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# Comparison of the Effect of Non-surgical Periodontal Therapy with and without Systemic Doxycycline on the Health of Periodontium and $HbA_1c$ in Type 2 Diabetic Patients without Good Glycemic Control

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## *Abstract*

***Background and aims.*** The aim of the present study was to evaluate the result of full scaling and root planning with and without systemic administration of doxycycline on periodontium and metabolic control in type 2 diabetes mellitus (DM) patients.

***Materials and methods.*** Thirty patients with type 2 DM with poor glycemic control were selected and randomly assigned into two groups. Case group received scaling and root planning and doxycycline (SRP + Doxy) and control group received only SRP. Probing pocket depth (PD) and bleeding on probing (BOP) as the most important indicators for periodontal health were recorded at baseline, 3- and 6-month follow-up. Fasting blood sugar (FBS), glycated hemoglobin ($HbA_1c$), total cholesterol (TC), and triglyceride (TG) were analyzed before and after periodontal treatments.

***Results.*** A statistically significant reduction was observed for PD and BOP for the treatment groups. $HbA_1c$ levels in SRP group decreased more significantly than SRP + Doxy group (9.15 ± 0.76 to 7.73 ± 1.41% and from 8.41 ± 0.49 to 7.88 ± 1.77%, respectively).

***Conclusion.*** Non-surgical periodontal treatment is associated with improved periodontal health and glycated control in DM type 2 patients and could be considered as an important part of the diabetic patient care.

***Key words:*** **Diabetes, glycemic control, periodontitis.**

### *Introduction*

Diabetes Mellitus type 2 is a complex metabolic disease that creates a wide range of complications in humans over 40 years of age.[1] There is no significant disorder in production and secretion of insulin; however, malfunctions such as increase in insulin resistance or disorders in insulin receptors of host cells occur.[2]

Studies show the prevalence of diabetes in Iran to be around 6.8%, which means almost 5.1 million Iranians suffer from this condition.[3]

Periodontitis is an infectious disease produced by different kinds of gram-negative anaerobic bacteria from subgingival microbial plaque. The prevalence of periodontal diseases in individuals with type 2 diabetes and improper glucose control is significantly higher than those with a normal systemic condition.[4,5] The prevalence of periodontitis in adults with type 2 diabetes is three times more than healthy individuals,[6] and the prevalence of gingivitis in young diabetic patients is more than the normal subjects in the same age.[7] The relationship between periodontal diseases and diabetes has been clearly observed in clinical studies and periodontal disease is now considered as one of the six most common complications of diabetes.[8]

Diabetes is considered a risk factor for periodontitis especially in subjects with poor metabolic control and there are evidences that emphasize on the effect of periodontal infections on the diabetic complications and the level of glucose control.[9] During the acute phase of bacterial infection, the insulin resistance raises up to 33% and after resolution of infection, a 28% decrease in resistance is observed.[10] Nelson et al[11] in a two-year prospective study found glucose control in diabetic patients was poorer in those who suffered from severe periodontitis in baseline.

Papers have claimed periodontal mechanical debridement had some positive effects on the level of glucose control in diabetics.[12,13] However, other clinical trials have shown existence of infectious agents such as *Porphyromonas gingivalis* and *Tannerella forsythensis* can be considered as a marker of tissue destruction.[14] In other words, closed scaling in moderate to severe periodontal pockets and good oral hygiene in diabetic patients would not be sufficient for stable periodontium or improving metabolic control.[14-16] The use of systemic antibiotics can be effective in decreasing the total count of bacteria in periodontal infections. As a result, the secretion of inflammatory mediators would be decreased, and thus, the level of glucose control in type 2 diabetic patients would improve. Decrease in the level of $HbA_1c$ after treatment with doxycycline,[17] and less need for insulin after prescription of penicillin,[12] can be attributed to the antimicrobial effect of these drugs. Several studies indicate non-surgical periodontal therapy does not significantly reduce the level of $HbA_1c$ in diabetic patients.[15,16,18,19]

Stewart et al[1] reported a decrease of $HbA_1c$ level from 9.5 to 7.6 (17.1%) by treating 36 diabetic patients with phase 1 periodontal therapy including scaling/root planning and extraction of hopeless teeth. They claimed a important finding that the decrease vatic was much more significant in patients who received insulin and other kinds of glucose reducing agents compared to those who had only diet regimen. Other word, better improvement in metabolic control could be achieved in subjects with lower level of glucose control. The effect of non-surgical periodontal therapy in maintaining teeth, improving masticatory system, and quality of life has been demonstrated by several researches; however, the impact of these procedures on systemic condition of patients is not clear yet.[15,20,21]

Borrell & Papapanou[22] recommended that more clinical trials should be designed in order to show whether periodontal therapy has any effect on metabolic control of diabetics or not.Therefore, we designed a sudy to compare the clinical efficacy of non-surgical periodontal therapy with and without systemic doxycycline on the periodontal health and $HbA_1c$ level in type 2 diabetic with poor glycemic control.

## *Materials and Methods*

### *Subjects*

The experimental subjects were referred from the Diabetes Clinic, Namazi Hospital, Shiraz, Iran to the Department of Periodontology, Shiraz University of Medical Sciences Faculty of Dentistry, Shiraz, Iran, during 2005-2006. The inclusion criteria were the following: Subject aged over 40 years, minimal 1-year history of type 2 diabetes, no need for prophylaxis regimen, no use of antibiotic in the past 6-month, no pregnancy or lactation for women, having at least 16 teeth with moderate to severe periodontitis so that at least six of them have $\geq$ 5 mm periodontal pocket, $\geq$ 2 mm loss of attachment, and bleeding on probing. The selected patients had not received any kind of scaling or periodontal surgery since 4 and 6 months, respectively. All patients were tested for glycolic control and only subjects with poor metabolic control ($HbA_1c$ level > 7%) were included in the study design.[23]

### *Clinical measurements*

All subjects were examined by one examiner (RA) after receiving an informed consent. Clinical examinations performed for evaluating the health of periodontium included:

a) Plaque index: using proximal plaque index according to Lange for evaluating the proximal surfaces that covered by plaque.[12]
b) Gingival inflammation: After mild probing into the depth of pocket, the percent of bleeding sites calculated (Mohlemann & Saxer).

c) Clinical probing depth: the distance between gingival level and depth of pocket in four different sites of each tooth: mesiobuccal, buccal, distobuccal, and lingual evaluated by Williams periodontal probe.

*Laboratory examinations*

Evaluating the systemic conditions of all patients was performed by using following measurements in a specialized laboratory: $HbA_1c$ by chromatography; fast blood sugar (FBS), triglyceride (TG), total cholesterol (TC), and C-reactive protein (CRP).

*Procedure*

Periodontal treatment included two phases. In the first stage, patient motivation, oral hygiene instruction, supragingival scaling, temporary restorations, removing improper restorations, extraction of infectious and hopeless teeth, and splinting of mobile teeth were accomplished.

Phase 2 therapy was performed as non-surgical periodontal therapy, including subgingival scaling and root planning by hand instruments and ultrasonic device.

The subjects were randomly divided into two groups. The first group (control) received only the scaling and the second one (case) received systemic doxycycline (100 mg daily for 10 days). All doxycycline capsules were provided by the clinical researcher to prevent the bias that may be caused by using different products in the market.

Administration of antibiotic in patients who showed side effects like reflux, burning sensation, or sensitivity to tetracycline group was discontinued and they were excluded from the trial.

Oral hygiene instructions were repeated one month after initial therapy. Follow-up periods included one short-term evaluation at 3 months and another visit after 6 months. Since most clinical changes in periodontal pockets with the depth of 4–7 mm occur during the first 4–5 months after non-surgical therapy,[24,25] the final evaluation was established at 6 months. All clinical and laboratory measurements were repeated 3 and 6 months after baseline. Patients who missed these reevaluation visits were excluded from the study.

*Statistical analysis*

All statistical analyses were carried out with the SPSS 11.5 computer software for Windows. The changes during follow-up visits in each group were analyzed by Wilcoxon test, and the differences between case and control groups were evaluated with Mann-Whitney U test. A 5% significance level ($P < 0.05$) was chosen.

## *Results*

Interestingly, all of 30 subjects who completed the trial were females. The average age of patients was 52 years old and all of them received the periodontal and systemic antibiotic therapy without any significant complication.

Data and findings of the study are summarized in Table 1. There were differences in initial probing depth (PD) and $HbA_1c$ level at baseline. However, this difference was not statistically significant. To evaluate the clinical criteria of treatment outcomes in more detail, two different analyses were performed for all periodontal pockets and initial moderate to deep ones ($PD \geq 4$ mm). PD decrease from baseline to 3-and 6-month evaluations were significant in both groups. However, the most significant differences were observed between baseline and 3-month follow-up ($P = 0.001$ in case and $P = 0.000$ in control group). The same findings could be seen in initial $PD \geq 4$ mm, except for that the differences between 3-and 6-month evaluation was not significant ($P = 0.099$).

Bleeding on probing (BOP), as the most important criteria for determining soft tissue inflammation, decreased from 88% (control group) and 94% (case subjects) to below 40% at 6-month follow-up. Similar to PD reduction, this decrease in BOP was significant in all comparison with the exception of between 3-and 6-month periods ($P = 0.69$). BOP in the final visit was 37% and 38%, for control and case subjects respectively.

The reduction of $HbA_1c$ level occurred through all visits. However, only the difference between baseline and reevaluation in case group was significant ($P = 0.004$). The 0.53 reduction in $HbA_1c$ obtained in control subjects was not significant ($P = 0.47$).

Fasting blood sugar (FBS) measurements showed a reduction of 34 mg/cc in case and 20 mg/cc in control subjects, which were not statistically significant ($P = 0.059$ and $P = 0.77$, respectively).

Repeated oral hygiene instructions, presentation of brushing methods, and application of 0.2% chlorhexidine mouthwash were not effective in putting the plaque index below the ideal 20% level.

## *Discussion*

For the past two decades, the periodontal disease has not only considered an intra-oral infectious disease, but it is looked as a chronic anaerobic infection which can lead to systemic conditions.[9] In addition, there are several reports showing the higher prevalence and severity of this disease in diabetics. It seems that progression of periodontitis would be more severe in patients with

**Table 1. Comparison of the clinical and laboratory measurements in case and control groups**

| | Case subjects (SRP + doxycycline) | | Control subjects (SRP only) | |
|---|---|---|---|---|
| **Variables** | **Measurement** | **Differences (P-value)** | **Measurement** | **Differences (P-value)** |
| **Clinical probing depth** | $PD_0$: 4.14 ± 0.86 mm | $PD_0$–$PD_3$: 0.001 | $PD_0$: 3.34 ± 0.40 mm | $PD_0$–$PD_3$: 0.000 |
| | $PD_3$: 2.84 ± 0.38 mm | | $PD_3$: 2.43 ± 0.40 mm | $PD_3$–$PD_6$: 0.02 |
| | $PD_6$: 2.42 ± 0.60 mm | $PD_0$–$PD_6$: 0.002 | $PD_6$: 2.26 ± 0.38 mm | $PD_0$–$PD_6$: 0.002 |
| **Clinical probing depth** | | | | |
| | $PD_0 \geq 4$ mm: 5.05 ± 0.54 mm | $PD_0$–$PD_3$: 0.001 | $PD_0 \geq 4$ mm: 4.62 ± 0.35 mm | $PD_0$–$PD_3$: 0.000 |
| | $PD_3 \geq 4$ mm: 3.16 ± 0.43 mm | | $PD_3 \geq 4$ mm: 2.99 ± 0.65 mm | $PD_3$–$PD_6$: 0.005 |
| | $PD_6 \geq 4$ mm: 2.87 ± 0.50 mm | $PD_0$–$PD_6$: 0.002 | $PD_6 \geq 4$ mm: 2.92 ± 0.62 mm | $PD_0$–$PD_6$: 0.002 |
| **Bleeding on probing** | | | | |
| | $BOP_0$: 94 ± 9.5% | $BOP_0$–$BOP_3$: 0.001 | $BOP_0$: 88 ± 10% | $BOP_0$–$BOP_3$: 0.000 |
| | $BOP_3$: 52 ± 15% | $BOP_3$–$BOP_6$: 0.02 | $BOP_3$: 44 ± 11% | |
| | $BOP_6$: 38 ± 76% | $BOP_0$–$BOP_6$: 0.002 | $BOP_6$: 39 ± 23% | $BOP_0$–$BOP_6$: 0.002 |
| **Glycosylated hemoglobin** | | | | |
| | $HbA_1c_0$: 9.15 ± 0.76% | $HbA_1c_0$–$HbA_1c_3$: 0.004 | $HbA_1c_0$: 8.41 ± 0.49% | |
| | $HbA_1c_3$: 8.10 ± 1.15% | | $HbA_1c_3$: 8.25 ± 1.43% | |
| | $HbA_1c_6$: 7.73 ± 1.41% | $HbA_1c_0$–$HbA_1c_6$: 0.01 | $HbA_1c_6$: 7.88 ± 1.77% | |
| **Fasting blood sugar** | | | | |
| | $FBS_0$:203 ± 41 mg/cc | | $FBS_0$: 206 ± 97 mg/cc | |
| | $FBS_3$:180 ± 46 mg/cc | | $FBS_3$: 186 ± 59 mg/cc | |
| | $FBS_6$:169 ± 71 mg/cc | | $FBS_6$: 186 ± 79 mg/cc | |
| **Triglyceride** | | | | |
| | $TG_0$: 371 ± 294 mg/dl | | $TG_0$: 194 ± 104 mg/dl | $TG_0$–$TG_3$: 0.008 |
| | $TG_3$: 289 ± 109 mg/dl | | $TG_3$: 130 ± 48 mg/dl | |
| | $TG_6$: 195 ± 45 mg/dl | | $TG_6$: 120 ± 39 mg/dl | $TG_0$–$TG_6$: 0.02 |
| **Total cholesterol** | | | | |
| | $TC_0$: 204 ± 56 mg/dl | | $TC_0$: 211 ± 35 mg/dl | $TC_0$–$TC_3$: 0.002 |
| | $TC_3$: 171 ± 24 mg/dl | | $TC_3$: 185 ± 42 mg/dl | |
| | $TC_6$: 177 ± 20 mg/dl | | $TC_6$: 180 ± 41 mg/dl | $TC_0$–$TC_6$: 0.005 |

$_0$: Initial measurement; $_3$: 3-month evaluation; $_6$: 6-month reevaluation; PD: clinical probing depth; BOP: bleeding on probing; $HbA_1c$: glycosylated hemoglobin; FBS: fasting blood sugar; TG: triglyceride; TC: total cholesterol.

poor glycemic control.[26,27] A recent epidemiological study revealed there are important requirements for periodontal therapy in diabetics.[28]

Existence of a two-way relationship between periodontitis and diabetes is accepted generally. The possible effect of treatment of oral cavity infections on the improvement of glycemic control level was considered for a long time. Khader et al[30] evaluated more than twenty cross-sectional and longitudinal studies and concluded that the plaque index, gingival index, clinical probing depth, and clinical attachment level would be worse in diabetics than normal population; however, the severity and extension of periodontal diseases were the same in both groups. An animal study demonstrated experimental periodontitis in rats could increase the glucose level in serum of subjects with uncontrolled diabetes.[33] Several clinical trials evaluated the effect of periodontal therapy on improving glycemic control. Some of them showed useful effects, but the others could not find any effectiveness.[15,28]

For better outcomes, some researchers used antibiotic therapy as adjunctive procedure for scaling.[29] Rodriguez et al[31] used amoxicillin aleuronic acid adjunct to scaling for 30 diabetic patients and the results showed PD reduction was significant in both control (scaling) and case groups (scaling + antibiotic), and decrease of $HbA_1c$ level occurred from 8.8 ± 1.8% to 7.6 ± 1.4% in scaling group. They hypothesized non-significant difference of two modalities was a result of bacterial resistance to the antibiotic used. Higher reduction in $HbA_1c$ level was seen in patients with a higher initial level.[31] The design of the present study allowed patients with initial $HbA_1c$ level of more than 7%. Therefore, it was not surprising to see significant changes in $HbA_1c$ level of diabetic subjects during the follow-up period (Table 1).

Ryan et al[32] reported the decrease of $HbA_1c$ level and collagen destruction rate after administration of doxycxcline or other tetracycline derivatives. They suggested these effects may be a result of preventing localization of extra-cellular proteins rather than anti-collagenase process. Other published data have also demonstrated the effect of local tetracycline derivatives (minocycline) on clinical measurements due to decreased tissue healing time and improved capability of tissue regeneration.[40,41]

Lames et al[37] compared the effect of scaling (control) and adjunctive doxycycline (case) on clinical measurements and found the probing depth in sites with initial PD ≥ 4 mm decreased 65 ± 35% and 88 ± 22% in control and case subjects, respectively (P = 0.03). Average probing depth in their study ranged form 3.35 to 2.70 mm (scaling only) and from 3.43 to 2.69 mm in case group. In the present study, PD in control and case subjects showed a significant reduction of 1.08 and 1.62 mm, respectively, a finding which is in line with

the results of the latter study.

Grossi et al[17] reported the most reduction of probing depth in doxycycline group. In three experimental groups that used doxycyline, there was a significant reduction of $HbA_1c$ level (average: 10%), although the reduction was not significant after 3-month reevaluation. Similar results were found in the present study, as the reduction in $HbA_1c$ level in case and control groups were 1.42 and 0.53%, respectively, and the most changes occurred during the first three months (1.05%). The antibacterial effect of doxycycline can be responsible for this kind of 'systemic effect' by decreasing the number of periopathogenes such as *P. gingivalis*. Less noticeable changes after the first 3-month also can be explained by reduction of this antimicrobial effect.[17] We did not find any significant reduction in TG, TC and FBS levels in any groups, which is in agreement with previous studies.[43,49]

The systemic effect of periodontal therapy, however, has been rejected by a number of studies. Clinical efficacy of non-surgical and periodontal flap surgery in periodontal health has been shown in a study on 10 subjects (without controls) with no significant improvements on $HbA_1c$ level.[38] Others have hypothesized the improvements in glycemic control may be due to special oral hygiene instructions, and changes in diet regimen, and not merely from periodontal therapy. A 4-month follow-up clinical experimental study found scaling adjunct 2 weeks doxycycline would decrease $HbA_1c$ level more than 0.5% in 55% and 1.0% in 41% of subjects.[42] However, rather similar reductions (34% and 52%) could be seen in the control group without any significant differences ($P = 0.31$ and $P = 0.38$, respectively). The present study, on the contrary, demonstrated continuous reduction of $HbA_1c$ in all evaluation periods and both case and control groups. However, these changes were only significant in case subjects between baselines and 3-and 6-month reevaluation. The systemic effects of periodontal therapy can be explained by proven benefits in an ultra-structural level, such as: (a)reduction of a pro-inflammatory cytokine (IL-17) which is produced by T-helper cells;[35] (b) significant reduction of systemic IL-1β and prostaglandin E2 (PGE2) reported after simple therapy (scaling and sub-gingival irrigation by water);[36] and (c) 47% and 78% reduction of blood monocyte and macrophages, respectively, responsible for secretion of tumor necrosis factor (TNF), as reported by Lalla et al[20] after subgingival debridement in diabetic patients with moderate to severe periodontitis. The level of C-reactive protein (CRP) and soluble inflammatory receptors (E-selectin) also decreased to 37% and 16.6%, respectively.

Scaling adjunct doxycycline can be more efficient in decreasing the sites with bleeding on probing compared to scaling alone ($P = 0.03$).[37] In the present study, significant reduction in sites with BOP during the first 3 months was observed. However, in final reevaluation, the percentage of sites with BOP was still 37% in the control and 38% in the case group. This can be mainly explained by less than optimal plaque control. The clinical observer gave oral hygiene instructions and performed prophylaxis in every visit. Unfortunately, the 3-month interval between visits prevented us from maintaining the plaque index below 20%.

One study evaluated the effects of scaling and doxycycline on diabetics over 55 years old and did not find any significant improvements in FBS and $HbA_1c$ level.[43] Therefore, further studies with large-size aged samples are recommended. Considering limitations such as the lack of placebo in control subjects and restricted sample size in the present study, we recommend non-surgical debridement and doxycycline as a standard protocol in diabetics with initial $HbA_1c \geq 7\%$. A review of recent published clinical and laboratory data following periodontal therapy in diabetic patients are summarized in Table 2.

### *Conclusions*

1. Non-surgical periodontal treatment can be effective on periodontal health indicators such as pocket depth.
2. Adjunctive doxycycline therapy can be used successfully in uncontrolled diabetic patients for controlling glycemic control. The significant reduction was seen in $HbA_1c$ level rather than FBS.

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**Table 2. Summary of clinical trials on systemic effects of non-surgical periodontal therapy in diabetic patients**

| Study | Type of Diabetes | Number of subjects | Follow-up Period | Interventional procedure | Results |
|---|---|---|---|---|---|
| Miller et al[13] (1992) | 1 | 9 | 4-8 weeks | Non-surgical debridement Doxycycline | $HbA_1c$ decreased from 9.44 ± 1.69% to 9.01 ± 2.1% PD reduction; average: 1 mm |
| Sppala & Ainamo[46] (1994) | 1 | 60 | 1-2 years | Non-surgical debridement osteosurgery | $HbA_1c$ reduction: Not significant |
| Aldridge et al[21] (1995) | 1 | 31 | 2 months | Non-surgical debridement | More significant reduction of gingival health in case group. $HbA_1c$ decrease: 9.4→9.1% in case and 10.1→10.1% in control group |
| Aldridge et al[21] (1995) | 1 | 22 (with periodontitis) | 6 weeks | Non-surgical debridement | $HbA_1c$ level change: 9.8→10.4% in case and 9.7→9.5 in control group |
| Westfelt et al[16] (1996) | 1,2 | 40 | 5 Years | — | Improvements in gingival heath not significant different in $HbA_1c$ level |
| Smith et al [14] (1996) | 1 | 36 | 2 months | Non-surgical debridement | Improvements in gingival heath. Non-significant reduction in $HbA_1c$ level |
| Grossi et al[15] (1997) | 2 | 113 | 3,6,12 months | Non-surgical debridement Chlorhexidine or doxycycline | $HbA_1c$ decrease (10.5 → 9.56%, 10.4 → 9.89%, 10.3 → 9.79%, 10.7 → 10.5%, and 9.2 → 8.9% in different groups) |
| Christgau et al[17] (1998) | 1,2 | 40 | 2 weeks, 4 months | Non-surgical debridement Chlorhexidine | Improvements in gingival heath not significant change in $HbA_1c$ level |
| Stewart et al[1] (2001) | 2 | 72 | 9 months | Non-surgical debridement Extraction of hopeless teeth | $HbA_1c$ decreased from: 9.2±2.2% → 7.6±1.4% in case and 8.5±2.1% → 7.7±1.4% in control subjects |
| Iwamoto et al[47] (2001) | 2 | 13 | 8 weeks | Debridement every week local minocyline | Reduction in insulin and TNF levels decrease of $HbA_1c$ level from 7.96±1.98% to 7.12±1.48% |
| Rodrigues et al[31] (2003) | 2 | 30 (Nonsmokers) | 3 months | Oral hygiene + Scaling + Amoxicillin | Significant reduction of PD. Not significant reduction of CAL and FBS levels $HbA_1c$ decreased from 9.5 → 9.2% and 8.8 → 7.6% in different groups |
| Promsudthi et al[43] (2005) | 2 | 52 | 3 months | Scaling + doxycycline | Average PD reduction: 0.94 mm. Non-significant reduction of FBS and $HbA_1c$ levels |
| Kiran et al[48] (2005) | 2 | 44 | 1 and 3 months | Scaling | In case group: Significant reduction of PD and BOP% $HbA_1c$ decreased from 7.3± 0.7% to 6.51±0.8% FBS decrease from 132±31 to 128±29 mg/cc |
| Navarro-Sanchez et al[49] (2007) | 2 | 20 | 3 and 6 months | Scaling | Non-significant changes of cholesterol and triglyceride levels, reduction of GCF volume / IL1β and TNFα levels $HbA_1c$ decreased from 7.2±1.3 to 5.9±0.6% |
| Correa et al[50] (2008) | 2 | 23 | 3 months | Non-surgical debridement | Improvements in clinical measurements significant reduction of IL1β, elates activity, MMP-8, MMP-9 levels Non-significant reduction of $HbA_1c$ level |
| Concalves et al[51] (2008) | 2 | 20 | 3 months | Non-surgical debridement | Significant improvement of enzymatic parameter in GCF and saliva |
| Madden et al[52] (2008) | 2 | 42 | 6 months | Scaling + chlorhexidine | Improvement in PD. No Change of CAL. 1.10 to 1.38 reduction in $HbA_1c$ level |
| da cruz et al[52] (2008) | 2 | 10 | 3 months | Scaling | Significant improvements in clinical variables. Non-significant changes in bacterial frequency, FBS, and $HbA_1c$ levels. |
| O Connell et al[53] (2008) | 2 | 30 | 3 months | Scaling + chlorhexidine | Average PD reduction: 1.1 mm. 1.5% reduction in $HbA_1c$ level. Significant reductions in IL-6, Interferon-inducible protein 10, soluble fat ligand, and granulocyte colony-stimulating factor |
| Present study (2009) | 2 | 30 | 3 and 6 months | Scaling or Scaling + chlorhexidine | PD decreased from 4.14 → 2.42 mm $HbA_1c$ decreased from 9.15% → 7.73% in doxycycline group Non-significant reduction of FBS, TG, and TC. |

PD: probing depth; CAL: clinical attachment level; FBs: fasting blood sugar; $HbA_1c$: glycolated hemoglobin; TC: total cholesterol; TG: triglyceride; IL: interleukin; TNF: tumor necrosis factor; MMP: matrix metalloproteinase; GCF: gingival crevicular fluid.

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