# Evaluation of adjunctive systemic doxycycline with non-surgical periodontal therapy within type 2 diabetic patients

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## ABSTRACT

**الأهداف:** تقييم آثار مادة الدوكسيسايكلين على المعاملات السريرية والميكروبولوجية لمرضى السكر مع التهاب اللثة المزمن.

**الطريقة:** تم عمل دراسة لمدة 9 أشهر متعددة المراكز، عشوائية، متماثلة خلال الفترة من أبريل 2010م وحتى ديسمبر 2010م، بإجمالي أفراد عينة 76 مريض سكري مع التهاب اللثة المزمن تم تقسيمهم بشكل عشوائي إلي مجموعتين: المجموعة الضابطة (CG) الذين تلقوا تخطيط جذري وتجميعي فقط (SRP) ومجموعة العلاج (TG) اللذين تلقوا مادة دوكسيسايكلين بشكل نظامي خلال عملية إعادة التقييم بعد 45 يوم من الزيارات و استكمال SRP. تم جمع PPD، المستوي الإكلينيكي المرفق (CAL)، مؤثر اللثة (GI)، مؤشر بروش الأسنان (PI) والنزف والجس (BOP) وذلك بعد مرور 45 على SRP و1، 3 و6 أشهر بعد استخدام مادة الدوكسيسايكلين النظامية. لقد كشف التحليل الإكلينيكي عن وجود (*Tf*) *Tannerella forsythia* *Aggregatibacter actinomycetemcomitans*(*Aa*). *Porphyromonas gingivalis*, *Prevotella intermedia (Pi)* بطريقة رد فعل سلسلة البلمرة.

**النتائج:** 68 (33 من المجموعة الضابطة و35 من مجموعة العلاج) خضعوا للدراسة بالكامل. لوحظ انخفاض أكبر في نسبة *Tf*، *Pg* و*Pi* لمجموعة العلاج بالمقارنة مع المجموعة الضابطة في الشهر الأول بعد استخدام مادة الدوكسيساسيكلين النظامية. أظهرت مجموعة العلاج تحسن كبير في درجات GI بالمقارنة مع المجموعة الضابطة ($p<0.05$) بنهاية الشهرين الأول والسادس بعد استخدام الدوكسيسايكلين.

**الخاتمة:** الاستخدام المباشر لمادة الدوكسيسايكلين يمكن أن يرتبط بانخفاض *Tf*، *Pg* و*Pi* في الشهر الأول بعد استخدام الدوكسيسايكلين مع تحسن في الـ GI.

**Objectives:** To evaluate the effects of systemic doxycycline on clinical and microbiological parameters of diabetic subjects with chronic periodontitis.

**Methods:** This 9-month multi-center, randomized, parallel, single-blinded study was conducted from different hospitals in Riyadh, Saudi Arabia between April 2010 and December 2010. A total of 76 diabetic subjects with chronic periodontitis were randomized into 2 groups: control group (CG) received only scaling and root planing (SRP), and the treatment group (TG) receiving systemic doxycycline during the reevaluation visit 45 days after the completion of SRP. Probing pocket depth, clinical attachment level, gingival index, plaque index, and bleeding on probing were collected at baseline, 45 days after SRP, and one, 3, and 6 months after the use of systemic doxycycline. Microbiological analysis comprised the detection of *Tannerella forsythia* (*Tf*), *Aggregatibacter actinomycetemcomitans* (*Aa*), *Porphyromonas gingivalis* (*Pg*), and *Prevotella intermedia* (*Pi*) by polymerase chain reaction method.

**Results:** Sixty-eight (33 CG and 35 TG) subjects completed the study. Greater reduction in the population of *Tf*, *Pg*, and *Pi* were observed in TG compared with CG in the first month after the administration of systemic doxycycline. The TG showed a significant improvement in gingival index scores compared with the CG ($p<0.05$) by the end of the first and 6 months after the administration of doxycycline.

**Conclusion:** Adjunct systemic doxycycline can be associated with a reduction of *Tf*, *Pg*, and *Pi* in the first month after the administration of doxycycline with an improvement in the GI.

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The relationship between periodontal diseases (PD) and diabetes are bidirectional,[1] which provides an example of systemic disease predisposing to oral infection, established infection, and exacerbating the systemic disease.[2] Diabetic patients are known to be susceptible to infectious diseases.[3] The influence of diabetes on the onset and development of PD has been widely studied.[4,5] The PD is now considered the sixth complication of diabetes mellitus.[6,7] Diabetes in itself does not cause PD, but it makes the patients more susceptible to periodontal destruction. Diabetics exhibit greater severity and a faster rate of PD progression.[8,9] Treating chronic periodontitis in diabetic patients poses numerous challenges, especially with regards to the control of oral microorganisms. Treatment of PD is directed to the elimination of sub-gingival bacterial infections. More than 700 different bacterial species are found in the sub-gingival environment.[10] Several studies have reported that the bacteria involved in periodontitis are usually anaerobic Gram-negative bacteria.[11] *Aggregatibacter actinomycetemcomitans* (*Aa*), *Tannerella forsythia* (*Tf*), and *Porphyromonas gingivalis* (*Pg*) were directly implicated in the destruction of periodontal tissues, and the presence of any of these pathogens is considered a risk factor for future periodontal destruction.[12] Direct and indirect damage to periodontal supporting tissues are well-documented pathogenic effects of Gram-negative bacteria due to their toxic products and the activation of a series of inflammatory reactions.[13] Mechanical means using non-surgical and surgical techniques is the primary approach employed in the treatment of PD. Subgingival scaling and root planning (SRP) is an effective method to slow or arrest the progression of PD.[14,15] Even after meticulous SRP, some patients may still experience continuous loss of attachment due to the inability of the therapy to suppress periodontal pathogens to the optimal levels.[16] The *Aa* and *Pg,* is likely to evade SRP, especially in the subgingival niche, due to limited access to the root surface and the tissue-invading skills of the bacteria.[17] The efficacy of SRP may also be compromised by the remaining bacterial virulence factors and ineffective personal plaque control.[18] Thus, various pharmacological agents were used as adjunctive therapy to improve the treatment outcome of non-surgical periodontal therapy.[19] Adjunctive antimicrobials can be used for local or systemic delivery. The benefits of using various adjunctive antibiotics such as penicillin, tetracycline, amoxicillin, and metronidazole along with SRP have been reported to improve periodontal health.[20-22] Studies that evaluated the antimicrobial effect of systemic doxycycline on the periodontal tissues of diabetic patients are scarce. This study aims to investigate the effect of SRP in conjunction with the administration of an antimicrobial dose of systemic doxycycline on the clinical and microbiological parameters in diabetic patients with chronic periodontitis.

**Methods.** This 9-month multi-center, randomized, parallel, single-blinded study was conducted between April 2010 and December 2010 at King Faisal Specialist Hospital & Research Center, King Abdulaziz Medical City, Naval Base Hospital, and Sultan Bin Abdulaziz Humanitarian City, Riyadh, Saudi Arabia. A total of 76 diabetic subjects with chronic periodontitis were included in this study. This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000, and the protocol of this study was approved by the research ethics committee of Sultan Bin Abdulaziz Humanitarian City, Riyadh, Saudi Arabia. Informed written consent was acquired from each subject that agreed to participate voluntarily.

***Study population.*** Diabetic subjects with moderate to severe chronic periodontitis were recruited into this study following a screening examination, including full mouth probing and radiographic evaluation. The inclusion criteria were as follows: age between 21 and 80 years, type 2 diabetes, diabetes diagnosed for ≥1 year, good physical condition with no additional serious medical conditions, the presence of at least 16 teeth, and a minimum of 8 sites with pocket depth of >5mm and clinical attachment level >5mm.

Subjects were excluded if they: 1) were using any contradicted medications, 2) smoked within the past 5 years, 3) presented with compromised medical condition, 4) had been treated with SRP within 6 months of the baseline visit, 5) used antibiotics within 3 months prior to the study or 6) pregnant or breast feeding. Subjects who failed to appear at any time after the baseline visit or failed to attend the last visit (6 months) were also excluded from the study.

The study included 76 diabetic patients with chronic periodontitis who were randomized by a computer-generated system into 2 groups. Of these, 38 subjects were assigned to the control group (CG), for whom only SRP would be provided. Three subjects from this group discontinued the study, and 2 were excluded due to lack of compliance with the medication use and visits. Three out of the 38 subjects assigned to the treatment group (TG) were excluded due to lack of compliance.

***Microbiological sampling. Bacterial examination for pathogenic anaerobes:*** *Tannerella forsythia, Aa, Pg,* and *Prevotellaintermedia* (*Pi*) was performed by using the polymerase chain reaction (PCR) method. For

each patient, 4 sites with pocket depths of ≥5 mm were randomly selected. The supragingival plaque was removed for the selected teeth, and the Florida probes were wiped with 70% isopropyl alcohol between measurements to reduce bacterial cross-contamination of the sites.[23] After the clinical measurements were recorded, a subgingival plaque sample was taken from each site with separate sterile curettes. Each sample was instantly placed in a sterile micro centrifuge tube containing 0.5 ml Trisethylenediaminetetraacetic acid (EDTA [TE]) buffer (10 mM Tris hydrogen chloride [HCl] [pH 7.6], and 1 mM EDTA [pH 8.0]). For PCR analysis, 90 ml of vortex-mixed subgingival plaque was added to 10 µl of 10 x lysis buffer (100 mM Tris-HCl, pH 8.0, 10 mM EDTA, 10% Triton X-100), and boiled for 5 min, and 5 µl of this lysate was used in each PCR reaction. The species specific primers used for the PCR analyses are shown in **Table 1**. The PCR amplification was carried out in a reaction volume of 25 µl consisting of 5 µl sample lysate, 20 µl reaction mixture containing 1 x PCR buffer (10 mM Tris-HCl, pH 8.8, 1.5 mM magnesium chloride, 50 mM potassium chloride, 0.1% Triton X-100), 2 units of Taq DNA polymerase (Amersham Pharmacia Biotech Inc, Piscataway, NJ, USA), 0.2 mM deoxynucleotide triphosphates, and 100 pmol of each primer. The PCR cycling was carried out in a DNA thermal cycler PE 480 (PerkinElmer, Covina, California, USA). The cycling conditions for *Tf, Aa,* and *Pg* consisted of an initial denaturation for 5 min at 95°C, 35 amplification cycles of denaturation at 95°C for one minute, annealing of primers at 55°C (*Aa*) or at 60°C (*Tf*) or 70°C (*Pi* & *Pg*) for one minute, and primer extension at 72°C for one to 2 minutes, followed by a final extension step at 72°C for 2-10 minutes. The cycling conditions for *Pi* were the same as those for *Tf, Aa*, and *Pg*, except if the annealing temperature was 58°C. The reaction products were examined immediately after completion of the PCR. Ten microliters of each reaction product was fractionated in a 1.5% agarose gel containing ethidium bromide (0.5 mg/ml) with 50 or 100 bp DNA ladder (Amersham Pharmacia Biotech Inc, Piscataway, NJ, USA) as a size marker, and visualized and photographed using a gel documentation and analysis system (Ultra-Violet Products Ltd, Cambridge, England). Samples from the same sites were collected for bacterial analysis at baseline, reevaluation visit (fourthy-fifth day after SRP), and at one, 3, and 6 months after treatment with systemic doxycycline.

***Clinical procedures.*** During the study, clinical dental examinations for all subjects were carried out in 4 study centers by 4 trained and pre-calibrated examiners (periodontists) who were supported by trained dental assistants. Probing depth (PD), clinical attachment level (CAL), plaque index (PI), gingival index (GI), and bleeding on probing (BOP) were measured on all existing teeth at the mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, and disto-lingual areas[24] with manual periodontal probes (Florida Probe Corporation, Gainesville, FL, USA). The CAL was calculated by adding PD with the distance between cemento-enamel junction and gingival margin.

After baseline data collection, each subject received 6-8 sessions of scaling and root planing with ultrasonic and hand instrumentation until the root surface felt smooth with the tip of a metallic probe. Four trained dental hygienists at 4 centers performed the SRP. The dental hygiene aids were provided for the subjects. Written oral hygiene guidelines were given to all subjects within the different treatment groups at each session, including proper tooth brushing technique. After 45 days of completion of SRP, the patients were recalled for the reevaluation visit and the clinical measurements and sub-gingival plaque samples were taken. At this time, all individuals underwent sub-gingival debridement with an ultrasonic device to disturb the sub-gingival bio-film and allow better action of the drug. Randomization of the subjects into treatment and control groups was performed by using computer-generated random codes. Subjects belonging to the treatment group received an antimicrobial dose of systemic doxycycline, 100 mg per day for 14 days with a loading dose of 200 mg on

**Table 1 -** Primers for polymerase chain reaction-based identification of periodontopathogens.

| Species | Primer pairs |
|---|---|
| *Tannerella forsythia* | GCG TAT GTA ACC TGC CCG CA<br>TGC TTC AGT GTC AGT TAT ACCT |
| *Aggregatibacter actinomycetemcomitans* | AGA GTT TGA TCC TGG CTG AG<br>CAC TTA AAG GTC CGC CTA CGT GCC |
| *Porphyromonas gingivalis* | TGT AGA TGA CTG ATG GTG AAA ACC<br>ACG TCA TCC CCA CCT TCC TC |
| *Prevotella intermedia* | TTT GTT GGG GAG TAA AGC GGG<br>TCA ACA TCT CTG TAT CCT GCG T |

the first day. The control group received no treatment other than oral hygiene during the study. They were instructed to brush and floss 2 times a day. Clinical measurements were taken at each of the subsequent visits at the first, third, and sixth months. After obtaining the measurements and samples from the subjects, they were provided with professional supragingival plaque control measures, and oral hygiene was reinforced. This was repeated in the following recall visits.

*Data analysis.* All statistical analyses were carried out using the Statistical Package for Social Sciences for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA). The presence or absence of *Tf, Pg, Pi,* and *Aa* were evaluated with McNemar's test, and the results are presented in terms of the percentage of sites with the microorganisms. The results of dental parameters (PPD, CAL, GI, PI, and BOP) were analyzed using the 2-way analysis of variance (ANOVA). A value of $p<0.05$ was considered statistically significant.

**Results.** Of the 76 subjects included in the study, 68 (33 CG and 35 TG) subjects completed the study. Most of the subjects (61.8%) were male, and the mean age of the participants was 42±6.41 years. On average, the subjects had 27 teeth in the oral cavity. The analysis of the periodontal parameters is shown in **Table 2**. There were significant ($p<0.05$) changes in PPD, PI, GI, and BOP for all the follow-up visits when compared with the baseline measurements. The PPD was reduced by 0.93 mm for the treatment and 0.88 mm for the control group in the reevaluation visit, which was statistically significant ($p<0.01$). The CAL for CG was reduced by 0.84 mm during the reevaluation visit and by 0.96 mm from the baseline measurements by the end of 6 months. For TG, CAL was reduced by 0.39 mm ($p=0.09$) in the reevaluation visit and by 0.74 mm by the end of 6 months. However, no significant difference was observed between CG and TG in the reevaluation visit or during any of the remaining follow-up visits. Gingival index was the only parameter that showed any significant difference between TG and CG after one, 3, and 6 months after the administration of systemic doxycycline (**Table 2**).

The results showing the effects of different treatments on *Tf* are described in **Figure 1A**. In the first month after administering doxycycline, a significantly higher decline in the percentage of sites harboring *Tf* was observed for TG compared with CG ($p=0.02$). However, a better reduction was observed in the CG as compared with the TG at the third-month visit, though this reduction was not statistically significant (**Table 3**).

The results showing the effect of systemic doxycycline on *Pg* and *Pi* are shown in **Figures 1B & 1C**. One month after the administration of doxycycline, both *Pg*, and *Pi* showed significant reduction in the percentage of site for TG compared with CG ($p<0.01$ and $p=0.04$). A minimal decline was observed in the following visits. There was no significant difference between CG and TG at different time points of the reduction in the percentage of sites with *Aa* (**Figure 1D**). The percentage reductions in the sites harboring the different species at each of the follow-up visits are shown in **Table 3**.

**Discussion.** Periodontal disease involves complex interactions between microbial factors, and a susceptible host.[25] One of the biological mechanisms reported is through the accumulation of glucose-mediated advanced glycation end products (AGEs), which leads to the impairment of the chemotactic and phagocytic functions of polymorphonuclear leukocytes. The bacterial products of the Gram-negative

**Table 2 -** Dental parameters of diabetic study subjects at baseline, re-evaluation, one, 3, and 6 months after administering systemic doxycycline.

| Variable | Group | Baseline mean±SEM | Re-ev mean±SEM | *P*-value baseline x re-ev | One month mean±SEM | P value Re-ev x one month | 3 months mean±SEM | *P*-value re-ev x 3 month | 6 months mean±SEM | *P*-value re-ev x 3 month |
|---|---|---|---|---|---|---|---|---|---|---|
| PPD (mm) | CG | 3.82±0.15 | 2.94±0.24 | <0.01* | 2.81±0.10 | 0.38 | 2.60±0.73 | 0.46 | 2.42±0.32 | 0.19 |
| | TG | 3.89±0.13 | 2.96±0.13 | <0.01* | 2.72±0.11 | 0.42 | 2.67±0.21 | 0.61 | 2.39±0.21 | 0.09 |
| CAL (mm) | CG | 5.31±0.21 | 4.47±0.27 | <0.01* | 4.45±0.21 | 0.88 | 4.43±0.16 | 0.87 | 4.35±0.25 | 0.64 |
| | TG | 4.92±0.17 | 4.53±0.28 | 0.09 | 4.49±0.25 | 0.64 | 4.44±0.17 | 0.90 | 4.18±0.19 | 0.17 |
| GI (mean) | CG | 2.08±0.11 | 1.54±0.15 | <0.01* | 1.48±0.15 | 0.28 | 1.36±0.29 | 0.56 | 1.29±0.23 | 0.22 |
| | TG | 2.12±0.11 | 1.97±0.14 | <0.01*,† | 1.57±0.10 | 0.03*,† | 1.46±0.11 | 0.04* | 1.36±0.21 | 0.02*,† |
| PI (mean) | CG | 2.18±0.12 | 1.61±0.11 | <0.01* | 1.58±0.11 | 0.76 | 1.47±0.21 | 0.12 | 1.33±0.21 | 0.26 |
| | TG | 2.14±0.16 | 1.68±0.18 | <0.01* | 1.56±0.12 | 0.21 | 1.42±0.13 | 0.27 | 1.39±0.12 | 0.31 |
| BOP (%) | CG | 63±5.8 | 29±12.2 | <0.01* | 26±8.7 | 0.66 | 24±9.3 | 0.71 | 23±6.6 | 0.82 |
| | TG | 66±6.9 | 31±8.4 | <0.01* | 26±11.3 | 0.59 | 27±9.5 | 0.83 | 19±5.3 | 0.15 |

CG - control group, TG - test group, PPD - probing pocket depth, CAL - clinical attachment level, GI - gingival index, PI - plaque index, BOP - bleeding on probing, Re-ev - re-evaluation. *Statistically significant difference between groups ($p<0.05$). †Statistically significant difference between CG and TG ($p<0.05$).

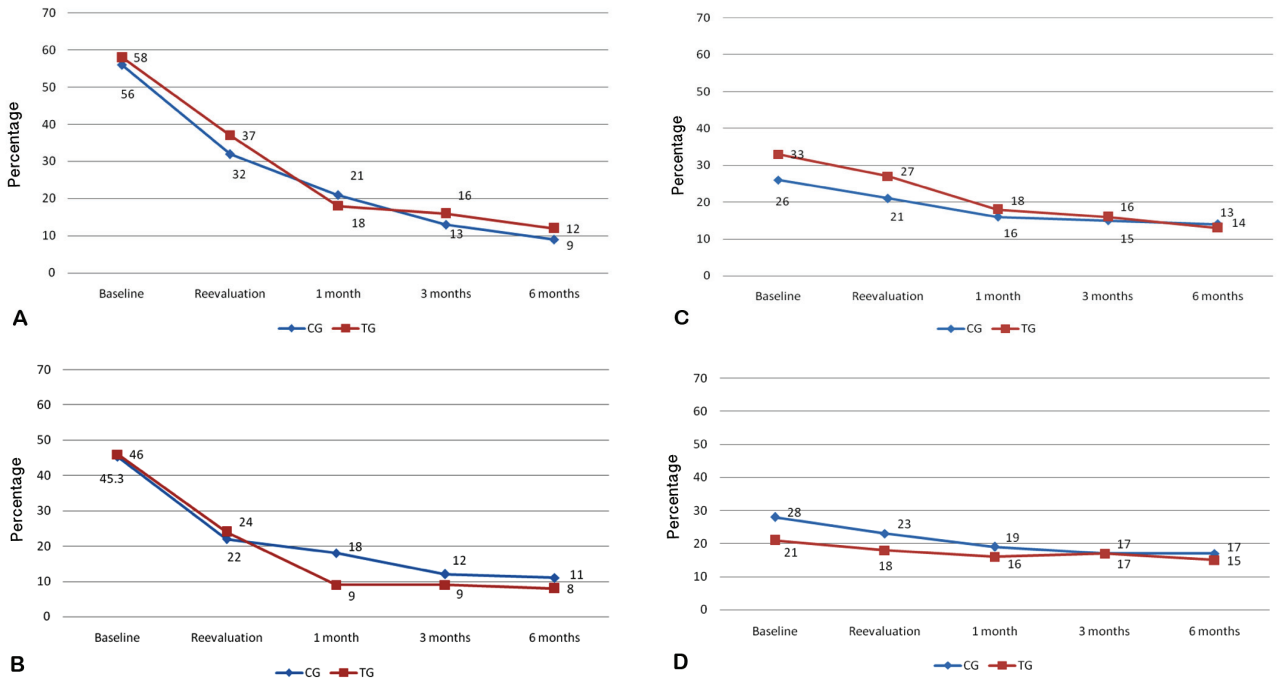


**Figure 1 -** Percentage of site harboring **A)** *Tannerella forsythia (Tf)*, **B)** *Porphyromonas gingivalis (Pg),* **C)** *Prevotella intermedia (Pi)*, and **D)** *Aggregatibacter actinomycetemcomitans (Aa)* as measured at the different time intervals among 76 diabetic patients with chronic periodontitis. CG - control group, TG - test group

**Table 3 -** Percentage reduction in sites harboring different species at each follow up visit compared to the values obtained in the previous visit among 76 diabetic patients with chronic periodontitis.

| Species | Period | CG | TG | *P*-value |
|---|---|---|---|---|
| *Tf* | Re-evaluation | 24 | 21 | 0.63 |
| | 1 month | 11 | 19 | 0.02* |
| | 3 month | 8 | 2 | 0.08 |
| | 6 month | 4 | 4 | 0.41 |
| *Pg* | Re-evaluation | 23.3 | 22 | 0.82 |
| | 1 month | 4 | 15 | 0.01* |
| | 3 month | 6 | 0 | 0.12 |
| | 6 month | 1 | 1 | 0.98 |
| *Pi* | Re-evaluation | 5 | 6 | 0.56 |
| | 1 month | 5 | 9 | 0.04* |
| | 3 month | 1 | 2 | 0.68 |
| | 6 month | 1 | 3 | 0.33 |
| *Aa* | Re-evaluation | 5 | 3 | 0.08 |
| | 1 month | 4 | 2 | 0.21 |
| | 3 month | 2 | -1 | 0.16 |
| | 6 month | 0 | 2 | 0.28 |

*Statistically significant difference between groups ($p<0.05$).
CG - control group, TG - test group, *Tf - Tannerella forsythia, Pg -Porphyromonas gingivalis, Aa - Aggregatibacter actinomycetemcomitans, Pi - Prevotella intermedia*

periodontopathic bacteria in periodontal pockets were found to increase the secretion of interleukin-1 beta (IL-1b), interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), and prostaglandin E2 (PGE2). The TNFα is a pro-inflammatory cytokine that has been implicated in insulin resistance. Adjunctive antimicrobial periodontal treatment has been reported to significantly reduce circulating TNFα and glycosylated hemoglobin (HbA1C) levels.[26,27] Also, doxycycline at lower doses has been reported to reduce the periodontal tissue destruction by inhibiting collagenase activity and synsthesis.[28] The reduction in HbA1c levels with the use of low dose doxycycline has been previously reported.[29] In this study, the clinical and microbial effect of an antimicrobial regimen of systemic doxycycline on the periodontal tissues of diabetic patients with chronic periodontitis was evaluated.

The occurrence of periodontal pathogens in subgingival flora in periodontitis is a risk for periodontal disease progression.[30,31] Therefore, microbiological diagnostic procedures are justifiably indicated in the detection of pathogens as well as in monitoring of therapeutic success and result of the disease. Specific bacterial species are now considered to be vital in the initiation and progression of periodontitis, and *Aa, Pg, Tf*, and *Pi*[30,32] are some of the more frequently encountered species. Doxycycline has been reported to substantially reduce or eliminate pathogenic species, especially Gram-negative bacilli.[33] Several studies[34] have reported that due to the tissue-invading nature of periodontal pathogens such as *Pg* and *Aa*, mechanical therapy alone may not be sufficient to eliminate these

pathogens. Hence, it may be useful to administer antibiotics that will help in eliminating these pathogens. In this study, the administration of systemic doxycycline was effective in the reduction of *Tf, Pi,* and *Pg*. The greatest reduction in the percentage of sites after the administration of doxycycline was observed for *Pg*. This finding is agreeing with results from a previous study performed on smokers.[12] *Porphyromonas gingivalis* induces a local chronic inflammatory response that results in oral inflammatory bone destruction, which manifests as periodontal disease.[35]

Eradication of *Aa* from deep periodontal pockets could be difficult. It is reported that the decrease in *Aa* is often not as great as that for other bacteria following SRP.[36] A study by Muller et al,[37] reported that *Aa* at subgingival and extra-crevicular sites are suppressed with the use of adjunct antimicrobial therapy. Similarly, in this study, the reduction of *Aa* was observed, although it was less than that observed with other pathogens. Additionally, in the case of *Aa* and *Tf*, there was a slight increase in the percentage of sites after 3 months. This is similar to the study by Colombo et al,[38] where the frequency of *Aa* increased after therapy, probably due to an absence of antibiotic protection. Compared with the baseline measurements, all the clinical parameters in both, the CG and TG had significantly improved at the reevaluation visit during the follow up visits. However, with exception to GI, no other clinical parameters showed a significant difference between the CG and TG. The GI significantly improved with the administration of adjunct systemic doxycycline. This could be due to the inhibitory effect of doxycycline that significantly reduces the periodontal tissue destruction by inhibiting collagenase activity and synthesis.[28] Many previous studies[28,39] administered adjunctive antimicrobial agent along with SRP. However, to understand the effectiveness of an antimicrobial drug, it should be introduced after SRP; however, only microorganisms that were resistant to SRP would be present.[40] Also, it is well known that the number and percentage of *Tf, Pg,* and *Pi* decrease with decreasing pocket depth with or without treatment.[41] Therefore, it would not be possible to state conclusively the role of the antibiotic in the reduction of the microbial population. Hence, during the reevaluation visit, doxycycline was administered 45 days after SRP.

***Study limitations.*** The major limitation of this study was the limited number of patients and limited number of bacteria examined. Further research is needed to support a causal relationship and its clinical implications.

In conclusion, the TG showed significant reduction of *Tf*, *Pg*, and *Pi* in the first month after the administration of systemic doxycycline. However, this did not improve the periodontal status of the subjects. There were minimal differences between CG and TG at the 3 and 6-month follow-up visits. Additional long-term studies with larger sample sizes are required to provide a more comprehensive picture of the effects of SRP and systemic doxycycline at clinical and microbial levels in diabetic patients with chronic periodontitis.

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