

Effect of periodontal therapy on metabolic control and levels of IL-6 in the gingival crevicular fluid in type 2 diabetes mellitus

Gabriela Alessandra da Cruz Galhardo Camargo, Meyriane de Andrade Lima¹, Tânia Vieira Fortes¹,
Cristiane Salgado de Souza¹, Amélia Maria de Jesus², Roque Pacheco de Almeida²

Department of Periodontology,
Fluminense Federal University,
Nova Friburgo, Rio de Janeiro,
¹Departments of Periodontology
and Operative Dentistry,
and ²Medicine, Division of
Immunology, Federal University
of Sergipe, Aracaju, Sergipe,
Brazil

ABSTRACT

Background: The aim of this study was to compare the efficacy of metabolic control and levels of interleukin 6 (IL-6) in gingival crevicular fluid after periodontal therapy in type 2 diabetes mellitus (DM) and nondiabetic (NDM) patients.

Methods: This study was performed in 20 subjects (10 type 2 DM and 10 NDM patients with generalized chronic periodontal disease. Both groups were recorded for clinical parameters (plaque index (PI), gingival index (GI), probing depth (PD), gingival recession (GR) and clinical attachment level (CAL)), metabolic control (fasting glucose levels, glycated a-hemoglobin (HbA1c), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TR)), and IL-6 levels at baseline and 3 months after periodontal treatment.

Results: DM and NDM patients revealed significant statistical reductions for clinical parameters ($P < 0.05$, RM ANOVA) after 3 months. DM group had improvements on HbA1c and had significant statistical increased of TRG ($P < 0.05$, RM ANOVA) after 3 months. No differences of LDL/HDL and IL-6 levels were found after 3 months in both groups.

Conclusion: DM group presented a significant reduction of HbA1c levels after periodontal therapy. However, TRG levels increased after 3 months, which suggest more confirmatory studies to investigate if these results will be repeated in other studies.

Key words: Diabetes, interleukin, periodontal disease

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Diabetes mellitus (DM) is a metabolic disorder and has been considered a risk factor for periodontal disease. DM has two major forms, type 1 and 2, which have distinct etiology. Type 1 diabetes occurs when autoimmune-induced inflammation provokes destruction and apoptosis of beta cells pancreas leading to insufficient insulin production. Type 2 is characterized as an alteration of insulin production and it is almost found in obese people or patients with an increase percentage of body fat in the abdominal region.^[1,2]

The presence of diabetes increases the prevalence, incidence and severity of periodontitis.^[3] Epidemiological studies

of National Health and Nutrition Survey (NHANES) III confirm the increase in periodontitis prevalence among diabetics.^[4] Longitudinal Pima Indian Population studies showed enhance in the prevalence of attachment and bone loss after periodontal exams in poor metabolic control.^[5] The relationship between glycemia control of diabetes and periodontal disease is unclear due to some uncontrolled diabetic patients may develop extensive periodontal destruction or not, as well as, controlled diabetic patient can have an excellent periodontal healthy or may develop periodontitis.^[6]

Several studies have been reported potential mechanisms involving interactions with periodontitis, diabetes, metabolic control, tissue repair, and immune cell function.^[7,8] Periodontal destruction observed in periodontitis is host-mediated through release of proinflammatory cytokines by local immune cells in response to bacterial flora and products/metabolites, especially lipopolysaccharide (LPS).^[9,10] Tumoral necrosis factor alpha (TNF- α) and interleukin 1 beta (IL-1 β) are significantly elevated in periodontal disease sites and demonstrates inflammation during periods of active disease and tissue destruction.^[11] TNF- α is a major signal for cellular apoptosis, bone resorption, methalloproteinase (MMP) secretion, intercellular adhesion molecule (ICAM)

Address for correspondence:

Dr. Gabriela Alessandra da Cruz Galhardo Camargo
E-mail: gabyccruz@vm.uff.br

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expression, and IL-6 production. IL-6, once produced, stimulates osteoclast activation, thus, bone resorption, and facilitates T-cell differentiation.^[12] Pro-inflammatory cytokines, interleukin-1 (IL-1) and TNF- α are elevated in the gingival crevicular fluid or serum of diabetic patients, and they were correlated with periodontal tissue destruction.^[13]

Based on these facts, the aim of this study was to evaluate if DM type 2 and NDM patients, both with chronic periodontal disease, would present changes between groups and timing evaluations, at baseline and in 3 months follow-up, in periodontal status, metabolic control and interleukin 6 (IL-6) levels in the gingival crevicular fluid after periodontal therapy.

MATERIALS AND METHODS

A total of 20 patients (30-65 years old) from Graduate Clinic with clinical diagnosis of generalized chronic periodontitis defined by probing depth >5 mm at least in 10 teeth, radiographic bone loss ranging from 30% to 50% and presence of at least 20 teeth per mouth, were included. Exclusion criteria were: Use of antibiotics during the previous 6 months, pregnancy, smoking, other systemic diseases, use of immune suppressive medication, phenytoin, cyclosporine, calcium channel blockers or any medication that could interfere in the periodontium or in response to periodontal therapy.

To compute required sample size the standard deviation was estimated from study Da Cruz *et al.*^[14] that considered means and standard deviations of sites with probing depth >5 mm for diabetes mellitus groups (DM) (33.60 ± 15.70), and nondiabetes mellitus group (NDM) (20.1 ± 7.24), using G*Power (Version 3.1.2, Franz Faul, Universität Kuel, Germany, 1992-2009) based on t-test means difference between two independent means, considering $\alpha = 0.07$ and power of 0.80, respectively, so we have obtained a sample size equal to 10 patients.

The selected patients were divided into two groups: An experimental group of 10 patients diagnosed with type 2 DM (medication supplementation attested by an endocrinologist) and 10 NDM. Diabetic patients informed the diabetes diagnosis duration (in years) and their daily consumption of medication. The patients were evaluated for 3 months, from August to November 2008. This research was conducted after approving by the Ethical Committee of Research.

Blood samples were taken at baseline and at 3-month recall visit. Fasting glucose levels, glycated a-hemoglobin (HbA1c), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TR), were evaluated in all patients. Clinical parameters were also measured at baseline and 3 months after therapy. Probing depth (PD), gingival recession (GR), clinical attachment level (CAL),

plaque index (PI), and gingival index (GI)^[15] were measured by a single examiner with a PCP (PCP-UNC15, Hu-Friedy, Chicago, IL) periodontal probe at four sites per tooth at all teeth, excluding third molars.

After clinical measurements, the supragingival biofilm was removed with sterile gauze. Gingival crevicular samples were taken from two sites with the deepest PD (≥ 5 mm) in each patient using a sterile paperpoint from the deepest pocket for 30 s. Gingival crevicular fluids were inserted in two eppendorf tubes containing phosphate buffer saline and were stored at -80°C . The samples were collected in the same site at baseline and 3 months post-therapy and were analyzed by ELISA (enzyme-linked immunosorbent assay) using commercial kits (R&D Systems, Minneapolis, MN, USA).

After removing baseline samples of biofilm, full-mouth scaling and root planning (SRP), under local anesthesia, was performed in all sites with periodontal disease in a single session. Oral hygiene instructions for home care procedures (tooth brushing technique, interdental cleaning and use of tongue scrapers) were given by an experienced periodontist. The maintenance therapy included professional plaque control at 2 weeks interval during the 3 months of the study.

Statistical analysis

Statistical tests were accomplished using the SAS software (Institute Inc., Cary, NC, USA, Version 9.1, 2003). Repeated measures analysis of variance (RM ANOVA) was performed to compare clinical parameters (PI, GI, PD, GR, and AL) and metabolic parameters (fasting glucose, HbA1c, LDL, HDL, TRG) between both time intervals and DM and NDM groups. All variables were normally distributed, except IL-6. The Mann-Whitney test was used to analyze differences in IL-6 levels between baseline and at 3-month recall. Statistical significance for all variables was defined at the 5% level.

RESULTS

Periodontal results

Descriptive statistics with means and standard deviations of the variables are presented in Table 1. Statistically significant differences were observed for age between DM and NDM groups (paired *t*-test ($P = 0.002$). Regarding the distribution of sites, mean number of observed sites present in DM group was higher than NDM group. Mean number of sites with periodontal disease (with PD > 5 mm) were also highest in DM group.

Presence of plaque was evaluated on all tooth surfaces [Table 2]. Plaque index (PI) were determined for the whole mouth (%) in both DM and NDM groups at different time intervals (DM and NDM; $P = 0.0301$; baseline and 3 months

$P = 0.0184$; RM ANOVA). DM group exhibit more numbers of sites with plaque at the initial of treatment than NDM group. Significant reduction of plaque was found in DM and NDM groups after 3 months. Gingival index (GI) was evaluated on all tooth surfaces [Table 2]. Gingival index was determined for the whole mouth (%) in both DM and NDM groups in different time intervals (DM and NDM; $P = 0.3034$; baseline and 3 months; $P = 0.0015$; RM ANOVA). No significant difference was found between DM and NDM groups, but statistically significant reduction of bleeding on probing after 3 months. Both groups demonstrated reduced plaque and bleeding on probing after 3 months and improvement in oral hygiene. Based on PI and GI changes, the response to the oral hygiene procedures was similar for the two groups.

Table 3 summarizes probing depth, gingival recession, and attachment level. The probing depth had no statistically significant difference between groups DM and NDM and between time intervals (DM and NDM; $P = 0.0199$; baseline and 3 months; $P = 0.001$; RM ANOVA). No differences were found for gingival recession between DM and NDM groups at baseline and after 3 months (DM and NDM; $P = 0.1858$; baseline and 3 months; $P = 0.7486$; RM ANOVA). Clinical attachment levels had no statistically differences between groups DM and NDM between the different time intervals (DM and NDM; $P = 0.6958$; baseline and 3 months; $P = 0.4486$; RM ANOVA).

Metabolic analysis

Metabolic control was expressed by means of fasting glucose level, HbA1c, LDL, HDL, TRG. The fasting glucose levels showed significant differences between DM and NDM groups at baseline ($P = 0.0034$; RM ANOVA), but no significant statistically differences between the baseline and 3 months ($P = 0.9426$; RM ANOVA) [Figure 1]. The HbA1c had significant statistically difference between NDM and DM groups at baseline ($P = 0.0108$; RM ANOVA) and significant statistically reduction between the baseline and 3 months after periodontal treatment ($P = 0.040$ RM ANOVA) [Figure 2]. The LDL showed significant statistically difference between DM and NDM group at baseline ($P = 0.0265$; RM ANOVA), but no significant statistically difference after 3 months ($P = 0.6289$; RM ANOVA) [Figure 3]. The HDL presented no significant statistically difference between DM and NDM groups and between baseline and 3-month recall ($P = 0.9471$; RM ANOVA; $P = 0.1098$; RM ANOVA) [Figure 4]. The TRG showed significant statistically difference between DM and NDM groups and between baseline and 3 months ($P = 0.0488$; RM ANOVA; $P = 0.0571$; RM ANOVA) [Figure 5].

Modulation of IL-6 production of gingival fluid

Modulation of IL-6 production in gingival crevicular fluid was presented on Figure 6. No statistically significant

Table 1: Subjects characteristics (mean±S.D.) at baseline

	DM group (n = 10)	NDM group (n = 10)
Age (years)	52±8.72*	41.6±7.55
Total sites (N)	71.6±21.37	94.4±15.8
Sites with PD>5 mm	16.2±12.02	12.5±5.97
Diabetes duration (years)	6.6±4.17	NA
Medicine consumption (mg/dia)	1445±806.38	NA

*Statistically significant difference between groups for age (Student test; $P < 0.05$). NA=Not applicable, DM=Diabetes mellitus, NDM=Nondiabetic mellitus

Table 2: PI and GI values (mean±S.D.) for DM and NDM group at baseline and 3 months

	DM group	NDM group
PI		
Baseline	83.64±14.09*	52.85±26.56
3 months	29.39±18.30†	30.35±13.95†
GI		
Baseline	61.11±15.91	39.39±20.31
3 months	13.51±3.9†	22.44±14.87†

*Statistically significant differences ($P < 0.05$) were noted in PI between DM and NDM groups. †Statistically significant reduction ($P < 0.05$) were noted to PI and GI between baseline and 3 months values to DM and NDM groups DM=Diabetes mellitus, NDM=Nondiabetic mellitus, PI=Plaque index, GI=Gingival index

Table 3: Whole-mouth clinical indices (mean±S.D.)

	Baseline	3 months	Change (baseline to 3 months)
PD (mm)			
DM group	3.46±0.55*	2.62±0.6	0.9±0.37
NDM group	2.81±0.55	2.49±0.48†	0.33±0.31
GR (mm)			
DM group	1.68±0.72	1.51±0.62	0.18±0.23
NDM group	1.9±0.85	2.02±0.41	-0.13±0.77
CAL (mm)			
DM group	3.71±0.62	2.85±0.66†	0.85±0.28
NDM group	3.30±0.90	2.92±0.48†	0.37±0.63

*Statistically significant differences ($P < 0.05$) were noted between DM and NDM groups for PD. †Statistically significant differences ($P < 0.05$) between baseline and 3 months values to DM and NDM groups for PD and CAL DM=Diabetes mellitus, NDM=Nondiabetic mellitus, GR=Gingival recession, CAL= Clinical attachment level, PD=Probing depth

differences for IL-6 levels ($P < 0.05$) were detected between DM and NDM groups at baseline and 3 months follow-up (Mann-Whitney test). Nevertheless, the number of sites detected with IL-6 was reduced. At the beginning of study, 40% and 45% of sites presented IL-6 in NDM and DM groups, respectively, but only 20% of the sites presented this interleukin at the final exam in both groups.

DISCUSSION

In the present study, DM and NDM groups with generalized chronic periodontal disease were selected and treated by full mouth scaling and root planning to verify whether there were changes in metabolic control, periodontal status, and IL-6 levels between DM and NDM groups and baseline and 3 months after periodontal therapy. Periodontal status and IL-6 levels reveal similar responses after periodontal therapy in both groups. Improvements of HbA1c and increased of

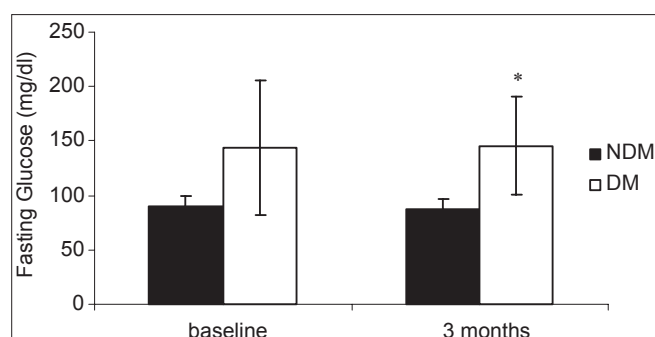


Figure 1: Mean values and standard deviations of fasting glucose level (mg/dl) for DM and NDM patients at baseline and 3 months after full-mouth scaling and root planning. *Statistically significant reductions ($P<0.05$) were detected between DM and NDM

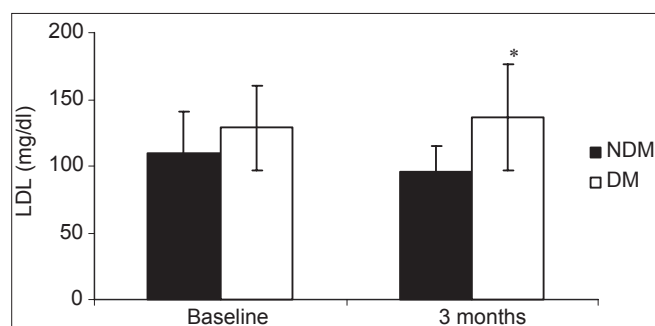


Figure 3: Mean values and standard deviations of low-density lipoprotein (LDL mg/dl) for DM and NDM group at baseline and 3 months after full-mouth scaling root planning. *Statistically significant differences to LDL ($P<0.05$) were detected between DM and NDM

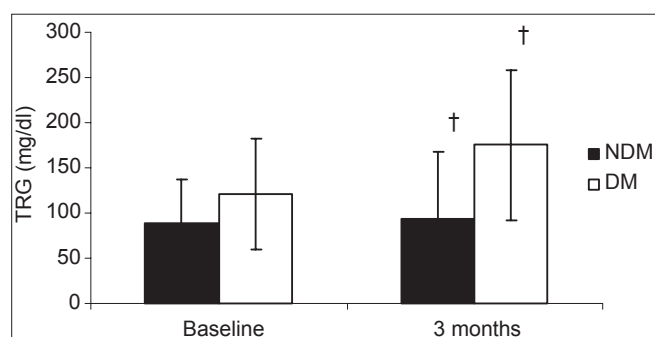


Figure 5: Mean values and standard deviations of triglycerides (TRG mg/dl) for DM and NDM group at baseline and 3 months after full-mouth scaling root planning. †Statistically significant increased to TRG ($P<0.05$) were detected between baseline and 3 months to DM and NDM

LDL were found in DM group after 3 months after full-mouth scaling and root planning.

Ternoven and Oliver^[16] evaluated the long-term control of diabetes and periodontitis and reported that uncontrolled diabetes patients should present more calculus and extensive periodontal pocket. According to these observations in the initial exam of this study, found at baseline, more number of sites with periodontal disease, height PI and GI almost 83% and 61%, respectively, and attachment loss to DM group, uncontrolled diabetes

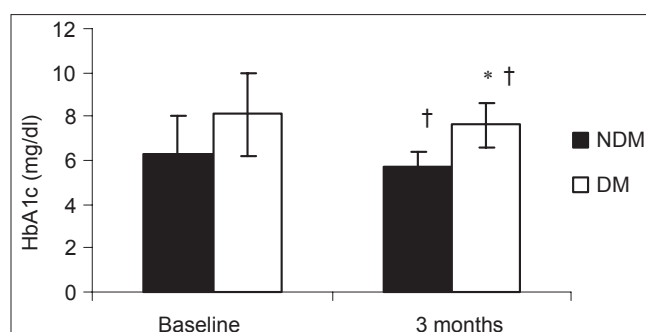


Figure 2: Mean values and standard deviations of glycated a-hemoglobin (HbA1c mg/dl) for DM and NDM group at baseline and 3 months after full-mouth scaling root planning. †Statistically significant differences to HbA1c ($P<0.05$) were detected between DM. *Statistically significant reductions to HbA1c ($P<0.05$) were detected between baseline and 3 months to DM and NDM

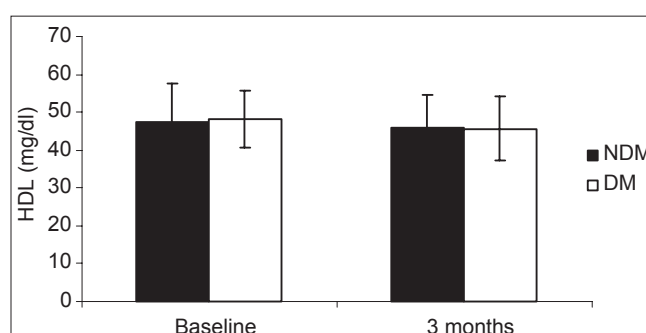


Figure 4: Mean values and standard deviations of high-density lipoprotein (HDL mg/dl) for DM and NDM group at baseline and 3 months after full-mouth scaling root planning

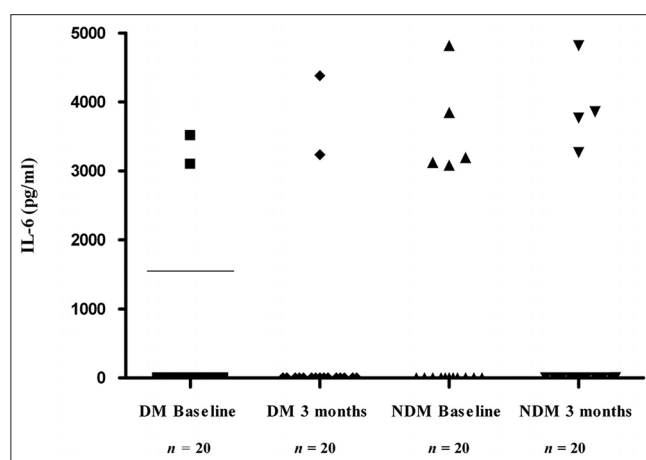


Figure 6: Medium of interleukin 6 (IL-6) cytokine production of gingival crevicular fluid for DM and NDM group at baseline and 3 months after full-mouth scaling root planning. No Statistically significant differences to IL-6 ($P<0.05$) were detected between DM and NDM and baseline and 3 months (Mann-Whitney test)

type 2, when compared NDM group, Tables 1-3, respectively. However, no differences were found to PD, GR, CAL between DM and NDM groups, but statistically significant reductions of clinical parameters were found after 3 months.

The benefit of periodontal therapy by full-mouth scaling and root planning in a single session was previously reported by Da Cruz *et al.*,^[14] which also showed significant reductions in clinical parameters when treated for DM type 1 group. Although no effect on the glycemia control was observed. However, in this study the same methodological aspect were repeated in type 2 diabetes patients and improvements of HbA1c were found. These results suggest that type 1 diabetes should have other variables involved in the control of diabetes than type 2 diabetes. Additional advantages were reported by Da Cruz *et al.*^[14] in the aspects of advantage of full mouth root planning when compared with the conventional therapy, it was effective to reduce the number of scaling sessions, i.e., the bacterial plaque and calculus removal occur in just one appointment and when it is associated with a rigorous oral hygiene control the periodontal clinical results can be maintained.

Controversies about the influence of periodontal treatment in metabolic control have been discussed.^[3,6,7] Herring and Shah,^[17] Taylor^[18] and Mealey and Oates,^[19] reported improvements on glycemia control occur due to the reduction of tissue inflammation after periodontal treatment. Rodrigues *et al.*^[20] Kiran *et al.*^[21] Faria-Almeida *et al.*^[22] and Schara *et al.*^[23] reported statistically significant reduction of HbA1c after 3 or 6 months periodontal treatment in diabetic patients. However, Kawamura *et al.*^[24] Al-Mubarak *et al.*,^[25] and Da Cruz *et al.*^[14] did not find significant differences to glycemia control in DM group after the periodontal treatment. In this study, at the initial exam were selected uncontrolled diabetics type 2 and after 3 months the periodontal treatment, alone, was capable of improving metabolic control by analysis of HbA1c, Figure 2, although fasting glucose levels did not changes, Figure 1. Soskolne and Klinger^[8] suggest that a meticulous control of the hyperglycemia is necessary to consider the levels of glycated serum proteins, especially HbA1c which because its incorporation in to the red blood cells, gives an indication of the serum glucose levels over the proceeding 2-3 months.

Other metabolic parameters evaluated in this study are the levels of LDL, HDL, and TRG. The levels of LDL/HDL did not change between initial and 3 months after the periodontal therapy. Even though, the levels of LDL were high to DM group than NDM at baseline. The levels of TRG were high at the beginning of the study and increased after 3 months of periodontal therapy to DM group. According to these results, Iacopino,^[6] suggests that diabetes type 2 patients are prone to elevated LDL/TRG, because of diabetes and hyperlipidemia is often accompanied. Recent studies suggest that local chronic and acute systemic infections have to induce profound changes in plasma cytokines and hormones, leading to a catabolic state altered lipid metabolism.^[6,26] Herzberg *et al.*,^[27] Colombo *et al.*,^[28] Haraszthy *et al.*,^[29] reported that a localized oral infection

such as periodontitis, can lead to generalized alterations in lipid metabolism.

In periodontitis, proinflammatory cytokines IL-1 β , TNF- α , and IL-6 are produced in response to plaque bacteria. IL-1 β , TNF- α , IL-6 are mediators of tissue destruction that induce degradation of connective tissue and resorption of alveolar bone.^[30] Persistent elevations of IL-1 β , TNF- α , and IL-6 in the diabetic state have an effect on the liver and stimulate the realization of acute-phase proteins, produce the dysregulation of lipid metabolism associated with diabetes type 2 and have effect on the pancreatic beta cells.^[31]

The volume of cytokine in the GCF is proportional to the degree of tissue inflammation and can be reduced after periodontal treatment.^[32] Navarro-Sanchez *et al.*^[33] reported the results of the efficacy of nonsurgical periodontal therapy between type 2 diabetes mellitus and nondiabetes patients above periodontal status, glycemia control and levels of IL-1 β and TNF- α . The author found similar response to both group DM and NDM, and improvements in glycemia control. The results of the authors suggest that there were no differences found between groups DM and NDM, and baseline and 3 months after the periodontal therapy. To levels of IL-1 β and TNF- α , significant reduction were reported after 3 and 6 months evaluations, although no differences were found between groups DM and NDM.

In the present study the IL-6 levels in the GCF were analyzed, and no differences were found between initial and final exams and between DM and NDM group after full mouth root planning. Mengel *et al.*^[34] and Buhlin *et al.*^[35] reported that periodontitis has been associated with increased circulating levels of IL-6. This increase appears to be correlated with disease severity.^[35] Furthermore, D'Aiuto *et al.*^[36] reveals that periodontal treatment can decrease inflammatory mediators due to inflammation control. Forner *et al.*^[37] evaluated the level of IL-6 after scaling and root planning and concluded that after 8 h the plasma concentration had increased. These results supported the presence of bacteremia after periodontal procedures. Adrianakaja *et al.*^[38] evaluated the levels of IL-6 in 725 subjects, NDM and DM type 2 with periodontal healthy or gingivitis and concluded that high levels of IL-6 were detected in DM group when biofilm was presented. Patricia *et al.*^[39] found significantly reduced IL-6 serum levels (by 48%) following the significant improvements in the clinical (PD, CAL, and BOP) and metabolic (HbA1c) measurements after periodontal therapy associated to doxycycline in diabetic type 2 patients after 3 months. The authors suggest that reductions of IL-6 levels were accompanied with the reductions of HbA1c. However, Talbert *et al.*^[40] investigated if scaling and root planning (SRP) could reduce IL-6 levels and TNF- α in diabetes type 2 population after 3 months and concluded that an increase in IL-6 levels and TNF- α could be found followed by SRP, but this result was not

statistically significant and they did not show the hypothesis of reduction agreement with the results of this study.

The findings of the present study should be considered with caution due to the relatively small sample size, however, this study was based on statistical analysis of clinical parameter relevance that calculated small differences between means of groups of 4% for PI (power analysis PI 4% = 0.9289), 4% for GI (power analysis GI 4% = 0.8199), 1 mm for PD (power analysis PD = 0.8749), 1 mm for GR (power analysis GR = 0.9989), and 1 mm for CAL (power analysis CAL = 0.9020), considering 5% of type I error ($\alpha = 0.05$). The power analyses were calculated based on means and standard deviations of control groups and the minimum power were 0.81 ($\beta = 0.19$) for all clinical parameters. Otherwise, no other published study has carried out similar analysis in diabetic patients submitted to scaling and root planning therapy in a single session.

CONCLUSION

Within the limits of this study, it can be concluded that periodontal therapy was effective to control the periodontal disease. Significant improvement of periodontal status was found in both groups DM and NDM after 3 months, but no significant changes were found between DM and NDM groups for gain of attachments. The metabolic control presented reduction of HbA1c to DM group after periodontal treatment and it is in accordance to the literature. However, LDL levels were still high and the TRG was increased in DM group after 3 months periodontal treatment. Therefore, confirmatory studies are needed to verify if LDL/TRG levels could be maintained for long-term evaluations.

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