

Evaluation of Subantimicrobial Dose Doxycycline as an Adjunct to Scaling and Root Planing in Chronic Periodontitis Patients with Diabetes: A Randomized, Placebo-Controlled Clinical Trial

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Abstract

Aim: Diabetic patients have more severe periodontal destruction, but periodontal therapy can improve metabolic control. Recently, interest has focused on the use of subantimicrobial dose doxycycline (SDD) as a treatment paradigm. Therefore, this study was undertaken to evaluate clinical efficacy of SDD with scaling and root planning (SRP) in chronic periodontitis patients with diabetes.

Methods and Materials: Twenty chronic periodontitis patients with diabetes mellitus were randomly allocated to either a test and a control group. Clinical measurements were recorded at baseline and at six months for probing pocket depth (PPD), clinical attachment level (CAL), and gingival recession (GR). After SRP, patients in the test group were instructed to take SDD 20-mg capsules twice a day while patients in the control group took a placebo twice a day. Both groups were on this regimen for a six-month period.

Results: A greater reduction in mean PPD was demonstrated in patients in the test group compared to the control group. The mean CAL increase observed in the test group was significantly greater (0.67 mm) than that in the control group.

Conclusion: It can be concluded that SRP, in conjunction with the SDD therapy described, is more effective than SRP alone in terms of CAL



gain and PPD reduction in diabetic patients with severe periodontal disease.

Clinical Significance: Given the widespread prevalence of both chronic periodontitis and diabetes, the proposed treatment approach will prove to be of great value and contribute significantly to the overall health of the patients.

Keywords: Diabetes mellitus, periodontal disease, chronic periodontitis, subantimicrobial dose doxycycline, SDD, root planing

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Introduction

Diabetes mellitus is an extremely important endocrine disease from a periodontal standpoint. It is generally characterized by abnormal blood glucose level due to deficiencies in the insulin production or activity. Diabetes is now clearly established as a major risk factor for periodontitis. Clinical and epidemiological studies have shown that patients with a long history of diabetes seem to have more periodontal tissue destruction than nondiabetic controls.¹

The influence of diabetes over periodontal diseases is well established, but the effect of periodontal disease and its treatment on diabetes control is not so clear. Some authors have shown that nonsurgical periodontal therapy could improve metabolic control, especially when doxycycline was used as an adjunct.²⁻⁴ Doxycycline, a member of the tetracycline family of antibiotics, has been shown to reduce GCF collagenase level in patients with chronic periodontitis.⁵

Recently, interest has focused on the concept of host modulatory therapy as a treatment



paradigm in the management of periodontitis. Host modulation therapy aims to enhance traditional periodontal therapies by modifying destructive aspects of the immune inflammatory host response, so that periodontal breakdown is reduced and the periodontium is stabilized. One such host modulation therapy involves the use of subantimicrobial dose doxycycline (SDD 20 mg twice daily) as an adjunct to conventional nonsurgical periodontal therapy in the management of chronic periodontitis. This is the first FDA-approved host modulation agent to adjunctively treat periodontal disease. The mechanism of action is by suppression of the activity of collagenase, particularly that produced by polymorphonuclear leukocytes. Furthermore long-term use of SDD is not associated with the development of antibiotic resistance or detrimental shift in the normal periodontal microflora,⁶ as the dose is too low to affect bacteria. As a result, resistance to this medication cannot develop.

Long-term, placebo-controlled, double-blind clinical studies have demonstrated the clinical benefit of SDD when used as an adjunct to scaling and root planing (SRP) compared with SRP alone.^{7,8} These studies have reported improvement in clinical attachment level (CAL) and probing pocket depth (PPD) that were significantly greater compared with those observed in patients who received adjunctive placebo.

Previously, few studies have shown considerable improvements in periodontal health and improvement in glycemic control following SRP combined with systemic doxycycline for 14 days.^{2,3} Furthermore, few recent studies,^{9,10} also have demonstrated short-term improvements in glycemic control when SRP in combination with SDD was used in diabetics.

Therefore, the present study was undertaken to evaluate clinical efficacy of SDD as an adjuvant to SRP over a six-month period in chronic periodontitis patients with diabetes.

Methods and Materials

Twenty chronic periodontitis patients (8 male and 12 female, mean age 37.1 ± 3.96 years) with diabetes and no other major illness or severe diabetic complications were included in the study. After proper examination and diagnosis, initial



therapy was provided. Prior to initiation of the study, the purpose and design of this clinical trial were explained to each patient and an informed consent form was signed by every patient. This was a randomized, placebo-controlled, parallel-design clinical trial of six months' duration. The selected patients underwent scaling and root planing and then were randomly allocated to either a test or a control group. The test group received doxycycline hyclate 20 mg twice a day (b.i.d), while patients in the control group received a placebo capsule b.i.d. for the treatment period of six months. Clinical measurements were recorded at baseline and again at six months. Full-mouth supragingival plaque was assessed using a plaque index,¹¹ and gingival inflammation was recorded by the papillary bleeding index (PBI).¹² The probing measurements recorded were probing pocket depth (PPD), clinical attachment level (CAL), and gingival recession (GR). Probing pocket depths were recorded at six sites and CAL was measured at four sites around each experimental tooth. The means of all sites were taken into consideration for the assessment of results. All the probing measurements were made with a Williams graduated periodontal probe (Hu-Friedy, Chicago, Illinois, USA). These measurements were rounded to the nearest millimeter.

Treatment was provided at baseline following evaluation. Patients in both the test and control groups received full-mouth scaling and root planing (SRP), using manual (standard Gracey currettes) and powered instruments (EMS±mini Piezon) within 24 hours by the same examiner. Root surfaces were instrumented until they became free of deposits as determined by visual or tactile examination.

After completion of scaling and root planing, the test group received SDD 20 mg capsules twice a day for six months, while patients in the control group received indistinguishable placebo capsules taken in a similar manner.

Results

During the course of the study, wound healing was uneventful. No patient showed adverse reaction to SDD therapy. None of the selected patients dropped out before the termination of the study. In general, patients showed good oral hygiene throughout the study.

The baseline mean probing pocket depth (PPD) was 5.66 mm in the test group and 5.73 mm in the control group. Similarly, the baseline mean clinical attachment level (CAL) was 6.05 mm in the test group and 6.03 mm in the control group. The baseline mean gingival recession (REC) was 0.39 mm in the test group and 0.32 mm in the control groups. At baseline, no statistically significant differences in any of the investigated parameters were observed between the test and control groups, indicating that the randomization process was effective.

In the test group, the mean PPD at baseline was 5.66 mm and at six months it was 2.60 mm. In the control group, the mean PPD at baseline was 5.73 mm and at six months it was 3.19 mm. After six months the mean PPD reduction was 3.06 mm for the test group and 2.54 mm for the control group. Student's paired *t*-test indicated that both the test (SRP + SDD) and control (SRP + placebo) groups showed significantly greater mean PPD reduction at six months compared to baseline ($p < 0.05$).

When the differences in mean PPD reductions at six months for the test group (3.06 mm) versus the control group (2.54 mm) were analyzed by Student's unpaired *t*-test, a statistically significant difference was noted ($p < 0.05$). A greater reduction in mean PPD was demonstrated in the test (SRP + SDD) group compared to the control (SRP + placebo) group. An additional benefit of 0.52 mm PPD reduction was observed in the test group. The mean residual probing pocket depth at six months was 2.60 mm for the test group and 3.19 mm for the control group.

Table 1. Comparison of clinical parameters of test group (SRP+ SDD) at baseline and six months (mean ± SD).

Parameters	Baseline	Six Months	Difference	p Value
PPD (mm)	5.66 ± 0.50	2.60 ± 0.33	3.06 ± 0.30	0.000 S
CAL (mm)	6.05 ± 0.25	3.80 ± 0.23	2.25 ± 0.09	0.000 S
GR (mm)	0.39 ± 0.26	1.19 ± 0.20	0.80 ± 0.28	0.000 S

S—statistically significant ($p < 0.05$)

Table 2. Comparison of clinical parameters of control group (SRP + placebo) at baseline and six months (mean ± SD).

Parameters	Baseline	Six Months	Difference	p Value
PPD (mm)	5.73 ± 0.22	3.19 ± 0.13	2.54 ± 0.10	0.000 S
CAL (mm)	6.03 ± 0.45	4.45 ± 0.30	1.58 ± 0.25	0.000 S
GR (mm)	0.32 ± 0.22	1.25 ± 0.19	0.93 ± 0.15	0.000 S

S—statistically significant ($p < 0.05$)

Table 3. Comparison of clinical parameters of test and control groups at six months (mean ± SD).

Parameters	Test Site	Control Site	Difference	p Value
	SRP + SDD	SRP + Placebo		
PPD reduction (mm)	3.06 ± 0.09	2.54 ± 0.10	0.52 ± 0.10	0.000 S
CAL gain (mm)	2.25 ± 0.09	1.58 ± 0.25	0.67 ± 0.08	0.000 S
GR increase (mm)	0.80 ± 0.28	0.93 ± 0.15	0.13 ± 0.10	0.215 NS

S—statistically significant ($p < 0.05$); NS—not statistically significant ($p > 0.05$)

In the test group, the mean clinical attachment level (CAL) at baseline was 6.05 mm and that at six months was 3.80 mm. In the control group, the mean CAL at baseline was 6.03 mm and that at six months was 4.45 mm. The mean CAL gain of 2.25 mm was observed in the test (SRP + SDD) groups, while the control (SRP + placebo) group displayed mean CAL gain of 1.58 mm. The observed differences between baseline CAL and the CAL at six months were analyzed

by Student's paired *t*-test and were found to be statistically significant in both the groups ($p < 0.05$).

When the differences in CAL gain for the test group (2.25 mm) versus control group (1.58 mm) were analyzed by Student's unpaired *t*-test, a significant difference ($p < 0.05$) was observed. The mean CAL gain observed in the test group was significantly greater than for the control group. The additional benefit of CAL gain was 0.67 mm.

At six months, the mean increase in gingival recession was 0.80 mm in the test group and 0.93 mm in the control group. A statistically significant increase in gingival recession was found in both the groups ($p < 0.05$). No statistically significant difference was found in the increase in gingival recession between the test and control groups ($p > 0.05$).

Discussion

Previous studies evaluating the efficacy of adjunctive SDD therapy in chronic periodontitis patients have revealed the additive effect of the treatment modality on mean PPD reduction and CAL gain when compared with SRP.^{6,7,13–15}

In the present study SDD was well tolerated with no difference between treatment groups in the incidence of adverse events, including those events related to infection or associated with the gastrointestinal and urogenital tracts. The severity of chronic periodontal disease was similar in both the SDD and the placebo group at the beginning of the study, as indicated by no significant differences in investigated parameters between the two groups.

The successful long-term management of adult periodontitis (AP) may require an integrated treatment approach that addresses both periodontopathic bacteria and the ensuing destructive host response. The results of the present study showed that use of SDD in combination with SRP in chronic periodontitis patients with diabetes provided a better clinical improvement beyond that obtained by SRP therapy alone. In particular, a significant decrease in PPD (3.06 mm) and significant gain in CAL (2.25 mm) at six months was observed in the SDD group compared to the placebo group. Previous studies^{6,7} have emphasized the effectiveness of SDD therapy on clinical parameters. These studies have shown that SDD + nonsurgical periodontal therapy resulted in significantly greater reduction in probing pocket depth (PPD) and improvement in clinical attachment level (CAL) compared with the nonsurgical periodontal procedure alone in treating the chronic periodontitis patient.

Crout et al.¹³ and Golub et al.¹⁶ reported that SDD therapy in combination with nonsurgical periodontal therapy can inhibit the activity or down regulate the expression of host collagenase by a

mechanism unrelated to the antimicrobial efficacy of the drug. Tetracycline agents have the ability to inhibit neutrophils, osteoclasts, and matrix metalloproteinase, involved in the destruction of periodontium.¹⁷ (Tetracycline has an anti-inflammatory action and may be bone sparing through inhibition of osteoclasts. Doxycycline is the most studied and strongest collagenase inhibitor of the tetracyclines used. Based on these findings, it can be suggested that significant improvement in CAL and PPD in the SDD group could be dependent on the host modulation property of SDD.

As a mechanical intervention SRP has been shown to slow or arrest the progression of the destructive periodontal disease.¹⁸ Periodontal pathogens may lead variation in clinical outcomes that are less than optimal because they do not address the complex etiology of this chronic disease. The tetracyclines have been found to be effective inhibitors of matrix metalloproteinase-mediated connective tissue destruction in a variety of pathological processes. In addition to the possible effects of tetracyclines on expression, activation, and catalytic activity of matrix metalloproteinases, these compounds may have actions on other processes involved in the overall pathophysiology of multiple disease states, including regulation of release of inflammatory cytokines and glycosylation of connective tissue proteins. They also may even upregulate the expression of matrix constituents, which are produced at a deficient rate during diabetes.¹⁹ These multiple modes of action may account for the positive results obtained with use of tetracyclines as therapeutic agents in models of periodontitis.

Other advantages for periodontal treatment are that tetracyclines, particularly doxycycline,²⁰ tend to be highly concentrated in the gingival crevicular fluid at levels 5–10 times greater than those found in serum. These antibiotics also show substantivity because they bind to the tooth structure and are slowly released as still-active agents. As an inhibitor of MMPs implicated in periodontal tissue destruction, SDD may improve the outcome of a variety of mechanical nonsurgical interventions currently used as first-line therapy.

The study had a few limitations as well. Small sample size limited the statistical analysis. In addition, long-term analysis is needed to determine the stability of the results observed in the present study. Moreover, biochemical analysis of inflammatory mediators in GCF would have been

helpful in correlating the clinical parameters and assessment of results. Also, microbiological assay would have been beneficial for assessing the effect of SDD therapy on periodontopathic microbial load in diseased sites.

Conclusion

Probing pocket depth reduction was greater in the SDD group compared to the placebo group. Mean gains of clinical attachment were also greater in the test group compared to the control group. From the analysis of the results, and within the limitations of the present study, it can be concluded that nonsurgical periodontal therapy (SRP) in combination with a subantimicrobial dose of doxycycline (SDD) is more effective than SRP alone in terms of CAL gain, PPD reduction, and gingival recession.

Subantimicrobial dose of doxycycline (SDD) therapy may represent a new approach in long-term management of adult periodontitis with diabetes.

Clinical Significance

Given the widespread prevalence of adult periodontitis and diabetes, and the bidirectional association between the two, a treatment approach that addresses both chronic disorders will prove to be of great value to the patients and the clinicians. This proposed treatment approach will contribute significantly to the overall health of the patient.

References

1. Cohen DW, Friedman LA, Shapiro J, Kyle GC, Franklin S. Diabetes mellitus and periodontal disease: two-year longitudinal observations. I. *J Periodontol.* 1970; 41(12):709-12.
2. Miller LS, Maxwell MA, Newbold D, Reding ME, Rasheed A, Blodgett J, Kornman KS. The relationship between reduction in periodontal inflammation and diabetes control: a report of 9 cases. *J Periodontol.* 1992; 63(10):843-8.
3. Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, Genco RJ. Treatment of periodontal disease in diabetics reduces glycosylated hemoglobin. *J Periodontol.* 1997; 68(8):713-9.
4. Iwamoto Y, Nishimura F, Nakagawa M, Sugimoto H, Shikata K, Makino H, Fukuda T, Tsuji T, Iwamoto M, Murayama Y. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycosylated hemoglobin level in patients with type 2 diabetes. *J Periodontol.* 2001; 72(6):774-8.
5. Golub LM, Lee HM, Greenwald RA, Ryan ME, Sorsa T, Salo T, Giannobile WV. A matrix metalloproteinase inhibitor reduces bone-type collagen degradation fragments and specific collagenases in gingival crevicular fluid during adult periodontitis. *Inflamm Res.* 1997; 46(8):310-9.
6. Caton JG, Ciancio SG, Blieden TM, Bradshaw M, Crout RJ, Hefti AF, Massaro JM, Polson AM, Thomas J, Walker C. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *J Periodontol.* 2000; 71(4):521-32.
7. Novak MJ, Johns LP, Miller RC, Bradshaw MH. Adjunctive benefits of subantimicrobial dose doxycycline in the management of severe, generalized, chronic periodontitis. *J Periodontol.* 2002; 73(7):762-9.
8. Preshaw PM, Hefti AF, Novak MJ, Michalowicz BS, Pihlstrom BL, Schoor R, Trummel CL, Dean J, Van Dyke TE, Walker CB, Bradshaw MH. Subantimicrobial dose doxycycline enhances the efficacy of scaling and root planing in chronic periodontitis: a multicenter trial. *J Periodontol.* 2004; 75(8):1068-76.
9. Al-Ghazi MN, Ciancio SG, Aljada A, Bessinger M, Marther M, Mohanty P, Dandona P. Evaluation of efficacy of administration of sub-antimicrobial-dose doxycycline in the treatment of generalized adult periodontitis in diabetics. *J Dent Res.* 2003; 82(Spec Iss A):1752.
10. Engebretson SP, Hey-Hadavi J, Celenti R, Lamster IB. Low-dose doxycycline treatment reduces glycosylated hemoglobin in patients with type 2 diabetes: a randomized controlled trial. *J Dent Res.* 2003; 82(Spec Iss A):1445.
11. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of vitamin C. *J Periodontol.* 1970; 41(1):41-3.

12. Mühlemann HR. Psychological and chemical mediators of gingival health. *J Prev Dent*. 1977; 4(4):6-17.
13. Crout RJ, Lee HM, Schroeder K, Crout H, Ramamurthy NS, Wiener M, Golub LM. The "cyclic" regimen of low-dose doxycycline for adult periodontitis: a preliminary study. *J Periodontol*. 1996; 67(5):506-14.
14. Golub LM, McNamara TF, Ryan ME, Kohut B, Blieden T, Payonk G, Sipos T, Baron HJ. Adjunctive treatment with subantimicrobial doses of doxycycline: effects on gingival fluid collagenase activity and attachment loss in adult periodontitis. *J Clin Periodontol*. 2001; 28(2):146-56.
15. Emingil G, Atilla G, Sorsa T, Luoto H, Kirilmaz L, Baylas H. The effect of adjunctive low-dose doxycycline therapy on clinical parameters and gingival crevicular fluid matrix metalloproteinase-8 levels in chronic periodontitis. *J Periodontol*. 2004; 75(1): 106-15.
16. Golub LM, Sorsa T, Lee HM, Ciancio S, Sorbi D, Ramamurthy NS, Gruber B, Salo T, Kontinen YT. Doxycycline inhibits neutrophil (PMN)-type matrix metalloproteinases in human adult periodontitis gingiva. *J Clin Periodontol*. 1995; 22(2):100-9.
17. Ingman T, Sorsa T, Suomalainen K, Halinen S, Lindy O, Lauhio A, Saari H, Kontinen YT, Golub LM. Tetracycline inhibition and the cellular source of collagenase in gingival crevicular fluid in different periodontal diseases. A review article. *J Periodontol*. 1993; 64(2):82-8.
18. Badersten A, Nilvesus R, Egelberg J. Effect of nonsurgical periodontal therapy. II. Severely advanced periodontitis. *J Clin Periodontol*. 1984; 11(1):63-76. Cited by Caton JG, Ciancio SG, Blieden TM, Bradshaw M, Crout RJ, Hefti AF, Massaro JM, Polson AM, Thomas J, Walker C. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. *J Periodontol*. 2000; 71(4): 521-32.
19. Sasaki T, Ramamurthy NS, Golub LM. Tetracycline administration increases collagen synthesis in osteoblasts of streptozotocin-induced diabetic rats: a quantitative autoradiographic study. *Calcif Tissue Int*. 1992; 50(5):411-9.
20. Pascale D, Gordon J, Lamster I, Mann P, Seiger M, Arndt W. Concentration of

doxycycline in human gingival fluid. *J Clin Periodontol*. 1986; 13(9):841-44.

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