Evaluation of Periodontal Status in Diabetes Mellitus Type 2 Patients Based on HbA1c and CRP

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Introduction: During the last decades, there has been an increasing interest in the relationship between diabetes mellitus (DM) and periodontitis. Some evidence has suggested that inflammatory factors like C-reactive protein (CRP) can be contributing factors to both periodontitis and diabetes. This study was aimed at assessing periodontal position in diabetes mellitus type 2 patients based on HbA1c and CRP. **Materials and Methods:** 76 patients with diabetes mellitus2 (DM2) were divided based on glycemic control: 35 subjects with HbA1c less than 7% and 41 subjects with HbA1c≥7%. The following measurements were conducted: Serum HbA1c and C-reactive protein (CRP), gingival Index (GI), plaque Index (PI), clinical attachment loss (CAL), bleeding on probing (BOP), and probing depth (PD). Moreover, age, gender and duration of diabetes of the patients were also analyzed. **Results**: In this study, 24 women and 11 men by mean age of 55/31±8/37 were in a good diabetic patients' group (HbA1c<7%) and 30 females and 11 males by the mean age of 53/76±9/91 were in poor control diabetic patients (HbA1c≥7%). A significant correlation between the elevation of CRP and increased level of HbA1c was observed (*P*<0/001). The patients` age was associated with the duration of diabetes (*P*=0/024) and women had significantly more duration of diabetes than men (*P*=0/012). Regarding PD, CAL, BOP and PI, there was no significant difference between the analyzed groups. Also, no significant relationship between CRP and periodontal parameters has been found. **Conclusion:** CRP was found as a predictor of HbA1c in patients with poor glycemic control. This implies higher infection rates due to diabetes.

Keywords: Diabetes Mellitus; Periodontal Disease; HbA1c; C- reactive protein

Introduction

Periodontitis is a disease with many complications, including toothache, tooth loss and bone resorption, resulting in reduced ability to chew, aesthetic risk and need for prosthetic restorations (1, 2). Periodontitis is an inflammatory disease caused by bacterial biofilms that ultimately results in bone loss (3). Diabetes, HIV infection and disorders in neutrophil cells can speed up the progression and incidence of periodontal disease as a predisposing factor (4). Several studies have shown a significant increase in serum C-reactive protein (CRP) levels in periodontitis (3).

Periodontal probe and panoramic photographs are used to diagnose periodontal disease (5). In the early stages, symptoms of periodontitis are mild, but if it persists, the symptoms develops and gingival redness, gingival bleeding on brushing and dental floss, bad breath and deep pocket and, loss of bone and tooth would observed (6).

Diabetes mellitus are among the group of metabolic diseases categorized as hyperglycemia caused by the defects in insulin secretion and action, or both. The chronic hyperglycemia of diabetes is related to the dysfunction, long-term damage, and failure of various organs, particularly the kidneys, eyes, heart, nerves, and blood vessels (7).

Type 2 diabetes is the most common kind of diabetes, which is resultant from peripheral resistance to insulin, impaired secretion of insulin, and incremented glucose production in the liver. In this type of diabetes, there are symptoms like fullness, fever, and urine in patients, and such a kind of diabetes is more common in adults than type 1(8).

In cases where the diagnosis of diabetes is decisive, the most important test for blood glucose control is the evaluation of HbA1c.

This test represents the average blood sugar level in the last 2-3 months (9).

Markers such as CRP and interleukin 6 (IL6) Indicators are important for cardiovascular disease and also the progression of type 2 diabetes (10, 11).

Scientific evidence supports many relationships between diabetes and periodontitis, as periodontitis was accepted as the 6th complication of diabetes mellitus. Although the onset of periodontal disease is related to a bacterial infection, the disease severity is largely influenced by the response and host conditions, such as diabetes (7).

Diabetes is known as a key risk factor for gingivitis and periodontitis. The basis of this relationship is the secretion of premature cytokines (12, 13). Hyperglycemia can inhibit the growth and function of osteoblasts and osteoclasts, and, by increasing the non-enzymatic glycation of intracellular and extracellular proteins, and the creation of ultimate glycemic products (AGEs), and a change in the spatial shape of proteins such as collagen, reduces Function of collagen, thereby, increase the rate of tissue destruction and increasing the degeneration of alveolar bone (14, 15).

On the other hand, diabetes leads to alterations in the function of immune cells such as neutrophils, macrophages and monocytes leading to a reduction in the primary defense of PMNs against periodontal pathogens (12, 16).

Regarding the relatively higher incidence of diabetes and its complications, many studies have done on the association between diabetes and periodontitis. Due to the interaction between these two diseases, it is essential that diabetic patients undergo periodontal treatments. Special attention should be paid to periodontitis.

The present work aimed to compare periodontal indices and CRP among diabetic patients with good and poor control of blood sugar according to measures of protein A1c. In addition, the correlation of periodontal indices and CRP was assessed.

Materials and Methods

In this descriptive study, 76 patients with type 2 diabetes with high blood glucose (FBS) above 126 mg/dl were included.

Inclusion Criteria

- Patients with at least eight teeth except third molars

Age 30-75 years

- Patients not receiving any periodontal treatment during the last 6 months
- Patients not receiving any anti-microbial therapy within the past 3 months
- Patients who had diabetes for at least 6 months

Exclusion Criteria

- Patients with advanced diabetic problems (macrovascular and microsurgical)
- Chronic pulmonary disease
- Advanced kidney and liver disease
- Malignancies
- Transplant
- History of infection and trauma, and any problems that require emergency treatment
- Alcohol consumption
- Pregnant
- People with inflammatory diseases like rheumatoid arthritis, inflammation of the joints and...

Informed consent was attained from all the participants. First, 95 diabetic patients underwent a full oral periodontal examination. Then, patients were asked to perform HBA1c and CRP tests; 19 patients were excluded from the study due to lack of cooperation. atients were categorized into 2 groups based on hemoglobin A1c:Group 1: poorly diabetic patients (Hba1c≥7%); Group 2: diabetic patients with proper blood glucose control (Hba1c <7%). Patients were also evaluated for age, sex, duration of illness and smoking, but due to the low number of smokers, they were excluded.

Periodontal indices such as gingival index (GI), plaque index (PI), probe depth (PD), gingival bleeding index (BOP), and loss of attachment (CAL) of all teeth were investigated.

PI was calculated using Colored surfaces/all dental surfaces*100. GI was used to measure gingival inflammation as followes: 1 ≥ GI: mild gingivitis; 1 <GI<2: moderate gingivitis and 2≤GI: severe gingivitis. PD was measured by probe periodontal o-Michigan at four surfaces of mesial, distal, lingual, and buccal of each tooth. BOP was measured in all teeth using a Michigan probe in mesio-lingual, mesiobacal, mid-buccal, mid-lingual, dystobuccal and diastolingual margin, and bleeding points up to 30 seconds after probing were evaluated. To measure CAL, CEJ distance to pocket depth was evaluated in all of the teeth with o-Michigan probe.

Statistical analysis

The analysis of the results of 76 patients with type 2 diabetes referred to Besat Specialty Clinic was done by SPSS 23 software and descriptive statistics (mean, standard deviation, tables and graphs). In all tables for comparing the age and duration of diabetes mellitus, Independent Samples Test, for comparing HbA1c and CRP from Mann Whitney U test, Chi-suared test for gender comparisons for the Indicator Comparison Periodontal PD, CAL, BOP, PI and GI have been used. Spearman's rho test was utilized to study the relationship between periodontal variables (PD, CAL, BOP, PI) and HbA1c with CRP. The Kruskal Wallis test was utilized to evaluate the relationship between CRP and GI index.

Results

The results of variables comparison based on HbA1c are provided in Table 1, 2. Table 1 showed that the mean CRP in the second group (HbA1C >=7) was higher significantly compared to the first group (P <0.001). The mean duration of diabetes (based on year) and mean CRP in the second group (HbA1c≥7%) were significantly higher than the first group (HbA1c <7%). According to Table 2, no significant difference was found between any of the periodontal indices in the two groups.

In Tables 3 and 4, variables are compared based on gender. According to table 3, the mean duration of diabetes in women (by year) was higher significantly than men (P = 0.12). According to the results of Table 4, no significant differences were found in gender between periodontal variables.

Table 1. Comparison of HbA1c-based demographic variables

	first group HbA1C <7 (35 = n)	The second group HbA1C> = 7 (41 = n)	*P* value
Average age (SD)	55.31 (8.37)	53.76 (9.91)	0.466
Gender (female / male)	(11.24)	(11.30)	0.659
Mean illness (SD)	9.33 (6.71)	11.41 (6.27)	0.168
Mean C-reactive (SD)	1.99 (1.40)	3.02 (1.38)	<0.001

Table 2. Comparison of periodontal variables based on HbA1c

	first group HbA1C <7 (35 = n)	The second group HbA1C> = 7 (41 = n)	*P* value
PD (SD)	2.04 (0.98)	2.16 (1.15)	0.369
CAL (SD)	1.63 (1.51)	1.87 (1.99)	0.729
PI (SD)	088 (016)	0.86 (0.15)	0.199
BOP (SD)	0.23 (0.27)	0.16 (0.26)	0.080
GI (SD)	1.24 (0.54)	1.34 (0.89)	0.544

Table 3. Comparison of variables based on gender

	Man (22 = n)	female (54 = n)	*P* value
Average age (SD)	57.41 (11.12)	83.25 (8.12)	0.124
HbA1C (SD)	8.16 (2.34)	7.84 (1.63)	0.801
Average disease (SD)	7.55 (5.49)	11.63 (6.57)	0.012
Mean C-reactive (SD)	2.81 (1.65)	2.43 (1.40)	0.359

Table 4. Comparison of periodontal variables based on gender

	Man (22 = n)	female (54 = n)	*P* value
PD (SD)	2.02 (1.04)	2.12 (1.09)	0.726
CAL (SD)	1.50 (1.64)	1.86 (1.83)	0.311
PI (SD)	0.86 (0.17)	0.87 (0.15)	0.939
BOP (SD)	0.16 (0.27)	0.20 (0.26)	0.156
GI (SD)	1.18 (0.59)	1.33 (0.80)	0.403

In Table 5 and Table 6, the variables were compared according to the duration of diabetes. According to Table 5, the mean age in people with a history of diabetes over 10 years of age was considerably higher than those with a diabetes mellitus duration of 10 years or less ($P = 0.024$).

Table 5. Comparison of variables based on the duration of diabetes

	Duration of the disease 10 < (35 = n)	Duration of the disease 10 ≥ (35 = n)	*P* value
Average age (SD)	57.03 (9.18)	52.29 (8.76)	0.024
Gender (female / male)	(6.29)	(16.25)	0.045
HbA1C (SD)	8.04 (1.46)	7.84 (2.15)	0.194
C-reactive protein (SD)	2.78 (1.49)	2.34 (1.45)	0.124

Table 6. Comparison of variables based on the duration of diabetes

	Duration of the disease 10 < (35 = n)	Duration of the disease 10 ≥ (35 = n)	*P* value
PD (SD)	2.14 (1.02)	2.05 (1.13)	0.562
CAL (SD)	1.90 (1.63)	1.63 (1.91)	0.192
PI (SD)	0.89 (0.14)	0.85 (0.17)	0.478
BOP (SD)	0.17 (0.25)	0.21 (0.28)	0.598
GI(SD)	1.31 (0.83)	1.27 (0.67)	0.751

Also, the proportion of women to men in the group whose incidence of diabetes is more than 10 years was higher significantly than the other group ($P = 0.04$).

According to the results of Table 7, no significant relationships were found between CRP and none of the periodontal variables.

Table 7. Relationship between CRP and periodontal indexes based on *P*-value

GI	PI	CAL	BOP	PD	Periodontal index
0.396	0.629	0.820	0.542	0.756	CRP

Discussion

Diabetes mellitus is one of the metabolic and serious chronic diseases with economic burden and substantial prevalence in the world (17, 18). Current evidence suggests that diabetes mellitus leads to disability-adjusted life years (DALYs) in 2012 with an increase of 89.7% in mortalities from diabetes between 1990 and 2013 (19). Individuals with diabetes are at higher risk of dysfunction and failure in heart, kidneys, nerves and damage to blood vessels and eyes (18). Diabetes mellitus cause 5.1 million deaths that half of them happen under the age of 60 and 11% of total health expenditure (USD 548 billion in health expenditure) (20).

On the other hand, the results of research have shown that high blood glucose concentration by producing advanced glycogen products reduces host defense against infections and can thus increment the periodontal disease's incidence and severity in affected individuals Increase diabetes (21, 22).

Periodontal diseases like chronic periodontitis have common inflammatory risk factors with other chronic and systemic inflammatory disorders. Mucosal tissues, like oral epithelial, are subjected to environmental factors including oral bacteria and tobacco possibly involved in enhancing a systemic inflammatory state (23). Periodontitis increases the CRP with the effects of inflammation and infection in the blood (24).

Studies showed that increased pre-inflammatory cytokines such as TNFα, IL6 and IL1 in periodontitis are likely to be in charge of insulin resistance and weak glycemic control (25). As a result, periodontal infection makes it harder to control blood glucose and should be treated decisively. Diabetic patients with periodontitis should be trained in oral hygiene education and mechanical debridement to remove topical factors. Regular maintenance therapy is especially important for these patients.

CRP is a liver-induced acute factor which has a relation with smoking, triglycerides, obesity, diabetes and periodontal disease (26). CRP has a key role in the host's defense against infection (27). Existing calcium, CRP specially binds to polysaccharides

like phosphocholine moieties existing on the cell surface of numerous pathogenic microbes. Thus, the classical complement pathway is activated along with the opsonises ligands for phagocytosis. It also neutralizes the down-regulates polymorphs and pro-inflammatory platelet-activating factor (28, 29).

Various studies have shown that CRP receptors are also present on macrophages, neutrophils and monocytes, therefore, bound CRP can target damaged and bacterial host cells for phagocytosis and assist direct and amplify the consequent local inflammatory responses to infection, necrosis and trauma (28). It has also been shown that the existence of periodontal pathogens, like bacteriothiazides, stimulates an inflammatory response and releases cytokines from monocytes and macrophages and endothelial cells; IL6 produces CRP, and CRP produces cytokines and activates sticky molecules in endothelial cells by affecting the inflammatory cells (26-28).

The results of this work showed no considerable association between periodontal variables in the group of people with controlled and uncontrolled diabetes and no significant differences in terms of duration of disease, age and sex between the two groups, only in women the duration of diabetes was higher than that of men. There was no significant association between CRP and any periodontal variables. The main finding of this study is that serum CRP level in the diabetic group with HbA1c≥7% is significantly higher than that of the diabetic group with HbA1c <7%.

In this study, CRP elevation is not the result of patients' periodontal condition, and is most likely to be affected by the effect of blood glucose and HbA1c elevation. Also, higher blood glucose did not have a definite effect on the periodontal condition, which requires further studies in this regard. In the present work, a significant and direct relationship was found between serum CRP and serum HbA1c level, which was consistent with Allen *et al.,* (28). Also, Wu *et al.,* (29) and Kiedrowicz *et al.,* (30) found a direct correlation between CRP and HbA1c, but their findings were not statistically significant, but in a study conducted in Indonesia by Susanto(31) to assess the relationship between CRP and HbA1c in 101 patients with type 2 diabetes and 132 healthy subjects, a significant relationship was also found between CRP and HbA1c. The causes of the differences in the results of our study with Susanto (31) study can be distinguished by the difference in the group of racial differences, BMI, nutritional and dietary regimens of individuals, athletic habits and educational level of patients.

A study by Aspriello *et al.,* they could not find a connection between CRP and HbA1c. Twenty-two patients with type 2 diabetes and 24 patients with type 1 diabetes were included in this work and patients were matched for severe chronic generalized periodontitis, but in our study, the number of people with type 2 diabetes was 76 and Patients were not matched in terms of the prevalence of periodontitis. In the study of Aspriello *et al.,* smokers and consumers of corticosteroid, anti-inflammatory, non-steroidal and antibiotic drugs were excluded from the study (32).

The analysis of the results of the present study showed no significant difference in the periodontal tissue degradation between the two controls and non-diabetic groups, but in patients with uncontrolled diabetes, PD, CAL and GI was higher. But this difference was not significant statistically.

Kiedrowicz *et al.,* (30) evaluated the periodontal status in type 2 diabetic patients based on hemoglobin glycoside (HbA1c≥7%, HbA1c <7%), and other risk factors. The results of the Kiedrowicz study on 75 diabetic patients showed that there were no significant differences between the two groups in terms of periodontal parameters. The results of this work were also in line with the Kiedrowicz *et al.,* study of periodontal parameters.

Other studies in diabetic type 2 diabetic patients with periodontitis did not find a meaningful difference between periodontal inflammation and poor glycemic control (33, 34). Santos pointed out that in addition to glycemic control, physical activity, drug sensitivity, and also regimen therapy, Nutrition and medicine are among the factors that influence the outcome (35-37).

Lim LP investigated the association between metabolic and inflammatory control markers and periodontal parameters in 118 diabetic patients and it showed that the severity of periodontitis was directly related to the severity of diabetes (15), which was not consistent with the outcome of the study. Differences in the size of the statistical community and the different grouping of HbA1c-dependent diabetic patients may be causes of difference with our study.

Carlen *et al.,* compared the glycemic control and severity of periodontitis in 4343 adults with type 2 diabetes, according to the study, those with a poor diabetic control group (HbA1c> 9%) possesses a higher incidence of severe periodontitis than those who had in the control group (HbA1c≤9%) (38). The results of this study were not consistent with our study. A large difference in the size of the statistical society, the different scales

of HbA1c for grouping individuals and racial segregation are one of the most important causes of the difference in outcome between Carlen *et al.,* study and our study.

Conclusion

Overall, the results of this study can be deduced that there is a direct correlation between increased blood CRP levels and high levels of HbA1c in blood. However, this rise in CRP still did not have a significant effect on periodontal disease, although periodontal parameters were clinically higher.

Conflict of Interest: 'None declared'.

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