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Dentistry Section

The Effect of Scaling and Root Planing on Glycaemic Control, Periodontal Status and Gingival Crevicular Fluid TNF-α Levels in an Indian Population- To Reveal the Ambivalent Link

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ABSTRACT

Context: Periodontal disease and diabetes mellitus(DM) share a two - way relationship. It can be hypothesized that successful management of periodontal infection in diabetes will lead not only to reduction of local signs and symptoms of the disease, but also to better control of glucose metabolism.

Aims: To monitor the effect of Scaling and Root planing (SRP) on glycaemic control in patients with type 2 diabetes mellitus by estimating the HbA1c and GCF TNF-αlevels.

Settings and Design: This Interventional clinicobiochemical study was carried out over a period of 6 months from December 2010-May 2011 in Bengaluru, Karnataka, India.

Materials and Methods: Fifteen well-controlled, 15 moderately controlled and 15 poorly controlled diabetic subjects were enrolled in this study. All participants were subjected to non-surgical periodontal (SRP) therapy. GCF sampling and clinical periodontal parameters assessment were done at baseline and 3 months post-therapy. TNF-α levels in GCF were analyzed by enzyme-linked immunosorbent assay (ELISA) at baseline and 3 months post therapy. The improvement in glycaemic control was assessed using HbA1c levels at 3 months reevaluation.

Statistical analysis: The data obtained were statistically analysed using Kruskal-Wallis test, Mann-Whitney test and Wilcoxon Signed Rank test.

Results: Following periodontal treatment, all patients demonstrated a significant improvement in periodontal status. A reduction in TNF-α level and the HbA1c values were also observed.

Conclusion: The result indicates that SRP is effective in improving metabolic control in Type 2 Diabetes Mellitus patients possibly through the reduction of TNF-α which in turn might improve the insulin resistance.

Keywords: Diabetes mellitus, HbA1c, Periodontal therapy, TNF

INTRODUCTION

Periodontitis, which is the most common oral infection in humans and the major cause of tooth loss in adults, has been considered as the sixth complication of diabetes mellitus (DM) [1]. The heightened periodontal destruction seen in diabetes may be explained by a number of cellular and molecular alterations taking place in the periodontium.

Elevated glucose concentrations induce non-enzymatic glycation and oxidation of proteins like collagen, and lipids, resulting in the accumulation of advanced glycation end products (AGEs) in diabetic tissues [2]. AGEs interact with their receptors present on the cell surface called the receptor for AGE (RAGE), bringing about various pathological changes. The AGE-RAGE interaction in the macrophages causes increased release of pro-inflammatory cytokines like Tumour Necrosis Factor alpha (TNF-α) and Interleukin -1 beta (IL-1β) [3,4].

TNF-α and IL-1β have been implicated in the immunology of perioodontitis [5-9]. TNF-α concentration may be increased in periodontal inflammation as a result of stimulation of monocytes. The elevation of this cytokine affects insulin sensitivity via direct and indirect mechanisms [5-7], thereby causing a worsening in the diabetic status. Worsening of the diabetic status may in turn lead to further periodontal breakdown [5-7]. Thus, TNF-α appears to play an important role in the vicious cycle linking periodontal disease and diabetes.

Treatment that reduces periodontal inflammation may restore insulin sensitivity, resulting in improved metabolic control. Studies assessing TNF-α level in the serum and gingival crevicular fluid before and after periodontal therapy have shown varying results [10,11].

Due to relative paucity of studies in Indian population comparing the levels of TNF-α in the gingival crevicular fluid (GCF) of type 2 diabetes mellitus patients following scaling and root planing, this study was undertaken to test the hypothesis that scaling and root planing could reduce TNF-α levels in the gingival crevicular fluid (GCF) of type 2 diabetes mellitus patients, bringing about an improvement in the glycaemic control.

MATERIALS AND METHODS

Sources of data

Ethical clearance for the study was received from the Institutional Ethical Committee and Review Board, DAPMRV Dental College, Bengaluru, India. Permission was obtained from the hospital authorities at the Diacon hospital, Bengaluru, to obtain the required data from subjects receiving treatment for diabetes at the Hospital. The data was collected over a period of 6 months, spanning from December 2010 to May 2011. Written informed consent was obtained from all patients. Patients with age range of 35-70 y were included in this study and comprised of individuals of both sexes.

Exclusion criteria were: Patients with systemic diseases such as type 1 diabetes mellitus, cardiovascular disorder, immunologic disorders, hepatitis and human immunodeficiency virus infections, smokers, pregnant and lactating women and those taking oral contraceptive drugs or any anti-inflammatory or corticosteroids drugs. Subjects who had received antibiotics or treatment for

Group	Mean	StdDev	Kruskal-Wallis Chi-sq	p- value	Mean	StdDev	Kruskal-Wallis Chi-sq	p-value
Group I	5.84	5.62	25.903	<0.001*	3.90	10.94	27.196	<0.001*
Group II	15.36	9.79			13.06	8.39		
Group III	29.52	9.83			27.87	10.94		

[Table/Fig-1]: Comparison of TNF-α between groups at baseline and at 3 months, ***Significant at p value <0.05*

Group	Mean	StdDev	Kruskal-Wallis Chi-sq	p- value	Mean	StdDev	Kruskal-Wallis Chi-sq	p-value
Group I	6.50	0.33	39.239	<0.001*	5.89	0.29	34.062	<0.001*
Group II	7.65	0.35			7.15	0.58		
Group III	9.79	1.02			8.91	1.04		

[Table/Fig-2]: Comparison of HbA1c between groups at baseline and at 3 months, ***Significant at p value <0.05*

Parameter	Time interval	Mean	Stddev	SE of Mean	Mean difference	Z	p-value
CPI	Pre op	3.86	0.36	0.10	1.357	-3.416	0.001*
	Post op	2.50	0.52	0.14			
PPD	Pre op	4.17	0.31	0.08	1.052	-3.296	0.001*
	Post op	3.11	0.48	0.13			
CAL	Pre op	2.69	0.93	0.25	0.417	-3.927	0.001*
	Post op	2.28	0.97	0.26			
HbA1c	Pre op	9.79	1.02	0.27	0.879	-3.301	0.001*
	Post op	8.91	1.04	0.28			
TNF-α	Pre op	29.19	10.11	2.70	1.322	-2.166	0.001*
	Post op	27.87	10.94	2.93			

[Table/Fig-3]: Comparison of different parameters at baseline and 3 months within Group III (Poor glycaemic control) using Wilcoxon signed rank test, ***Significant at p value <0.05*

Parameter	Time interval	Mean	Stddev	SE of Mean	Mean difference	Z	p-value
CPI	Pre op	3.86	0.36	0.10	1.500	-3.391	0.001*
	Post op	2.36	0.50	0.13			
PPD	Pre op	2.99	0.33	0.09	1.021	-3.297	0.001*
	Post op	1.97	0.33	0.09			
CAL	Pre op	2.00	0.15	0.04	0.647	-3.300	0.001*
	Post op	1.36	0.24	0.06			
HbA1c	Pre op	7.70	0.31	0.08	0.550	-2.861	0.004*
	Post op	7.15	0.58	0.15			
TNF–α	Pre op	14.67	9.77	2.61	1.610	-2.731	0.006*
	Post op	13.06	8.39	2.24			

[Table/Fig-4]: Comparison of different parameters at baseline and at 3 months within Group II (Moderate Glycaemic control)using Wilcoxon signed rank test, ***Significant at p-value <0.05*

periodontal disease in the 6 months preceding the study were also excluded.

From the power analysis it was shown that, to achieve 85% power and detect mean differences of the clinical parameters between groups, 45 samples were required in each group. Hence, a total of 45 subjects who had periodontitis, with a community periodontal index (CPI) score of 3 or more, were included in the study.Community Periodontal Index was measured using a community Periodontal Index for Treatment Needs-C probe. The criteria for the community periodontal index (CPI) are as follows.

Code-0- Coloured band of the probe remains completely visible in the deepest sulcus of the sextant-healthy.

Parameter	Time interval	Mean	Stddev	SE of Mean	Mean difference	Z	p-value
CPI	Pre op	3.62	0.51	0.14	1.231	-3.017	0.003*
	Post op	2.38	0.51	0.14			
PPD	Pre op	2.04	0.24	0.07	0.952	-3.181	0.001*
	Post op	1.09	0.27	0.07			
CAL	Pre op	0.95	0.10	0.03	0.204	-3.203	0.001*
	Post op	0.75	0.10	0.03			
HbA1c	Pre op	6.52	0.36	0.10	0.623	-3.194	0.001*
	Post op	5.89	0.29	0.08			
TNF-α	Pre op	4.63	3.91	1.08	0.735	-3.180	0.001*
	Post op	3.90	3.70	1.03			

[Table/Fig-5]: Comparison of different parameters at baseline and at 3 months within Group I (Good glycaemic control) using Wilcoxon signed rank test, ***Significant at p-value <0.05*

Code-1- Coloured band of the probe remains completely visible in the deepest sulcus of the sextant, some bleeding after gentle probing.

Code-2- Coloured band of the probe still completely visible, but there is bleeding on probing, supragingival or subgingival calculus and/or defective margins.

Code-3- The coloured band is partially submerged. Pocket 4-5 mm deep.

Code-4- The coloured band completely disappears in the pocket, indicating a depth greater than 5.5 mm and a loss of attachment of 3mm or more.

Code X- Excluded sextant.

Code 9- Not recorded.

Criteria for subject grouping

The selected subjects were then classified into three groups of 15 subjects each (N=15), based on their HbA1c, according to the guidelines by the American diabetes association [12].

Group I- well controlled diabetes – 6-7% HbA1c

Group II- moderately controlled diabetes- 7-8% HbA1c

Group III- poorly controlled diabetes- >8% HbA1c

Clinical evaluation of subjects

After the selection of patients based on CPI score, all the participants underwent a detailed periodontal examination for the measurement of probing pocket depth (PPD) and clinical attachment level (CAL) using a University of North Carolina Probe (UNC-15 probe).

PROCEDURE FOR SAMPLE COLLECTION

Method of collection of blood

After seating the patient comfortably, the procedure was explained once again before collection of blood. The left antecubital fossa was swabbed with an alcohol swab and a cuff was used to apply pressure above the fossa. Blood was drawn using a 5 ml syringe and immediately transferred to a vacutainer. HbA1c was estimated by the turbidimetric inhibition assay method.

Method of collection of GCF

The subjects were asked to rinse their mouth vigorously with water to cleanse the teeth of loosely adherent debris. Supragingival calculus if present was removed using universal scaler (Hu Freidy). Samples of GCF were obtained from predetermined sites by placing calibrated, volumetric, microcapillary pipettes with a 0-5µl range (obtained from Sigma Aldrich co., St. Louis, Missouri, USA). The test site was dried and isolated with cotton rolls. The micropipettes were placed extracrevicularly at the entrance of the gingival crevice. 3-4 µl of GCF was collected from each subject. The pipettes which

were contaminated with blood/saliva were discarded. The GCF was transferred into vials containing 100 µl phosphate buffer saline and the samples were frozen at -70°C till they were assayed for TNF-α.

Intervention

The treatment of every subject was carried out by a single investigator in the Department of Periodontics, DA Pandu Memorial RV Dental College, Bengaluru. After obtaining medical clearance, thorough scaling and root planing (SRP)and polishing were performed for all the patients included in the study. The patients were advised to follow the instructions rendered by their physician regarding medication and food prior to the procedure. The treatment procedures were kept short and as atraumatic as possible. After instrumentation, the root surfaces were carefully inspected to evaluate the adequacy of SRP. After the procedure, oral hygiene instructions were given to the patients.

Re evaluation

After three months, the glycated hemoglobin level of each patient was rechecked. The periodontal status of the patients was reanalyzed using the CPI score, PPD and CAL.

Measurement of TNF-α levels

TNF-α levels were determined in all the 45 patients at baseline and at three months using ELISA. The enzyme linked immunosorbent assay (ELISA) was done at the Department of Microbiology, Maratha Mandal's Nathajirao G Halgekar Dental College, Belgaum. The ELISA procedure was carried out using a commercially available ELISA kit for human TNF-α (DIA-source KAP1751, Belgium).

STATISTICAL ANALYSES

All data were analyzed using a software program Statistical Package for the Social Sciences (SPSS, version 14.0, SPSS, Chicago, IL). Kruskal-Wallis test was used to find the statistically significant difference in the parameters in the groups. In case of a significant difference, multiple comparisons using Mann-Whitney test was carried out. Pre and post treatment comparison of all the parameters were done using Wilcoxon Signed Rank test.

RESULTS

Glycaemic control and mean TNF-α levels

At baseline, it was seen that the mean TNF-α values increased with the decline in glycaemic control, that is, higher levels of TNF-α could be seen in individuals with poorly controlled diabetes mellitus (29.52 ± 9.83 pg/ml) followed by moderately controlled diabetes (15.36 ± 9.79 pg/ml) and well controlled diabetes (5.84±5.62 pg/ml) [Table/Fig-1].

The mean TNF - alpha values in poorly controlled diabetes mellitus at 3 months after therapy was 27.87±10.94 pg/ml, moderately controlled group was 13.06±8.39 pg/ml and that of well controlled group was 3.90 ± 3.70 pg/ml [Table/Fig-1].

Non-surgical Periodontal therapy (SRP)- Effect on Glycaemic Control, Periodontal Status, TNF-α Levels

The mean HbA1c at baseline and at reevaluation at 3 months are given in [Table/Fig-2]. Higher mean HbA1c was recorded in poorly controlled group followed by moderately controlled group and well controlled group respectively. It was noticed that there was a significant difference between the HbA1c levels before and after treatment in well controlled group (p<0.001), moderately controlled group (p<0.001) and poorly controlled group (p<0.001) [Table/Fig-3-5]. This could lead to an interpretation that periodontal therapy might have the potential to improve the glycaemic control in diabetic patients with varying glycemic control.

In the comparison between TNF-α levels at baseline and at 3 months in each group using Wilcoxon Signed Rank test, it was noticed that there was a significant difference between the TNF-α levels before and after treatment in poorly controlled group [1.32pg/ml] (p<0.001) [Table/Fig-3], moderately controlled group (p<0.001)[1.61pg/ml] [Table/Fig-4] and well controlled group (p<0.001) [0.74pg/ml] [Table/Fig-5]. It was observed that TNF-α level decreased with periodontal therapy in all the three groups.

The comparison between CPI scores at baseline and 3 months in each group showed a significant difference between the scores before and after treatment in poorly controlled group (1.35) (p<0.001) [Table/Fig-3], moderately controlled group (1.5) (p<0.001) [Table/Fig-4] and well controlled group (1.231) (p<0.001) [Table/Fig-5]. The PPD and CAL scores also showed statistically significant improvement at the time of reevaluation at 3 months in all the three groups [Table/Fig-3-5].

DISCUSSION

Findings from various studies indicate that diabetes mellitus leads to a hyper-inflammatory response to the periodontal microbiota and also impairs resolution of inflammation and repair, which leads to accelerated periodontal destruction [12-14].

Several proinflammatory cytokines, including TNF-α, have been implicated in the immunopathology of periodontitis as mentioned earlier and monocytes and macrophages from subjects with both diabetes and periodontitis appear to release considerable quantities of TNF-α. Presence of this cytokine may contribute to the heightened state of inflammation that is observed in diabetic subjects [14,15].

A number of interventional studies have shown that periodontal treatment may help in the improvement of metabolic control in type 2 diabetic patients [10,11,16-19]. However, contradictory results have been demonstrated in other studies regarding the effects of periodontal therapy on glycaemic control [20-22].

In order to unravel the ambiguity associated with the interpretation regarding the effects of periodontal therapy on glycaemic control, this study was undertaken to test the hypothesis that scaling and root planing might have the potential to reduce TNF-α levels in the gingival crevicular fluid (GCF) of type 2 diabetes mellitus patients, thereby bringing about an improvement in the glycaemic control.

The study sample consisted of 45 subjects with age ranging from 35 to 70 y. Age is a significant factor for periodontal disease, as the prevalence of periodontal disease increases rapidly with age and also most people with type 2 diabetes belong to this age group [23,24]. This age range is in accordance with other studies [25,26].

The patients were divided into three groups of those having well controlled, moderately controlled and poorly controlled type 2 diabetes, based on the guidelines set by the American Diabetes Association, each group consisting of 15 patients.

In the study, TNF-α level in GCF were estimated at baseline and three months after scaling and root planning. Based on the rate of healing, it has been cited that three months post treatment is a suitable interval for the primary evaluation of initial non-surgical therapy, even in areas with preliminary deep lesions [27]. Also, to estimate the glycaemic control, HbA1c was used in this study. Glycated haemoglobin indicates the glucose status during half of the life of RBC, that is, 30-90 d. Thus, HbA1c estimates the glycaemic control of patients over the preceding three months [26].

GCF collection was performed from the sites with the highest CPI score using the extra crevicular method which has an advantage of being non-invasive as compared to gingival biopsies [6,7]. Analysis of special constituents in the GCF provides a qualitative biochemical indicator for evaluation of local cellular metabolism that clearly reflects the existing periodontal status. Microcapillary pipettes were used for collection of GCF samples to avoid non-specific attachment of the analyte to filter paper fibers ensuing in false reduction in

the detectable TNF-α level which in turn can underestimate the correlation of TNF-α level to disease severity. Microcapillary pipettes facilitated the collection of a standardized GCF volume of 3 µl for all the subjects, as required for the biochemical analysis of GCF.

The current study demonstrated a statistically significant relationship between glycaemic control and mean TNF-α level in the GCF of the study population at baseline and at three months. The TNF-α level was higher for the subjects with poor glycaemic control followed by moderate and well controlled subjects. Venza et al., [28] have demonstrated that TNF-α gene expression was higher in poorly controlled than well-controlled type 2 diabetic subjects.

A significant reduction in GCF TNF-α levels after SRP in all the three groups was observed in the study. These findings were in accordance with the previous studies [10,21]. However, Talbert et al., demonstrated no changes in the TNF-α and IL-6 levels in GCF after non-surgical treatment of periodontitis in type 2diabetic subjects [11].

A statistically significant improvement in the CPI score, PPD and CAL was also observed in the study. Similar results have been observed by Lee et al., [29].

Maximum improvement in periodontal condition and TNF-α level were seen in group II followed by group I and group III. Though various studies have compared the reduction in TNF-α levels in diabetes patients and healthy/periodontits subjects [21], to the best of our knowledge, no study has been reported comparing the TNF-α levels between the poorly, moderately and well controlled diabetes subjects.

The hypothesis that metabolic control can be improved by the successful treatment of periodontitis was reinforced by this study. A significant reduction in HbA1c levels was obtained after therapy (SRP). The reduction obtained was in accordance with the findings in the meta analysis by Darre et al., [30]. Previous studies have also showed an improvement in glycaemic control with periodontal therapy (SRP) [16,19]. Conflicting results have also been reported in some studies where, although the cytokine levels improved with therapy, the glycaemic levels did not change significantly [31]. Conflicting results among studies may be explained by differences in study designs and interventions, types of DM, initial levels of HbA1c, methods for determining HbA1c values, severity of periodontitis and the role of other variables on the glycaemic condition such as diet, physical activity etc.

Results of the present study emphasize on the possible existence of a two way relationship between periodontitis and diabetes mellitus. The reduction in TNF-α owing to reduction in inflammation following therapy would have in turn led to decrease in insulin resistance. Reduced insulin resistance may have helped to obtain better glycaemic levels.

Limitation of the study is the limited sample size and the short follow up period. Despite the beneficial effect of periodontal treatment on glycemic levels in type 2 diabetic patients, and reduction in TNF-α level, it must be noted that this study did not measure other variables (motivation of the patient, genetic predisposition, dietary factors,smoking) that might influence the results of the therapy as well as the actual control of the diabetes.

CONCLUSION

Within the limitations of this study, it might be concluded that mechanical non-surgical periodontal therapy could reduce periodontal inflammation and the concentration of circulating cytokines (TNF-α), which in turn could help to improve the metabolic control in type 2 Diabetes Mellitus. Data from this study warrants further study of the role of periodontal infection in patients with type 2 diabetes, with a larger sample size and longer follow up period.

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