Adjunctive Effect of Doxycycline with Conventional Periodontal Therapy on Glycemic Level for Chronic Periodontitis with Type 2 Diabetes Mellitus Subjects

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ABSTRACT

Aims: This study aimed to assess the use of doxycycline in adjunct to periodontal therapy on the glycemic levels for chronic periodontitis patients with type 2 diabetes mellitus (DM).

Materials and methods: Fifty-one diabetic subjects with chronic periodontitis were selected and randomly assigned into 3 groups with 17 subjects each. Scaling and root planing (SRP) was done in group I, SRP and doxycycline was given in group II, and group III did not receive any periodontal treatment till 3 months. Probing pocket depth (PPD), clinical attachment level (CAL), plaque index (PI), gingival index (GI), and metabolic parameters were evaluated at baseline (day 0) and after 3 months (day 90). The statistical analysis was carried out using SPSS 17.0 software with significance fixed at 95% CI ($p < 0.05$).

Results: The mean difference between baseline and day 90 for all periodontal parameters was significantly higher ($p < 0.01$) in group I and group II compared to control (group III). The metabolic parameters such as fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG), and glycated hemoglobin (HbA1c%) level were reduced in groups I and II compared to group III; however, only HbA1c% values were found significantly reduced ($p < 0.01$) at day 90. Group II showed significantly better metabolic parameters than group I at day 90.

Conclusion: The adjunct of doxycycline to conventional periodontal therapy provides additional benefit in reducing glycemic level and improves periodontal health.

Clinical significance: The prevalence of diabetes as well as periodontitis is increasing nowadays in the world. With treatment of periodontitis, it is found that there is reduction of glycemic level in diabetes. So it is an alert to health professionals about the relation of diabetes and periodontitis and so that they conduct a multidisciplinary treatment.

Keywords: Diabetes, Doxycycline, Glycated hemoglobin, Periodontitis, Root planing, Scaling.

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INTRODUCTION

Periodontitis is an inflammatory condition affecting both soft and hard parts of periodontium, with multifactorial etiology.[1] Periodontitis is considered to be the major cause of tooth loss in adults and has also been claimed to affect the systemic conditions of the individual.[2] The inflammatory mediators released in chronic periodontitis affects the general health.[3] The pathophysiology of various inflammatory systemic conditions like rheumatic arthritis, cardiovascular diseases, and diabetes mellitus (DM), etc., is considered to be synergistically influenced by such inflammatory mediators.[3] Various studies were carried out to establish such association between the incidence of periodontitis and its effect on patient's systemic conditions. Diabetes mellitus is one such chronic systemic condition, which is adversely affected in presence of these inflammatory mediators.[4]

Diabetes mellitus (also known as noninsulin dependent diabetes or type 2 DM) is a chronic disease caused by a defect in the secretion of pancreatic insulin and/or an insensitivity of target tissues to its action leading to hyperglycemia, which is also noncommunicable and is considered as one of the major health conditions affecting public general health globally.[4,5] The association between diabetes and periodontitis is generally considered to be as a double-edge sword. The diabetes affects the onset and progression of periodontitis, and conversely, the periodontitis worsens the diabetic status of an individual by altering their glycemic control.[6,7] It is established that the prevalence of periodontitis is two–three times higher in diabetic patients.[8] Diabetes mellitus increases the

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severity of periodontitis compared to patients without diabetes.[9] And also the periodontitis is considered to be one of the diabetic complications.[10,11]

Conversely, there is also evidence to indicate the adverse effect of periodontitis on glycemic control in diabetics. Elevated levels of several

proinflammatory cytokines [tumor necrosis factor alpha (TNF-α), IL-6] are seen in periodontitis.[12–14] The alteration in monocyte/macrophage phenotype in cases of DM leads to increased production of these inflammatory cytokines, which further worsen the insulin resistance and, thereby, aggravate poor glycemic control.[15]

Considering these various mechanisms that promote insulin resistance, it is clear that a chronic systemic inflammatory state induced by periodontal disease may contribute further to insulin resistance in individuals with DM through a "feed-forward" mechanism.[16] This explains the mechanisms of poor glycemic control in diabetics with periodontal disease.[17]

It is believed that in patients with type 2 DM, antimicrobial periodontal therapy can cause a significant reduction of HbA1c value.[18] It is also found that SRP can improve the glycemic control in patients with type 2 DM with or without adjunctive systemic doxycycline therapy.[19] According to a recent finding, diabetic patients with chronic periodontitis treated with periodontal treatment and topical antibiotics can improve glycemic control and elevate serum adiponectin with improvement of periodontal status in type 2 diabetic patients.[20]

Doxycycline, which belongs to tetracycline group of antibiotics, is an inexpensive, well-tolerated, broad spectrum antibiotic with an array of additional benefits. Doxycycline is proved to have high sulcular availability concentration when administered systemically.[21] Further, it demonstrates an inhibitory effect on matrix metallo-proteinases which induces release of various inflammatory mediators.[22] Moreover, doxycycline also have an inhibitory effect on protein glycation, which is essential for production advanced glycation end products (AGE) and deposition.[23]

This study aimed at evaluating the effect of using systemically administered doxycycline at its recommended dosage, as an adjunct to the conventional periodontal therapy, by assessing the glycemic levels, in treatment of chronic periodontitis patients with type 2 DM.

MATERIALS AND METHODS

The present study was a prospective, randomized, parallel arm, double-centered clinical trial, which was carried out in the Department of Periodontics, Regional Dental College and Hospital, Guwahati, India in collaboration with the Department of Endocrinology, Guwahati Medical College and Hospital, Guwahati, India. The study was carried out in accordance to the ethical guidelines of Helsinki declaration of 1975, as revised in 2000. The Ethical Committee of Regional Dental College, Guwahati, approved the study with IHEC No. RDC/29/2009/1830 dated 23rd March, 2009. The study was performed from February 2009 to September 2010. The subjects were selected on the basis of the following criteria.

Inclusion Criteria

- Subjects with type 2 DM.
- Diabetics presented with moderate to severe periodontitis (where 30% or more of the teeth have ≥4 mm clinical attachment loss).
- Subjects ≥30 years of age regardless of gender.
- Subjects with no evidence of other oral and systemic diseases.
- Subjects under treatment of an endocrinologist.

Exclusion Criteria

- Subjects with uncontrolled DM.
- Subjects who have undergone periodontal therapy during last 6 months.
- Subjects administered antibiotic during last 3 months.
- Subjects with <20 natural teeth.
- Subjects allergic to tetracycline and its derivatives.
- Pregnant and lactating mothers.
- Persons consuming any form of tobacco.

A total of 1,000 subjects were screened to select 80 subjects having type 2 DM with periodontitis. Subsequently, 51 subjects were selected for inclusion into the study. Thorough medical history along with the diabetes record of the subjects was obtained in detail. The concerned endocrinologist was well-informed regarding the study design. Subjects were explained the entire procedure in detail and were included in the study after signing an informed consent form.

No change in the medication or diet was made for the subjects. None of the subjects received any additional guidance regarding the control of their diabetic status. A sample size of at-least 15 patients in each group was estimated to achieve 90% power to detect mean difference between the groups ($p < 0.05$).

The subjects were randomly categorized into three groups by single investigator (ACD) using a block randomization. The groups were named as I, II, and III (control). The subjects were not blinded with respect to treatment administered. After oral examination, the teeth with poor prognosis were extracted. Subjects taking antibiotics after extraction were included in the study after a period of 3 months.

All subjects underwent periodontal examination by a single examiner [Abhaya C Das (ACD)]. Periodontal status was assessed using PPD, CAL, PI,[24] and GI.[25] The metabolic parameters considered were FPG, PPG, and HbA1c% level.

The subjects in group I received oral hygiene instructions and full mouth SRP, while the subjects in group II received doxycycline (DOXT, Dr Reddy's Lab. Ltd, Hyderabad, India) (total dose 1,600 mg in equally divided 16 doses, start as 100 mg BD followed by OD for 14 days)[26] in addition to the same therapy as that of group I. The group III received no treatment that served as control. All the control group subjects were treated with required periodontal intervention after the final assessment of study parameters after 3 months.

All the periodontal and metabolic parameters were recorded on day 0 and 90. The data were then analyzed statistically using SPSS version 15 (IBM, Chicago, USA). The normality of the data distributions was assessed by means of the D'Agostino and Pearson omnibus normality test. Paired "t" test was used to compare the various parameters on day 0 and 90 within the same group, while Student's unpaired "t" test was used to compare the parameters between two groups. p value less than 0.05 was considered as statistically significant.

RESULTS

Out of 1,000 consecutive subjects screened, 80 subjects were selected for the study. Based on the inclusion criteria, 29 subjects were excluded (16 due to uncontrolled diabetes and 13 due to less number of teeth present). Finally, 51 subjects (30 males and 21 females), having a mean age of 45.92 ± 7.88 years (range 30–65 years), fulfilled all the criteria to be included as shown in Table 1. After randomization, 17 subjects were assigned to each group. A flow diagram representing the participants throughout the study is shown in Flowchart 1.

As shown in Table 2, on day 0, the mean PI was 1.99 ± 0.43 in group I and decreased by 47.3% on day 90 (1.04 ± 0.28). This difference was found to be statistically highly significant ($p < 0.01$).

Similarly, the mean difference in PI in group II between day 90 and 0 was 1.33 (53.20%) and was statistically very highly significant ($p < 0.001$). On the contrary, the PI in group III was found to be increased by 0.06 (2.46%) from day 0 to 90, though not statistically significant ($p > 0.05$).

The GI in group I decreased by 45.0% on day 90 compared to day 0, which was found to be statistically very highly significant ($p < 0.001$). Similarly, the reduction in GI in group II between day 90 and 0 was 46.08% and statistically very highly significant ($p < 0.001$). In contrast, the GI in group III was found to be increased by 0.03 (2.46%) from day 0 to 90, though not statistically significant ($p > 0.05$) as shown in Table 2.

As shown in Table 2, the mean PPD on day 0 was 3.08 ± 0.30 in group I and decreased by 24.67% on day 90 to 2.32 ± 0.28. This difference was found to be statistically very highly significant ($p < 0.001$). Similarly, the mean difference in PPD in group II between day 90 and 0 was 1.01 (30.51%) and was statistically very highly significant ($p < 0.001$). On the contrary, the PPD in group III was

Table 1: Baseline demographic characteristics of subjects who completed the study

Subjects	Group I (SRP)	Group II (SRP + Doxy)	Group III (control)
Gender			
Female (%)	7 (41)	9 (53)	6 (35)
Male (%)	10 (59)	8 (47)	11 (65)
Age (years)			
Mean ± SD	38 ± 11	42 ± 13	40 ± 12

found to be increased by 0.10 from day 0 to 90 (2.53%), though not statistically significant ($p > 0.05$).

The CAL was reduced by 0.73 (19.26%) and 0.93 mm (24.73%) on day 90 compared to day 0 in group I and II, respectively, which were found to be very highly significant statistically ($p < 0.001$). In contrast, CAL in group III was increased by 0.07 mm on day 90 from day 0, though not statistically significant ($p > 0.05$).

Intergroup comparison between the groups II and I revealed no statistically significant difference in the periodontal parameters ($p > 0.05$), except in PI ($p < 0.01$). Again, the differences between the groups II and III, and between the groups I and III, and significant differences were observed in all the periodontal parameters ($p < 0.01$).

As shown in Table 3, on day 0, in group I, the mean HbA1c was 7.58 ± 0.89, which was reduced by 0.61% on day 90 to 6.97 ± 0.86, though the difference was not significant statistically ($p = 0.14$). Similarly, the mean difference in HbA1c in group II between days 90 and 0 was 0.93 and was statistically very highly significant ($p < 0.001$). On the contrary, the HbA1c in group III was found to be increased by 0.06 from days 0 to 90, though not statistically significant ($p > 0.05$).

The FPG was reduced by 7.82 and 16.06 mg/dL on day 90 compared to that of day 0 in groups I and II, respectively. Again, in group III, it was increased by 2.83 mg/dL. However, these differences within the groups were not found significant statistically ($p > 0.05$), as shown in Table 3.

The PPG was reduced by 15.64 and 24.47 mg/dL from days 0 to 90 in groups I and II, respectively. Again, in group III, it was increased by 2.36 mg/dL (Table 3). However, these differences within the groups were not found statistically significant ($p > 0.05$).

Flowchart 1: A CONSORT flowchart representing the participants throughout the study
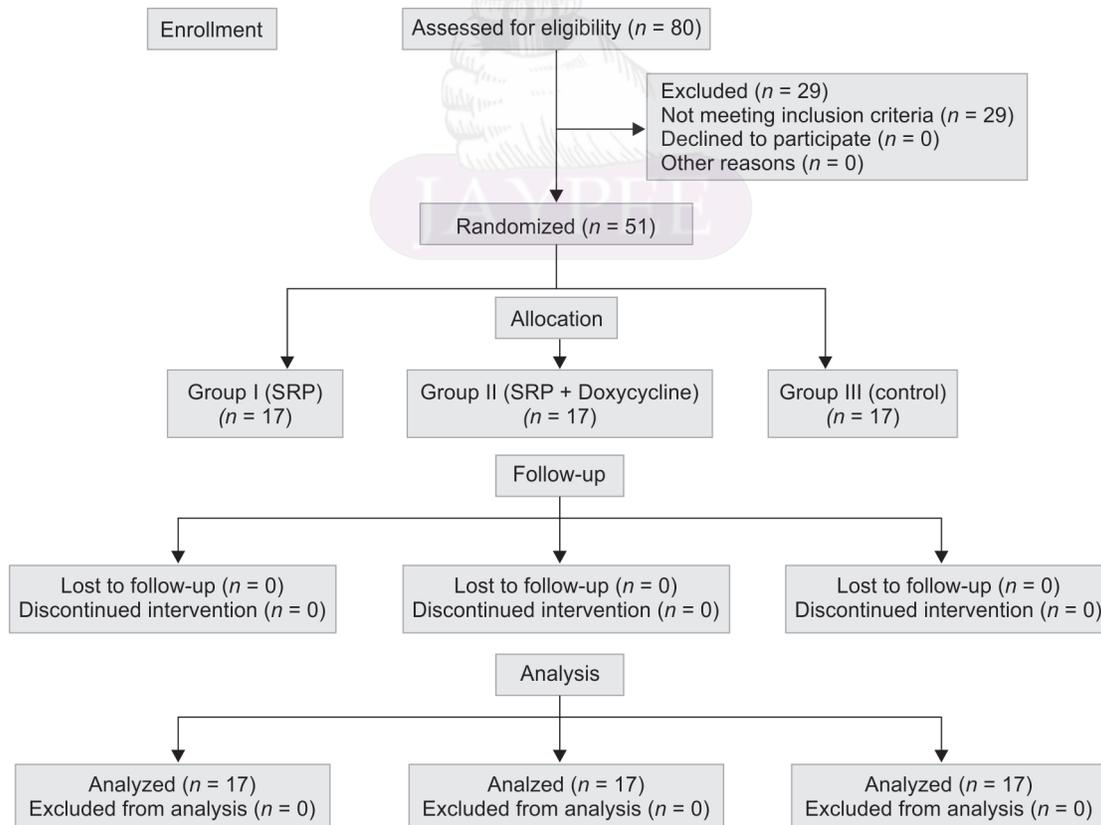
Table 2: Comparison of periodontal parameters in intragroup and intergroup

	PI	GI	PPD (mm)	CAL (mm)
Group I				
Day 0	1.99 ± 0.43	1.80 ± 0.39	3.08 ± 0.30	3.79 ± 0.40
Day 90	1.04 ± 0.28	0.99 ± 0.28	2.32 ± 0.28	3.06 ± 0.42
Δ^a	0.95	0.81	0.76	0.73
p value	<0.001[b]	<0.001[b]	<0.001[b]	<0.001[b]
Group II				
Day 0	2.50 ± 0.42	2.04 ± 0.33	3.31 ± 0.62	3.76 ± 0.66
Day 90	1.17 ± 0.22	1.10 ± 0.21	2.30 ± 0.45	2.83 ± 0.52
Δ^a	1.33	0.94	1.01	0.93
p value	<0.001[b]	<0.001[b]	<0.001[b]	<0.001[b]
Group III				
Day 0	2.37 ± 0.54	1.95 ± 0.42	3.42 ± 0.49	3.84 ± 0.50
Day 90	2.43 ± 0.51	1.98 ± 0.41	3.52 ± 0.49	3.91 ± 0.49
Δ^a	−0.06	−0.03	−0.10	−0.07
p value	0.74[c]	0.78[c]	0.58[c]	0.68[c]
Δ(Dox vs SRP)	0.38[b]	0.13[c]	0.25[c]	0.20[c]
Δ(Dox vs Non)	1.27[b]	0.91[b]	0.91[b]	0.86[b]
Δ(SRP vs Non)	0.89[b]	0.78[b]	0.66[b]	0.66[b]

Values are presented as mean ± standard deviation
PI, plaque index; GI, gingival index; PPD, probing pocket depth; CAL, clinical attachment level
[b]Statistically significant difference
[c]Not statistically significant difference
Δ^a: changes in-between day 90 and day 0
p value: comparison between day 90 and day 0
Δ(Dox vs SRP): changes in mean differences (day 90 vs day 0) between group II and group I
Δ(Dox vs Non): changes in mean differences (day 90 vs day 0) between group II and group III
Δ(SRP vs Non): changes in mean differences (day 90 vs day 0) between group I and group III

Table 3: Comparison of metabolic parameters in intragroup and intergroup

	HbA1c (%)	FPG (mg/dL)	PPG (mg/dL)
Group I			
Day 0	7.58 ± 0.89	155.06 ± 30.98	201.76 ± 34.36
Day 90	6.97 ± 0.86	147.24 ± 29.71	186.12 ± 35.37
Δ^a	0.61	7.82	15.64
p value	0.14[c]	0.46[c]	0.20[c]
Group II			
Day 0	8.42 ± 1.27	166.65 ± 48.06	248.71 ± 66.84
Day 90	7.49 ± 1.14	150.59 ± 41.88	224.24 ± 61.84
Δ^a	0.93	16.06	24.47
p value	<0.001[b]	0.31[c]	0.28[c]
Group III			
Day 0	8.35 ± 0.96	186.82 ± 24.47	211.76 ± 27.56
Day 90	8.41 ± 0.90	189.65 ± 24.68	214.12 ± 26.99
Δ^a	−0.06	2.83	2.36
p value	0.85[c]	0.74[c]	0.80[c]
Δ(Dox vs SRP)	0.32[b]	8.24[b]	8.83[b]
Δ(Dox vs Non)	0.87[b]	13.23[b]	22.11[b]
Δ(SRP vs Non)	0.55[b]	4.99[b]	13.28[b]

Values are presented as mean ± standard deviation
HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial glucose
[b]Statistically significant difference
[c]Not statistically significant difference
Δ^a: changes in-between day 90 and day 0
p value: comparison between day 90 and day 0
Δ(Dox vs SRP): changes in mean differences (day 90 vs day 0) between group II and group I
Δ(Dox vs Non): changes in mean differences (day 90 vs day 0) between group II and group III
Δ(SRP vs Non): changes in mean differences (day 90 vs day 0) between group I and group III

Intergroup comparison among the groups (II vs I; II vs III; and I vs III) revealed a highly statistically significant difference in all the metabolic parameters ($p > 0.01$).

DISCUSSION

Diabetes mellitus and periodontal diseases are thought to be associated biologically. Various possible mechanisms have been proposed regarding their influence on each other,[12,14–16,27–31] and also a high incidence and severity of periodontal disease is reported in diabetics compared to that of nondiabetics.[32–34] Similarly, improvement in the glycemic level following periodontal therapy has also been reported in various studies.[18,35–43] In contrast, few other studies failed to determine any positive effect of periodontal therapy on glycemic level.[44–48] Thus, the effect of periodontal therapy on glycemic level remains questionable.

For the present study, subjects with type 2 DM having chronic periodontitis were selected, because both type 2 DM and chronic periodontitis are highly prevalent among the adults; and type 2 DM has shown a spectacular increase in the past few decades as infections including periodontitis results in increased insulin resistance.[12,14,31] Subjects with type 1 DM were not selected, because

it is accepted to be having autoimmune pathophysiology[49,50] and is usually treated by administrating insulin. Besides, glucose levels in these subjects need to be monitored very steadily and adjusted frequently to prevent hypoglycemic crisis. In addition, the subjects with type 1 DM in general are too young to develop moderate to severe periodontitis.[47]

In the present study, it was chosen to administer systemic doxycycline in patients of group 2. The reason for selecting doxycycline is its well-documented anticollagenolytic effect and lowering effect on HbA1c by various authors like Iwamato et al. and Grossi et al.[18,26] In addition, the extracellular glycation of proteins, which are implicated in many of the long-term complications of diabetes, is also inhibited by tetracycline through the inhibition of nonenzymatic glycosylation.[18,26,51] Notably, none of the subjects of the present study experienced any adverse effects with the systemic doxycycline. The results of the present study lie in accordance to the study conducted by Gaikwad et al., where a statistical significant difference was observed for all clinical parameters like probing depth (PD), CAL, PI, and GI recorded between baseline and 4 months. However, this study failed to show a statistical significance in improvement of HbA1c level at the end of follow-up.[19]

Probing pocket depth reduction is considered as an important aspect for evaluation of the success of periodontal therapy. In the present study, the subjects were assessed for PPD on day 90 following SRP, as it is suggested that a period of 3 months after therapy is ideal for reassessment though the most appropriate timing for assessment of the healing response is controversial in the literature.[52,53] The reduction in PPD was found to be highly significant for the doxycycline with SRP group compared to control and SRP alone group. This finding is in accordance to the study conducted by Mubarak et al. stating the reduction of PPD to be highly significant ($p < 0.001$) for doxycycline and SRP group compared to SRP alone at the end of 3, 6, 9, and 12 months follow-up. The results were similar for CAL, PI, GI, TNF alpha levels, and HbA1c levels.[54]

Fasting plasma glucose and PPG are considered to be vital tests for the diagnosing diabetes, while the HbA1c value indicates a subject's overall glycemic control in diabetics. HbA1c depicts the mean glucose level in the blood for a period of 2–3 months prior to its measurement. Thus, the temporal gap in-between two evaluations should be at least 2 months apart.[55]

One of the important points noted in the present study is the significant reduction in HbA1c levels in patients of group II, which received systemic doxycycline in addition to SRP, but not in subjects of group I, which received only SRP. These results are in accordance to the study by Al Mubarak et al., where HbA1c showed significant improvement ($p < 0.05$) only for subjects with HbA1c% $\leq 8.8\%$ within each group.[54]

It may be due to the fact that antimicrobial therapy in addition to SRP pivots its efficacy by reduction of circulating TNF-α, which further reduces the levels of insulin and HbA1c.[18,26]

In the present study, conversely, FPG and PPG were not reduced significantly. This may suggest that HbA1c, FPG, and PPG levels are not correlated. Thereby, HbA1c value is difficult to predict from the evaluation of FPG and PPG.[56]

A recent systematic review by Santos et al. concludes the addition of systemic antibiotic use with SRP in diabetic patients to provide an additional benefit in terms of reductions in mean pocket depth and mean percentage of bleeding on probing (BoP). This systematic review and meta-analysis included five studies with at least 6-month follow-up to find a significant effect favoring SRP plus antibiotics for reductions in mean PD (-0.22 mm [-0.34, -0.11]) and mean percentage of BoP (4% [-7, -1]).[57]

LIMITATIONS OF THE PRESENT STUDY

Considering the small sample size and lack of nondiabetic subjects with periodontitis in the present investigation, further studies, possibly in collaboration with an endocrinologist, are required to confirm our findings. Long-term follow-up and more informative outcomes are necessary for better understanding the relationship between type 2 DM and chronic periodontitis. A disadvantage of block randomization is that the allocation of participants may be predictable and result in selection bias when the study groups are unmasked. However, further study involving larger sample size with longer follow-up is required to confirm the findings of the present study. The authors suggest the scope of performing another prospective clinical study on indoor subjects who are under proper medication and diet and directly under the supervision of an endocrinologist.

CONCLUSION

The observations indicate an improvement in HbA1c, FPG, and PPG related with improvement in periodontal health. Adjunctive doxycycline therapy improved the metabolic and periodontal parameters to a statistically significant extent when compared to the periodontal therapy alone.

CLINICAL SIGNIFICANCE

The prevalence of diabetes as well as periodontitis is increasing nowadays in the world. With treatment of periodontitis, it is found that there is reduction of glycemic level in diabetes. So it is an alert to health professionals about the relation of diabetes and periodontitis and so that they conduct a multidisciplinary treatment.

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