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The effect of periodontal therapy on glycaemic level in patients with controlled type 2 diabetes mellitus on sulfonylurea oral hypoglycaemic agents

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Abstract
Background: This study was aimed at evaluating the relationship between glycaemic level and inflammatory status of periodontium following a thorough non-surgical periodontal therapy in type 2 diabetic patients on sulfonylurea group of hypoglycaemic agents.
Methods: 28 chronic periodontitis patients having controlled type 2 diabetes (HbA1c ≤ 8%) on sulfonylureas were selected for the study. The gingival inflammatory status was evaluated by estimating aspartate aminotransferase in gingival crevicular fluid (GCF-AST) and gingival index (GI). The glycaemic condition was assessed using fasting blood sugar level (FBS). The FBS, GI and GCF-AST levels were assessed prior to periodontal therapy, after 24 hours, 7th day, 14th day and 3rd month of treatment.
Results: The study demonstrated a strong co-relation between the gingival inflammatory status and the glycaemic level of patients following periodontal therapy. Both GI and GCF-AST was found consistent with FBS under the study conditions. Statistically significant reduction (p<0.05) in mean FBS, GI and GCF-AST was observed.
Conclusion: The study proved that a thorough non-surgical periodontal therapy reduced the glycaemic levels in type 2 diabetic patients on sulfonylurea group of hypoglycaemic drugs. Among the hypoglycaemics, sulfonylureas are known agents that tend to cause sudden drop in fasting glycaemic levels. Owing to this, an alteration in the dosage of hypoglycaemic drugs or a monitored dietary supplement may be necessary prior to periodontal therapy.

Keywords: aspartate aminotransferase, fasting blood sugar, gingival crevicular fluid, hypoglycaemia, sulfonylureas, type 2 diabetes mellitus

Introduction
Diabetes has emerged as a major health problem in India. According to International Diabetes Federation every fifth diabetic in the world would be an Indian by the year 2025 [1]. The countries with the largest predicted increases are India, China and the United States [2].
Periodontal disease and diabetes mellitus (DM) are both chronic polygenic disorders that exhibit immunoregulatory dysfunction resulting in host tissue damage. Moreover periodontal disease is known to be one of the most common complications of diabetes and is clinically understood to be sharing a bidirectional relationship with it in terms of its expression. Therefore understanding diabetes and its relationship with periodontal disease is of great concern for us.
Several studies have examined the bilateral effects of diabetes and periodontal diseases and unquestionably state the beneficial effects on glycaemic levels following periodontal therapy. At the same time, patients with poor periodontal condition having a controlled glycaemic status following consumption of hypoglycaemic drugs are found to be at high risk of developing transient hypoglycaemia following an extensive periodontal therapy [3].
Among the common hypoglycaemic drugs insulin and sulfonylurea group of drugs are proven to have higher risks of developing hypoglycaemic complications [4]. Hypoglycaemia in diabetic patients occur when an imbalance between insulin/hypoglycaemic agent's intake and body's physiological need exists.

Among the oral hypoglycaemic agents, longer-acting sulfonylureas such as Glibenclamide and Chlorpropamide are associated with more severe hypoglycaemia, with occasional cases reported with drugs like Metformin.

Studies have shown that diabetic patients with periodontal infection have a greater risk of worsening glycaemic control over time compared to diabetic subjects without periodontitis [5]. The combination of scaling and root planing with systemic doxycycline therapy is associated with an improvement in periodontal status that is accompanied by significant improvement in glycaemic control, as measured by the glycated haemoglobin assay (HbA1c) [6, 7, 8].

The detection of some biochemical markers can provide current information about tissue destruction [9]. Among these markers, aspartate aminotransferase (AST) enzyme has been extensively studied in both animal and human models [10]. It is an enzyme normally confined to the cell, which is released to the gingival crevicular fluid (GCF) upon cell death in the active phase of periodontal disease [11]. The present study was undertaken to assess the progressive glycaemic level of a well-controlled diabetic patient on sulfonylurea group of hypoglycaemic agents, following scaling, root planing and antibiotic therapy. This study is aimed at knowing the need for any adjustment of dosage of oral hypoglycaemic drugs following extensive periodontal therapy to prevent transient hypoglycaemia, that would benefit such patients prone to develop its complications.

Materials and Method

The present study was designed as a prospective interventional study. Sample size of 25 subjects were calculated using WinPepi software with an acceptable difference of 10% and dropouts of 10% at 95% confidence level [12]. The study subjects, who fit the inclusion criteria, were selected from diabetic patients referred to the Department of Clinical Periodontology and Oral Implantology, for the treatment of periodontitis. The participants were explained about the study and a written consent was obtained. Ethical clearance for the study was received from the Institutional Ethical Committee, for periodontal intervention and collection of the required biological fluids for the study.

32 controlled type 2 diabetic patients with glycated haemoglobin (HbA1c) record of ≤ 8% consuming sulfonylurea group of oral hypoglycaemic drugs with chronic periodontitis were selected for the study. Base line HbA1c level of each patient was estimated and recorded. Routine clinical examination to confirm chronic generalized periodontitis was performed. Fasting blood sugar (FBS) level at the base line was recorded for future references.

Patients who agreed to the study protocol and instructions, within an age group of 30 -70 years, with a baseline HbA1c level ≤ 8%, consuming sulfonylurea group of hypoglycaemics for the treatment of diabetes with chronic generalized periodontitis, not received any antimicrobial therapy for the past 3 months and not undergone any periodontal therapy during the previous 6 months were included in the study. Patient with a history of other major systemic diseases or medication, having HbA1c level > 8%, smokers, alcoholics and pregnant women were excluded from the study.

Clinical Procedure

50 subjects complying with the inclusion-exclusion criterias were selected for the study. Only the subjects suffering from chronic periodontitis seeking its treatment were considered for the study. Every patient was assessed for their periodontal status through routine Gingival index (Loe & Silness, 1963) [13], periodontal pocket estimation and clinical attachment loss [14]. All the values were correlated and the patient was clinically confirmed to have chronic periodontitis. Out of the 50 participants, 32 of them who could cooperate with the study were selected.

The fasting blood sugar level of each patient was assessed and noted as the base line score. Sufficient gingival crevicular fluid was collected [Figure 1] from the gingival sulcus which showed a pocket depth of ≥4mm [Figure 2] for the assessment of aspartate aminotransferase (AST) in it, so as to identify the earlier changes of inflammation of gingiva.

GCF samples were obtained using the 5µl graduated micro-capillaries. 1µl of crevicular fluid was collected and emptied into a Cryovial containing 99µl of phosphate-buffered saline. The obtained samples were immediately transported in an icebox maintained at 4oC to the laboratory for the assessment of aspartate aminotransferase levels.

After scaling and root planing, a course of doxycycline for 10 days and 0.12% chlorhexidine oral rinse was prescribed. They were recalled after 24 hours, 7th day, 14th day and 3rd month. At each visit, fasting blood sugar level and gingival index was recorded and gingival crevicular fluid [Figure 3] was obtained to assess the aspartate aminotransferase level. Method used for GCF-AST assessment was according to the International Federation of Clinical Chemistry (IFCC) without pyridoxal phosphate, Kinetic, UV [15].

Data was recorded, tabulated and assessed for clinical parameter (GI) and biochemical parameters (GCF-AST, FBS) at baseline prior to non-surgical periodontal therapy and 24 hours, 7th day, 14th day and 3rd month after the procedure. The results were averaged (mean ± standard deviation) for each parameter.

All the statistical calculations were performed through SPSS for Windows (Statistical Presentation System Software, 1999, SPSS Inc, New York, Version 18.0). Repeated measures analysis of variance (r ANOVA) was used to compare three or more group means. The Bonferroni correction was used to reduce the chances of obtaining false-positive results. Pearson's Correlation Technique was used to test the relationship between GCF -AST levels, GI and FBS.

Results

In the present study a total of 32 patients were enrolled out of which 4 dropped after the 1st visit. Therefore 28 patients were considered for the study. The present study has found a mean reduction in FBS from the baseline to the 3rd month after scaling and root planning. The mean on the 7th day was the least among all the visits and showed further increase towards the 3rd month (Graph 1).

Similarly the gingival index also exhibited a statistically significant (p<0.05) reduction upto 14th day at each interval from the baseline, thereafter exhibiting a slight increase towards the end of the study (Graph 2).

GCF-AST also showed a significant reduction (p<0.05) in its value from the baseline upto 7th day (Graph 3). This was reverted back to the baseline value by the end of 3rd month. Out of the 4 intervals examined, gingival inflammation was found to be least at 7th to 14th day and thereafter tend to increase in both biochemical and clinical estimation.

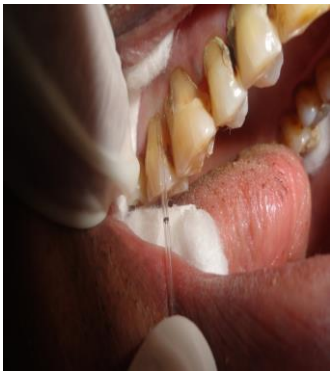


Fig 1: Collection of Gingival Crevicular Fluid Prior To Scaling

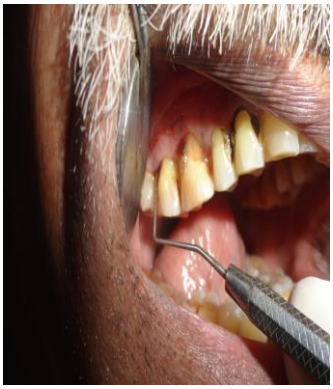


Fig 2: Probing For Pocket Depth

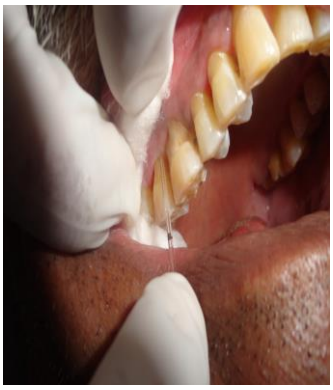
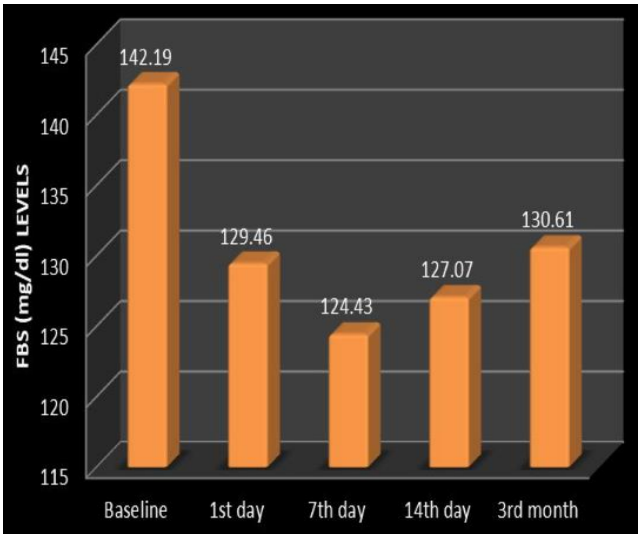
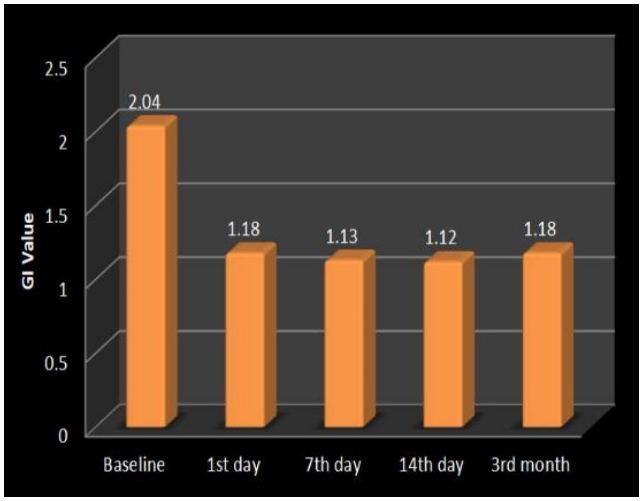


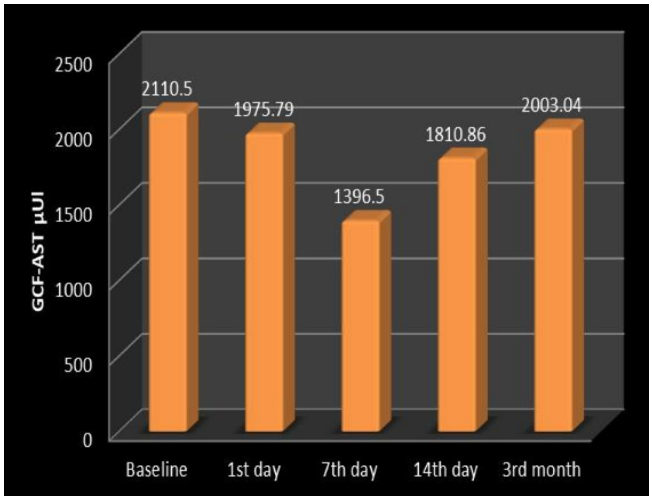
Fig 3: Collection of Gingival Crevicular Fluid After Scaling and Root Planing



Graph 1: Mean of Fasting Blood Sugar (Milligram per decilitre) at baseline, 1st day, 7th day, 14th day, 3rd month



Graph 2: Mean of Gingival Index at baseline, 1st day, 7th day, 14th day, 3rd month



Graph 3: Mean of Gingival Crevicular Fluid-Aspartate Aminotransferase (Microunits litre) at baseline, 1st day, 7th day, 14th day, 3rd month

Discussion

The relation between periodontal disease and diabetes has been discussed by many researchers over the years [16, 17, 18]. The observation that periodontal therapy appears to reduce periodontal infection and inflammation suggests that periodontal therapy may facilitate metabolic control of diabetes, improving insulin sensitivity by reducing peripheral inflammatory cytokine levels [19]. Therefore the present study was planned to explore the present hypothesis about the effect of phase 1 periodontal therapy on glycaemic control. The glycaemic control caused by periodontal therapy can be enhanced when the patient is on certain hypoglycaemics, especially insulin and sulfonylureas, thereby increasing the risk of hypoglycaemia.

In the present study the glycaemic levels were assessed using fasting blood sugar (FBS) level instead of glycated haemoglobin level since the immediate effect on fasting blood sugar after a thorough scaling and root planing could be evaluated.

Diabetics have a hyper-responsive monocyte/macrophage phenotype, resulting in significantly increased production of pro-inflammatory cytokines and mediators [20, 21]. This hyper-inflammatory response results in elevated levels of pro-inflammatory cytokines in the gingival crevicular fluid. Thus aspartate aminotransferase was considered a reliable factor in assessing the gingival inflammatory condition in this study.

The comparison between the aspartate aminotransferase in gingival crevicular fluid and fasting blood sugar showed an increase in the AST levels on the first day following the non-surgical periodontal therapy, whereas the FBS levels reduced immediately after the procedure. There was a reduction in both the parameters in subsequent visits and by the 3rd month an increase in both the values were observed. This increase in its value may be due to the sudden increase in the inflammatory process following gingival therapy.

The AST level in GCF and the GI score indicating gingival inflammation and the FBS level was shown to be directly proportional to each other with a constant decrease in it's values at each intervals as compared with the baseline values. Progressive reductions in all these parameters were observed on the first 2 intervals and thereafter an increase towards the 3rd month.

The results of this study shows that, following periodontal therapy, immediately there was a statistically significant improvement in glycaemic control in individuals with type 2 DM consuming sulfonylurea drugs, as supported by other studies [19]. There was a significant reduction in the fasting blood sugar level in the initial visits, the trend reverts back to the initial reading by the 3rd month.

As compared with other studies [22, 23], this study also supported the fact that, upon periodontal treatment an improvement in the gingival index in diabetic patients from 2.04 (±.32) at baseline to 1.18 (±.06) at the end of the third month was observed. They did not find any change in glycaemic control after periodontal therapy, in long terms as 3 months.

In a study by S. Al Mubarak [20] and also Williams and Mahan [21] showed a significant numeric reduction in glycaemic levels associated with an improvement in the periodontal health similar to the present study. Several studies demonstrated similar effects of significant improvement both in clinical parameters and in glycaemic control following periodontal therapy [19, 24].

Most of the studies reviewed have assessed the parameters only after a month or three months and more. None of the studies known had reviewed the parameters within 24 hours of periodontal therapy. Immediate effect of periodontal therapy on glycaemic levels is important to adjust the dosage of hypoglycaemic drugs to prevent any advertent effects. Understanding this, the glycaemic condition of the patient after 24 hours was also included in the study.

In this study periodontal disease activity was assessed based on two parameters, clinical and biochemical. The method of biochemical assessment based on the evidence that increased AST in crevicular fluid reflects active tissue destruction in periodontium is supported by earlier studies [25, 26].

Conclusion

In cases where the clinician anticipates a sudden downfall in the patient's glycaemic level following any dental treatments rendered, the normal dietary intake or the oral anti-diabetic medication dosages may need to be appropriately adjusted in consultation with the patient's physician especially in patients consuming sulfonylurea group of hypoglycaemic drugs. The drugs like salicylates have been proven to increase insulin secretion and sensitivity, thus such drugs when given in combination can potentiate the effects of sulfonylureas, resulting in more severe hypoglycaemia.

The present study demonstrated a dramatic downfall in the glycaemic level of Type 2 diabetic patients on sulfonylurea group having chronic periodontitis, following thorough non-surgical periodontal therapy. So every possible precaution to overcome post-operative hypoglycaemic complications is to be considered while treating controlled diabetic patients under sulfonylurea group of hypoglycaemics, especially if they require an extensive periodontal therapy.

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