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Effect of Non-Surgical Periodontal Treatment in Altering Salivary Concentration of Osteoprotegerin among Controlled Diabetics with Chronic Periodontitis

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Abstract
Forty patients were included in the present study; they were divided equally into four equal groups (10 each): Group I include healthy subjects, Group II includes adult periodontitis patients free from any systemic diseases, Group III includes diabetics and periodontal healthy status and Group IV includes diabetic patients with chronic periodontitis. Group II and IV patients were subjected to mechanical plaque control procedure including complete mouth scaling and root planning, in order to improve their periodontal status. No initial periodontal therapy was performed in both other groups (Group I and III). Clinical evaluation was done through use of the following parameters, pocket depth measurement, attachment level measurement and gingival, plaque indices. These evaluations were done at baseline, one and three months. All included patients were evaluated at the beginning of the study and at the subsequent scheduled visits for salivary level of OPG using ELISA system. Results showed that Groups II and IV had an improvement in the entire measured clinical parameters following the completion of periodontal therapy. The mean values of OPG level recorded at baseline among the all included groups, showed increased values following the periodontal therapy in Group II and IV; such increase in OPG level was statistically significant. A reverse relationship between clinical signs of periodontal disease and level of OPG in saliva was noted. At baseline, mean of GI, PI and PD in diabetic chronic periodontitis group showed statistically significantly higher value compared with that of chronic periodontitis group. Regarding the mean of CAL there was no statistically significant difference between the two groups. Finally, through all periods, no statistically significant difference between % changes in GI, PI, PD and CAL of the two groups was noted.
Keywords. *Diabetes mellitus, Chronic periodontitis, Osteoprotegrin.*

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INTRODUCTION

Periodontal disease has been considered as a group of inflammatory disorders that give rise to tissue damage and loss as a result of complex interaction between pathologic bacteria and the host's immune response (1). Chronic periodontitis is firmly based on the infection/host paradigm depending on the agreement that, all forms of periodontitis are infectious and characterized by chronic inflammation, pocket formation, deepening and loss of periodontal attachment and alveolar bone (2,3). The recognition that periodontitis involves an inflammatory component as well as altered bone metabolism have provided a new perspective on the disease etiopathogenesis. This interdisciplinary field of study integrated the disciplines of immunology and bone biology; which rendered a useful framework for improving knowledge about periodontal disease (4,5).

It is well documented that, inflammatory mediators that lead to progression of periodontal disease; depends on the expression of proinflammatory cytokines. On the other hand, anti-inflammatory cytokines and other mediators act as an antagonism and/or opposing the expression of the above-mentioned cytokines. Among those anti-inflammatory mediators is the osteoprotegrien (OPG) which serve to inhibit bone resorption (6). In fact, a balanced regulation of immune responses could maintain the interplay between both types of mediators in a settled status (7,8). OPG, a secreted glycoprotein, is a decoy receptor for a protein called receptor activation of nuclear-kappa B ligand (RANKL) on the osteoblast surface (9). Additionally, RANKL and decoy receptors OPG expressed by bone-associated cells play an important role during osteoclast formation by balancing induction and inhibition (10,11). Further studies suggested that involvement of RANKL and OPG in pathogenesis of periodontal disease (12,13).

It is well known that; the whole saliva is an important physiologic fluid that contains a highly complex mixture of substances. This rich mixture of substances makes saliva reliable source for identifying unique biomarkers that reflect oral and systemic health changes (14). It is well established that, contributing inflammatory mediators and tissue-destructive molecules have been detected in the gingival tissues, gingival crevicular fluid and saliva of patients affected by periodontitis. This finding could throw the light on their diagnostic and therapeutic significances (15-18). In fact, there is a high prevalence of periodontal disease among diabetic individuals particularly if it is uncontrolled; where alteration of all periodontal parameters could be noticed; including bleeding scores, probing depths and loss of attachment and missing teeth(19-

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22). It is needless to say that diabetes per see is the initiating factor for incidence of periodontal disease; but it can alter, modify and/or exaggerate the response of periodontal tissues toward the actual causative agent; namely; dental biofilm(23,24). Moreover, differences in host response among uncontrolled an controlled diabetics may play a pivotal role in the increased prevalence and severity of periodontal destruction seen in patients with uncontrolled diabetes (25). The present study was designed as an attempt to evaluate the ability of non-surgical periodontal treatment to alter the salivary concentration of OPG among controlled type II diabetics with chronic periodontitis.

METHODS

Selection of the Patients

The present study was conducted on forty male individuals, applying the following inclusion criteria: aged between 30 to 55 years, Chronic periodontitis patients have at least 5 teeth with advanced periodontal breakdown as evidenced by pocket depth greater than 5 mm and attachment loss more than 2 mm. No history of any antibiotic of anti-inflammatory drugs within the last 3 months prior to inclusion in this study. No smoking No history of systemic diseases except diabetes (for group III and IV). The diabetic patient had type II diabetes mellitus diagnosed for at least 5 years and current metabolic control above normal range (glycated hemoglobin test, HbA1c > 6%). The nature of the study was explained to all included patients and a written consent was obtained from all participants before the commencement of the study.

Grouping

The selected subjects were divided equally into four equal (10 each) according to their periodontal and diabetic status, as following:

Group I: Ten subjects with systemic and periodontal healthy status.
Group II: Ten systemically healthy subjects and clinically diagnosed with chronic periodontitis.
Group III: Ten patients with diabetes mellitus and periodontal healthy status.
Group IV: Ten diabetic patients and clinically diagnosed with chronic periodontitis.

Treatment Performed

Group II and IV subjects were initially managed by non-surgical therapeutic procedure, including; thorough supra- and sub-gingival scaling, root planning and instructions of oral hygiene regimen.

Clinical Evaluation

The following clinical measurements were obtained to assess the periodontal status of each subject at baseline, one month and three months after periodontal therapy for (group II and IV). Those included; Plaque index of Sillness & Loe (25), Gingival index of Loe & Sillness (26), Periodontal Pocket depth measured with graduated periodontal probe from gingival margin to base of pocket, clinical attachment level (CAL) as recorded from CEJ to pocket bottom to the nearest millimeter. Un-stimulated whole saliva was collected from each subject according to the method previously described by Navarro et al (27). Measurement of salivary OPG was performed utilizing ELISA system (16). The obtained data was collected and analyzed statistically with suitable tests and significance level was set at $p < 0.05$.

Results

Clinical Findings

All included subjects into the present study completed fairly the complete schedule (3 months). Through this study period, the mean PI scores in diabetic chronic periodontitis group showed an almost statistically significant higher value as compared to that of chronic periodontitis group. However, a fluctuating minimal changes were observed in the PI scores of both experimental groups; during the different follow-up periods; namely; initially and 3 months (Table 1).

Table 1. The means, standard deviation (SD) values and results of Student's t-test for comparison between PI of the two groups:

Group Period	Chronic periodontitis		Diabetic chronic periodontitis		*P-value*
	Mean	*SD*	*Mean*	*SD*	
Baseline	1.38	0.21	1.62	0.16	0.014*
1 month	0.39	0.09	0.55	0.11	0.003*
3 months	0.52	0.06	0.69	0.12	0.008*

**: Significant at P ≤ 0.05.*

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Regarding the Gingival index (GI) scores recorded from the both groups, it was evident that they were more or less and almost parallel to those of Plaque Index (PI) scores (Table 2).Thus, there was increased level in severity of gingival inflammation with the time of follow up period.

Table (2): The means, standard deviation (SD) values and results of Student's t-test for comparison between GI of the two groups

Group Period	Chronic periodontitis		Diabetic chronic periodontitis		*P-value*
	Mean	*SD*	*Mean*	*SD*	
Baseline	1.45	0.22	1.79	0.14	0.002*
1 month	0.68	0.17	0.85	0.19	0.138*
3 months	0.92	0.18	1.14	0.16	0.022*

**: Significant at P ≤ 0.05.*

The recorded measurements of periodontal probing pocket depth showed the following results; the initial mean PD in diabetic chronic periodontitis group recorded a statistically higher value compared with that of chronic periodontitis group. During the follow up period i.e., after 1 and 3 months, no statistically significant difference between the means of PD in the two groups was found (Table 3).

Table 3. The means, standard deviation (SD) values and results of Student's t-test for comparison between PD of the two groups

Group Period	Chronic periodontitis		Diabetic chronic periodontitis		*P-value*
	Mean	*SD*	*Mean*	*SD*	
Baseline	2.48	0.23	2.72	0.19	0.043*
1 month	1.46	0.26	1.73	0.21	0.075*
3 months	1.78	0.29	1.88	0.27	0.538*

**: Significant at P ≤ 0.05.*

Regarding the clinical attachment loss (CAL) recorded in the both study groups; the measurements were almost parallel to those of periodontal pocket depth measurements; during the various follow up periods (1 and 3 months); (these findings were presented in Table 4).

Table 4. The means, standard deviation (SD) values and results of Student's t-test for comparison between CAL of the two groups

Group Period	Chronic periodontitis		Diabetic chronic periodontitis		*P-value*
	Mean	*SD*	*Mean*	*SD*	
Baseline	2.18	0.18	2.34	0.17	0.077*
1 month	1.68	0.18	1.48	0.21	0.089*
3 months	1.59	0.23	1.47	0.22	0.391*

**: Significant at P ≤ 0.05.*

Results of OPG Levels

ELISA was carried out to measure the level of OPG among various included subjects of various groups of the present study; it was found that, through all periods, diabetic group showed a statistically significant higher mean of OPG; followed by diabetics with chronic periodontitis group. Healthy subjects group recorded the lower values, followed by chronic periodontitis group; which showed the lowest significant OPG mean; in a descending order (Table 5 and Figure 1). The comparison between glycated hemoglobin in the diabetic groups; showed no statistically significant difference in both groups; namely group III and IV (a data not presented).

Table 5. The means, standard deviation (SD) values and results of ANOVA test for comparison between OPG in the four groups

Group Period	Healthy		Chronic periodontitis		Diabetic		Diabetic chronic periodontitis		*P-value*
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	
Baseline	271.2c	13.8	44.7d	6.8	500.1a	14.5	330.2b	14.2	<0.001*
1 month	272.2c	14.2	121.4d	12.5	500.1a	14.5	406.8b	10.7	<0.001*
3 months	271.2c	14.1	131.7d	11.1	500.1a	14.5	411.2b	13.3	<0.001*

**: Significant at P ≤ 0.05. Means with different letters are statistically significantly different according to Tukey's test.*

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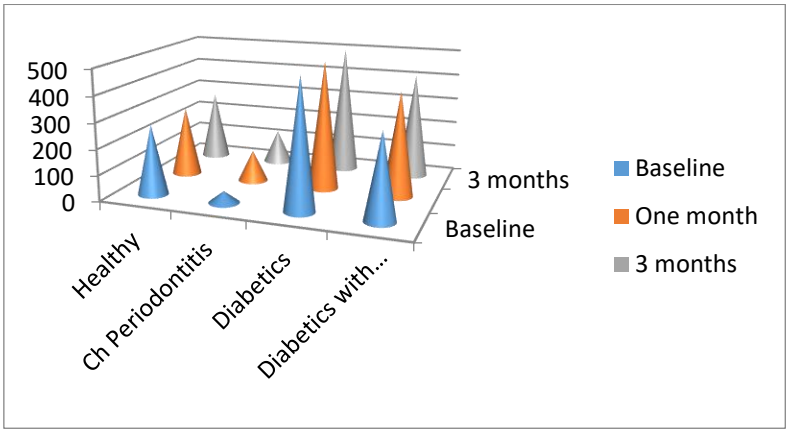

Figure 1. The measured levels of OPG among the included four groups.

Discussion

Diabetes mellitus is a complex multifactorial genetic disorder with common characteristic of altered glucose tolerance and impaired lipid and carbohydrate metabolism (28). Interplay has been postulated between the main local etiologic factor; namely dental plaque and diabetes mellitus as a systemic risk factor in a reciprocal way. However, the encountered interrelationship evoked a matter of debate; where some concepts were directed towards the possible influence of diabetes on the initiation and progression of periodontal disease (29). Such situation could be accomplished via alterations in host immune-inflammatory response to different virulent periodontal pathogens. In this respect, an entitled explanation based on considering diabetes mellitus as a modifier for all forms of chronic inflammatory periodontal disease was evidenced (30). Periodontal disease is, simply, can be regarded as a chronic bacterial infection characterized by a contributing inflammatory mediators and tissue destructive molecules; that have been detected in gingival tissues and saliva of affected patients (31).

It is worthy note to mention that, the included sample in the present study, was relatively small due to the strict inclusion and exclusion criteria applied here; it minimizes confounding factors and limitations of a study of this nature (3 months). Type II diabetes subjects were included in this study, as Type II diabetes mellitus and chronic periodontitis are present in the adults and highly prevalent among the general population. Additionally, Type II diabetes has shown a spectacular increase in the past few decades (24). The design applied in the present study was directed towards age and gender matching, periodontal status and diabetes condition; for all groups as possible. This way is able to render the obtained data and values within the accepted reasonable records; as it became far away from any favorable trends evoked by the investigators. It is of interest to mention that, in tan intention was paid to include male patients only to exclude the effect of gender difference in the periodontium, as elevated levels of ovarian hormones (estrogen and progesterone) may modify the action of immune system cells, including cytokine production and the increase of both gingival inflammation and exudates (32).

The age of included subjects ranged between 30-55 years seemed to be suitable because diagnosis of NIDDM (Type II Diabetes mellitus) usually occurs at this age, while IDDM (Type I) is diagnosed in childhood, adolescence and early adulthood; over 95 % of persons with Type II develops the disease after the age of 25 (24). The A1c test (previously referred to as glycated hemoglobin, A1c or HbA1 glycohemoglobin, glycosylated hemoglobin GHb) provides the most accurate account of overall glycemic control. Sugar not used for energy remains in the blood where it attaches to hemoglobin. The A1c test measures the amount of sugar that is attached to the hemoglobin in red blood cells. Because red blood cells live about two to three months, this test can measure the average blood glucose level over the past several months (33). This test is most useful because it is not affected by short-term changes (eating, exercise, etc.). The test is usually performed every 3 to 6 months. Treatment goal for diagnosed diabetics are for an A1c < 7% (33).

The applied clinical parameters used to evaluate the included patients in the present study are those commonly used in clinical trials; namely the Plaque Index, Gingival Index, Pocket depth and clinical attachment level. These reversible indices had proved to be useful means of screening the gingival condition. Moreover, they also provide the possibility of selecting specified areas on teeth when large numbers are examined, or utilizing all areas of all teeth in the examination of a small sample. In addition, these indices also combine the degree of inflammation with the assumed main etiological factors; dental plaque (34). The present study threw the light on saliva as a presentable media; because whole saliva is considered as an important physiologic fluid that contains a highly complex mixture of substances (35). Salivary gland secretions contain locally produced protein, as well as other molecules from the systemic circulation. It is this rich mixture of substances that makes saliva a likely source for identifying unique biomarkers that reflect oral and systemic health changes (36). The present study evaluated the level of a salivary biomarker

(OPG), which may be of value in chronic inflammatory periodontal diseases, and it has possible interrelationship with the clinical features of the disease. Unstimulated whole saliva samples were used in the present study, because stimulation may increase the flow of GCF and this may result in false increase in the concentration of evaluated biomarker in saliva (37). In addition, GCF collection was avoided due to the presence of some problems inherent in sampling and analysis of this fluid. Such sampling involves miniscule amounts of fluid, which can affect laboratory analysis. Contamination of the sample with blood, saliva or plaque also is a potential problem, which give false results, added to sampling time and the manner of strip insertion are also critical (38). The use of Enzyme Linked Immunosorbent Assay (ELISA) in the present study was utilized to determine OPG level, as it has bone turnover role that may permit to determine its potentiality as a biomarker of periodontal disease (39).

Osteoprotegrin was chosen among various salivary biomarkers specific for chronic inflammatory aspects of periodontitis; due to its pivotal role in such situations. This biomarker is a glycoprotein that acts as an osteoblast secreting decoy receptor and competitively inhibits osteoclast differentiation and activity by preventing osteoclast differentiation factor (RANKL) from binding to osteoclast precursors and promoting formation of bone-resorbing osteoclasts (40,41). In the present study, the obtained results showed that OPG salivary concentration was significantly lower in chronic periodontitis group than in control group. These findings are in agreement with those of others (37-40). However, this is not always the case, as on the contrary, these findings are in opposition to other findings reported OPG higher levels in periodontal patients compared to controls. This observation might be attributed to a possible biological mechanism at work, additional factors as for sample size and/or the episodic nature of periodontal disease (37,39,41). Additionally, the microvascular complications commonly associating diabetic patients; may also share in the elevated salivary OPG (33,40). In the present study; at base line the mean GI, PI and PD in diabetic chronic periodontitis group showed statistically significant higher values than chronic periodontitis group; it is more confirmed especially in uncontrolled diabetics (24). These clinical results were almost parallel to other clinical and epidemiologic studies encountered among age matched; non-diabetic controls (29,30,34). On the other hand, the present results are in opposition to other studies; who failed to find a definite interrelationship between diabetes and the increased incidence of periodontal disease (24,33). In addition, other studies revealed a good response to appropriate periodontal treatment and that the short- and long-term periodontal response is equal to non-diabetic patients. However, if diabetes is not well controlled, periodontal recurrence will be more frequent and more difficult to control (25,40). It seems likely to mention that the short-term effect of non-surgical periodontal therapy could be noticed as early as one month after completion of the therapy; a concept which is in agreement with the findings of other workers (11,34).

In view of the obtained results to conclude that the behavior of OPG towards the inflammatory conditions, suggesting that this biomarker may serve in a panel of salivary biomarkers that could facilitate the screening, diagnosis and management of periodontal disease. Moreover, the interrelationship between diabetes and OPG concentration in saliva could provide a further support for the concept that diabetes might increase the risk for periodontitis; added to its role as a modifier for all forms of periodontal diseases. Thus, detection of the presented salivary marker and/or others may help to clarifying some of idiopathic and/or query situations; which necessitate performing further investigations on larger sample and extended follow up period to reach clearer as well as stronger findings in this regard.

Conclusion

Non-surgical periodontall therapy significantly improved clinical periodontal parameters and increased Salivary Osteoproteogerin (OPG) Levels among both systematically healthy and controled diabetic patients with chronic periodontitis. A negative correlation between clinical signs of periodontal disease and salivary OPG Concentration was evident suggesting the potential utility of OPG as a biomarker for periodontal disease activity and treatment response. Furthermore, the findings support the rule of diabetes mellitus as a modifying factor that exacerbates periodontal destruction. Therefore, longitudinal studies with larger cohorts are warranted to confirm these findings and to explore the clinical applicability of salivary biomarkers in periodontal diagnostics and management.

Conflict of interest. Nil

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