prevalence of Periodontitis and Diabetes Mellitus in Uyghur Adults rom Rural Hotan Area in Xinjiang. Exp Diabetes Res. 2012; 2012:758921.
19. Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. J Periodontol. 2006 Aug;77(8):1289-303.
20. Chuang SF, Sung JM, Kuo SC, Huanf JJ, Lee SY. Oral and dental manifestations in diabetic and non-diabetic uremic patients receiving hemodialysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Jun;99(6):689-95.
21. Tsai 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 Jun;30(3):182-92.
22. Hodge PJ, Robertson D, Paterson K, Smith GL, Creanor S, Sherriff A. Periodontitis in non-smoking type 1 diabetic adults: a cross-sectional study. J Clin Periodontol. 2012 Jan;39(1):20-9.
23. Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, Genco RJ. Treatment of periodontal disease in diabetics reduces glycated hemoglobin. J Peri-odontol. 1997 Aug;68(8):713-9.
24. Bridges RB, Anderson JW, Saxe SR, Gregory K, Bridges SR. Periodontal status of diabetic and non-diabetic men: effects of smoking, glycemic control, and socioeconomic factors. J Periodontol. 1996 Nov; 67(11):1185-92.
25. Shimura F, Murayama Y. Periodontal inflammation and insulin resistance-lessons from obesity. J Dent Res. 2001 Aug;80 (8):1690-4.
26. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. J Am Dent Assoc. 2008 Oct; 139 Suppl: 19S -24S.
27. Almas K, Al-Qahtani M, Al-Yami M, Khan N. The relationship between periodontal disease and blood glucose level among type 2 diabetic patients. J Contemp Dent Pract. 2001 Nov 15;2(4):18-25.
28. Alpagot T, Silverman S, Lundergan W, Bell C, Chambers DW. Crevicular fluid elastase levels in relation to periodontitis and metabolic control of diabetes. J Periodontal Res. 2001 Jun;36(3):169-74
29. Grover HS, Luthra S.Molecular mechanisms involved in the bidirectional relationship between diabetes mellitus and periodontal disease. J Indian Soc Periodontol. 2013 May; 17(3):292-301.
30. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature. 1997 Oct 9;389 (6651):610-4.
31. Abdo JA, Cirano FR, Casati MZ, Ribeiro FV, Giampaoli V, Viana Casarin RC, Pimentel SP. Influence of Dyslipidemia and Diabetes Mellitus on Chronic Periodontal Disease. J Periodontol. 2013 Oct;84(10):1401-8.
32. Wise GE, Yao S, Odgren PR, Pan F. CSF-1 regulation of osteoclastogenesis for tooth eruption. J Dent Res. 2005 Sep;84(9):837-41.
33. Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. Ann Periodontol. 1998 Jul;3(1):51-61.
34. Furukawa T, Wakai K, Yamanouchi K, Oshida Y, Miyao M, Watanabe T, et al. Associations of periodontal damage and tooth loss with atherogenic factors among patients with type 2 diabetes mellitus. Intern Med. 2007;46 (17):1359-64.
35. Demmer RT, Holtfreter B, Desvarieux M, Jacobs DR Jr, Kerner W, Nauck M et al. The influence of type 1 and type 2 diabetes on periodontal disease progression: prospective results from the Study of Health in Pomerania (SHIP). Diabetes Care. 2012 Oct;35(10):2036-42.