

# Effect of nonsurgical periodontal therapy (with or without oral doxycycline delivery) on glycemic status and clinical periodontal parameters in patients with prediabetes: a short-term longitudinal randomized case–control study

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## Abstract

**Objective** The aim of the present short-term longitudinal randomized case–control study was to assess the effect of nonsurgical periodontal therapy (NSPT) (with and without oral doxycycline delivery) on glycemic status and clinical periodontal parameters in patients with prediabetes.

**Material and methods** Sixty-six patients with prediabetes and periodontal disease were included. Characteristics of the study cohort (age, gender, socioeconomic status [SES] education status, duration of prediabetes, and type of treatment adopted for prediabetes management) were recorded. Patients were randomly divided into two groups (33 patients/group). In group 1, scaling and root planing (SRP) was performed, and in group-2, patients underwent SRP and oral doxycycline (100 mg) administration once daily for 15 days. In each group, the following parameters were investigated at baseline and after 3 months: (a) fasting blood glucose level (FBGL), (b) hemoglobin A1c (HbA1c), and (c)

periodontal parameters (plaque index [PI], bleeding on probing [BOP], probing depth [PD], and clinical attachment loss [AL]). Statistical analysis was performed using Student's *t* test.

**Results** There was no significant difference in age, gender, SES, education status, and duration and treatment of prediabetes among individuals in groups 1 and 2. Three months post-NSPT, FBGL and HbA1c were significantly reduced among patients in group 1 ( $P<0.05$ ) and group 2 ( $P<0.05$ ) compared to baseline. Three months post-NSPT, PI ( $P<0.05$ ), BOP ( $P<0.05$ ), and PD ( $P<0.05$ ) were significantly reduced among patients in group 1 ( $P<0.05$ ) and group 2 ( $P<0.05$ ) compared to baseline. There was no difference in clinical AL between the groups after 3 months of NSPT.

**Conclusion** NSPT (with and without oral doxycycline delivery) reduces hyperglycemia and periodontal inflammation in patients with prediabetes.

**Keywords** Dental scaling · Hemoglobin A1c · Hyperglycemia · Nonsurgical periodontal debridement · Prediabetic state · Root planing

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## Introduction

A bidirectional relationship between periodontal disease and hyperglycemia has been reported [1]. Studies [2–6] have reported that periodontal disease is worse in patients with poorly-controlled diabetes compared to patients with well-controlled diabetes and nondiabetic controls. Recent studies [5, 7–9] have shown that patients with impaired glucose tolerance or prediabetes are also susceptible to periodontal destruction and alveolar bone loss compared to systemically healthy controls. A possible mechanism for the influence of periodontal disease on diabetes status may be that local periodontal infection augments the systemic burden of inflammatory

mediators (such as tumor necrosis factor alpha [TNF- $\alpha$ ]) that exacerbate the existing metabolic disorder in patients with diabetes [10]. Furthermore, the increased risk of periodontal destruction in patients with hyperglycemia has been associated with various factors including increased production and accumulation of advanced glycation end products in periodontal tissues, raised cellular oxidative stress, and production of proinflammatory cytokines (i.e., interleukin (IL)-6, IL-1beta [IL-1 $\beta$ ], IL-18, matrix metalloproteinase [MMP]-8, and MMP-9) in the serum, saliva, and gingival crevicular fluid of patients with chronic hyperglycemia [11–15].

Nonsurgical periodontal therapy (NSPT) (or scaling and root planing [SRP]) has been reported to improve glycemic status in patients with type 2 diabetes mellitus (T2DM) [16–22]. In a randomized controlled trial, Koromantzos et al. [22] demonstrated that NSPT contributes to improved glycemic control in patients with T2DM. However, it has also been reported that NSPT alone is inefficient in completely eliminating pathogenic microbes and their products from periodontal pockets and that NSPT with adjunct antibiotic therapy helps in the extermination of pathogenic microbes from infected periodontal tissues [23, 24]. Akalm et al. [23] compared the clinical efficacies of locally delivered and systemically delivered doxycycline when used as adjuncts to SRP in the treatment of periodontal disease. The results demonstrated that locally delivered or systemically delivered doxycycline when used as adjuncts to NSPT is equally effective in the treatment of periodontal disease [23].

It is noteworthy that previous studies [16–19, 23] where NSPT was reported to reduce glycemic levels in patients with hyperglycemia were performed only in patients with T2DM. In this regard, we hypothesized that NSPT reduces glycemic levels in patients with prediabetes. To our knowledge from indexed literature, the effect of NSPT on glycemic levels in patients with prediabetes is not yet investigated.

The aim of the present short-term longitudinal randomized case–control study was to assess the effect of NSPT (with and without oral doxycycline delivery) on glycemic status and clinical periodontal parameters in patients with prediabetes.

## Materials and methods

### Inclusion and exclusion criteria

Only individuals medically diagnosed with prediabetes (fasting blood glucose levels [FBGLs] between 100 and 125 mg/dL [5.6–6.9 mmol/L] and levels of hemoglobin A1c [HbA1c] between 5.7 and 6.4 %) were included [25]. Exclusion criteria comprised of (a) self-reported systemic diseases such as type 1 diabetes mellitus and T2DM, HIV infection/acquired immune deficiency syndrome, cardiovascular disorders, epilepsy, hepatic disorders, and renal disorders; (b) recent history of antibiotic and/or steroid intake; (c) crowding of

teeth and/or occlusal trauma; (d) edentulism; (e) self-reported habitual tobacco usage (smoking and/or chewing) and alcohol consumption; (f) history of any periodontal treatment within the past 6 months; and (g) pregnancy.

### Recruitment of study participants

A short-term longitudinal case–control study was conducted between September 2011 and July 2012 in which patients with medically diagnosed prediabetes were recruited from the diabetes care unit of Jinnah Hospital, Karachi, Pakistan. In total, 66 male patients with medically diagnosed prediabetes volunteered to participate in the present study. These individuals were requested to present their medical records to confirm the diagnosis of prediabetes. In all individuals, prediabetes had been diagnosed in accordance with the criteria proposed by the American Diabetes Association [25].

### Patient grouping

Sixty-six patients with medically diagnosed prediabetes were randomly divided into two groups (group 1 and group 2) by tossing a coin. In group 1, 33 males with prediabetes underwent full-mouth SRP, whereas in group 2, 33 males with prediabetes underwent full-mouth SRP and antibiotic administration (doxycycline 100 mg once daily for 15 days). All participants ( $n=66$ ) were given standardized oral hygiene instructions 1 week before NSPT.

### Interview questionnaire

A trained interviewer (A.M.) collected information regarding age, gender, socioeconomic status (SES), education status (graduate level), duration of prediabetes, and family history of diabetes from individuals in groups 1 and 2. Monthly salary was recorded in Pakistani rupees and converted into US dollars (USD). One USD was equivalent to 95.50 Pakistani rupees.

At baseline and 3 months after NSPT, participants in groups 1 and 2 were inquired about the number of times they brushed their teeth on a daily basis.

### Measurement of fasting blood glucose levels and hemoglobin A1c levels

Among individuals in groups 1 and 2, FBGL and HbA1c level were measured at baseline and after 3 months of NSPT. FBGLs were measured using a digital glucometer (Accu-Chek Active, Roche Diagnostics, Mannheim, Germany). Venous blood samples were drawn in the morning, and HbA1c levels were determined using the high-performance liquid chromatography method (Bio-Rad Laboratories, Inc., D-10™, Hemoglobin Systems, Hercules, CA, USA) [26].

## Periodontal parameters

A trained and calibrated examiner (A.M.) blinded to whether participants were in group 1 or in group 2 performed the clinical periodontal examinations. The kappa for intraexaminer reliability was 0.78. Full-mouth plaque index (PI) [27], bleeding on probing (BOP) [28], probing depth (PD) to the nearest millimeter (mm) using a graded probe (Hu-Friedy, Chicago, IL, USA) [3, 29], and clinical attachment loss (AL) [8, 30] were measured at six sites (mesiobuccal, midbuccal, distobuccal, distolingual/palatal, midlingual/palatal, and mesiolingual/palatal) on all maxillary and mandibular teeth. Fractured teeth with embedded roots and maxillary and mandibular third molars were excluded. Individuals with clinical AL  $\geq 3$  mm [31, 32] and PD  $\geq 5$  mm in more than 30 % sites were categorized as having periodontal disease.

## Ethical guidelines

The study was reviewed and approved by the research ethics review board of the Jinnah Hospital, Karachi, Pakistan. The study was performed in accordance with the Helsinki Declaration of 1975 as revised in 2000. All participants were provided with an information sheet that explained the objectives and methods of the present investigation. The information sheet also clarified that all participants reserved the right to retire from the research study at any stage of investigation without penalty. Volunteering participants were requested to sign a consent form.

## Statistical analysis

Statistical analysis was performed using a software program (SPSS, Version 18, Chicago, IL, USA). With inclusion of 33 patients per group (assuming a standard deviation of 1.0 %), the study power was estimated to be 85 % at a two-sided significance level of 0.05. Intergroup comparisons were performed using Student's *t* test, whereas for intragroup comparison, one-way analysis of variance and a paired *t* test were used.

## Results

### Characteristics of the study cohort

All participants ( $n=66$ ) were males. There was no statistically significant difference in age and duration of prediabetes among individuals in group 1 ( $44.2\pm 1.4$  years and  $8.3\pm 1.3$  months, respectively) and group 2 ( $40.7\pm 1.2$  years and  $10.2\pm 1.2$  months, respectively). A family history of diabetes was reported by  $52.4\pm 2.3$  % individuals in group 1 and  $48.7\pm 3.5$  % individuals in group 2. Nearly 50 % of the study

participants had attained graduate level education (group 1:  $60.4\pm 3.5$  % and group 2:  $50.3\pm 2.4$  %). There was no significant difference in the monthly income status among individuals in groups 1 and 2 (USD  $495.2\pm 38.2$  and USD  $550\pm 55.3$ , respectively). All participants with prediabetes had been prescribed dietary control regimens by health-care providers for the management of their prediabetes state (Table 1).

At baseline, 10/33 and 12/33 individuals in groups 1 and 2, respectively, reported to brush their teeth twice daily. Three months after NSPT, 25/33 and 28/33 individuals in groups 1 and 2 correspondingly reported to have been performing oral hygiene maintenance regimens twice daily.

Fasting blood glucose levels, hemoglobin A1c levels, and periodontal parameters at baseline and 3 months after nonsurgical periodontal therapy

At baseline, the FBGL and HbA1c level among individuals in groups 1 and 2 were 115.8 mg/dL (110.5–121.2 mg/dL) and 6 % (5.7–6.3 %) and 120.7 mg/dL (114.3–122.7 mg/dL) and 6.2 % (5.7–6.4 %), respectively. Three months after NSPT, FBGL and HbA1c level were significantly reduced among individuals in group 1 (82.3 mg/dL [80.5–90.2 mg/dL] and 5.1 % [4.9–5.3 %], respectively) ( $P<0.05$ ) and group 2 (80.4 mg/dL [80.1–86.5 mg/dL] and 5 % [4.8–5.3 %], respectively) ( $P<0.05$ ) compared to baseline values.

At baseline, there was no statistically significant difference in PI, BOP, PD ( $>4$  mm), and clinical AL among individuals in groups 1 and 2. After 3 months of NSPT, PI ( $P<0.05$ ), BOP ( $P<0.05$ ), and PD ( $>4$  mm) ( $P<0.05$ ) were significantly reduced in groups 1 and 2 compared to baseline. There was no statistically significant difference in clinical AL between the groups at baseline and 3 months after NSPT (Fig. 1).

## Discussion

To our knowledge from indexed literature, this is the first study in which the effect of NSPT on the glycemic and periodontal status of patients with medically diagnosed prediabetes has been investigated. The 3-month follow-up results demonstrated that hyperglycemia and periodontal inflammation among patients with prediabetes in group 1 (NSPT alone) and group 2 (NSPT + doxycycline) were effectively reduced compared to baseline values. It has been reported that periodontal disease elevates the systemic burden of inflammatory mediators (such as IL-1 $\beta$  and TNF- $\alpha$ ) that aggravate the existing metabolic disorder in patients with hyperglycemia [10, 33]. This suggests that NSPT reduces the severity of periodontal infection and decreases the systemic burden of inflammatory mediators, which in turn reduces the hyperglycemic state in patients with prediabetes. Furthermore, an interesting finding in the present study was that at baseline,  $\sim 30$  % of the patients with

**Table 1** Characteristics of the study cohort

	All individuals ( $n=66$ ) (mean $\pm$ SD)	Group 1 ( $n=33$ ) (mean $\pm$ SD)	Group 2 ( $n=33$ ) (mean $\pm$ SD)
Gender	66 males	33 males	33 males
Age in years	41.5 $\pm$ 2.2	44.2 $\pm$ 1.4	40.7 $\pm$ 1.2
Duration of prediabetes in months	9.5 $\pm$ 1.4	8.3 $\pm$ 1.3	10.2 $\pm$ 1.2
Family history of diabetes (%)	51.5 $\pm$ 0.6	52.4 $\pm$ 2.3	48.7 $\pm$ 3.5
Education status in % (graduate level)	54.3 $\pm$ 1.5	60.4 $\pm$ 3.5	50.3 $\pm$ 2.4
Socioeconomic status (monthly income in USD)	520.3 $\pm$ 45.4	495.2 $\pm$ 38.2	550 $\pm$ 55.3
Type of treatment recommended by physicians for prediabetes management			
Allopathic (%)	–	–	–
Homeopathic (%)	–	–	–
Herbal (%)	–	–	–
Dietary control (%)	100	100	100
Others (%)	–	–	–

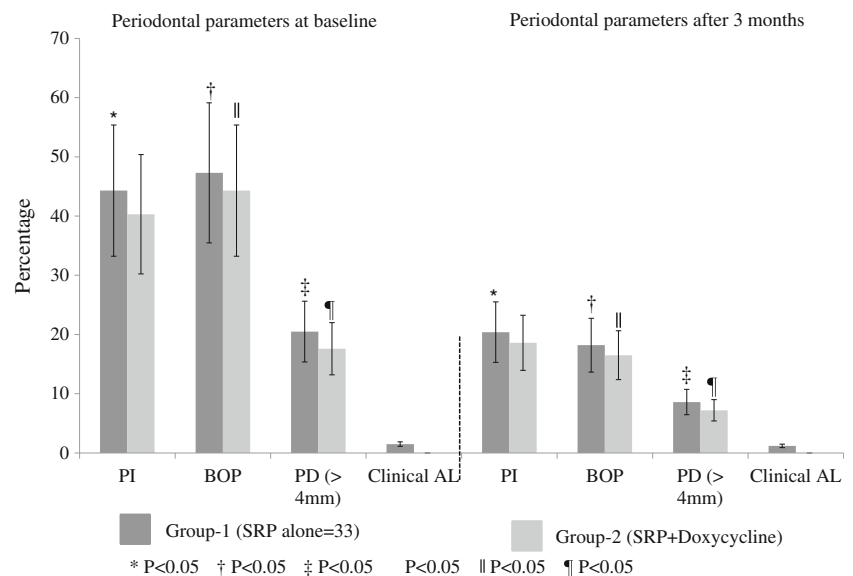
In the year 2011, the average monthly income of Pakistani individuals residing in urban Sindh was USD 351.21 ([www.pbs.gov.pk/](http://www.pbs.gov.pk/))

prediabetes in groups 1 and 2 reported to brush their teeth twice daily; however, 3 months post-NSPT, nearly 80 % of the patients in each group reported to brush their teeth twice daily. It is speculated that improvements in daily oral hygiene maintenance regimes also play a role in reducing the systemic burden of inflammatory mediators thereby reducing the state of hyperglycemia in affected patients.

Studies [34–36] have anticipated that bacteria and their products (such as lipopolysaccharides) enter systemic circulation from infected periodontal pockets, which may worsen insulin resistance by potentially increasing low-grade inflammation. This suggests that the systemic load of bacteria and their products is higher in individuals with persistent hyperglycemia compared to patients with well-controlled glycemic levels. Moreover, leakage of proinflammatory cytokines into the main bloodstream from inflamed periodontal tissues may

also result in the deterioration of the hyperglycemic state, which may in turn further aggravate periodontal inflammation [37]. Studies [19, 23, 24, 38] have reported that NSPT when used with adjunct antibiotic therapy eliminates pathogenic microbes and their products from periodontal pockets to a much greater extent compared to when NSPT is used alone to control periodontal disease. Likewise, another study [39] proposed that tetracycline inhibits the formation of extracellular glycation of proteins in patients with diabetes via a non-anti-collagenase mechanism. Our 3-month follow-up results showed that NSPT (with and without doxycycline delivery) significantly reduced FBGL, HbA1c, and periodontal inflammation among individuals in groups 1 and 2. Various explanations may be proposed in this regard. Individuals included in the present study were relatively newly diagnosed prediabetic patients (diagnosed within the past 10 months) and were

**Fig. 1** Means ( $\pm$ standard deviation) of periodontal parameters at baseline and 3 months post-nonsurgical periodontal therapy among patients in groups 1 (dark gray bars) and 2 (light gray bars)



supposedly using dietary control regimes to maintain their glycemic levels. Furthermore, nearly 50 % of the study population had attained graduate level education, which reflects that at least to an extent, these individuals were aware of the deleterious effects of hyperglycemia on overall health. It is therefore speculated that the short duration of prediabetes, education status, and dietary control attempts in the present study population prevented the systemic inflammatory burden from rising drastically. These factors could have defused the role of adjunctive use of doxycycline among individuals in group 2. Should NSPT + doxycycline improve glycemic status and reduce periodontal inflammation in individuals with a long history of prediabetes, underprivileged SES, and poor education requires further investigations.

It is known that a family history of diabetes is a significant risk factor of prediabetes [40, 41]. In the present study, nearly 50 % of the patients with prediabetes had a family history of diabetes. It is highly recommended that patients with chronic periodontal infections (having a family history of diabetes) perceiving to be systemically healthy should be educated and encouraged to maintain their oral health statuses and should be referred to medical health-care providers as these patients may be unaware of their “latent prediabetes” state. Such measures may help stabilize the oral as well as systemic health in vulnerable individuals.

Within the limits of the present study, it is concluded that NSPT (with and without systemic doxycycline delivery) reduces hyperglycemia and periodontal inflammation in patients with prediabetes.

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**Conflict of interest** The authors report no conflict of interest related to the present study.

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