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Effects of periodontal non-surgical therapy plus azithromycin on glycemic control in patients with diabetes: a randomized clinical trial

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Background and Objective: Periodontitis may alter the systemic condition in patients with diabetes and hence interfere with glycemic control. The objective of this study was to determine the quantifiable changes in glycated hemoglobin (HbA1C) after periodontal non-surgical therapy plus azithromycin in a mixed population of patients with poorly controlled diabetes.

Materials and Methods: One hundred and five patients were randomized to receive non-surgical therapy plus azythromycin (AZ-Sca =33), non-surgical therapy plus placebo (PB-Sca = 37) and supragingival prophylaxis plus azithromycin (AZ-Pro = 35). Glycated hemoglobin, glycemia and periodontal parameters were measured at baseline, 3, 6 and 9 mo after treatment.

Results: Periodontal parameters were improved in the AZ-Sca and PB-Sca groups as compared to the AZ-Pro group. A greater reduction in probing depth was observed in the AZ-Sca as compared to the PB-Sca group. Improvement in clinical attachment level was similar between AZ-Sca and PB-Sca groups. A reduction from 8.0% to 7.2% (Δ0.8%; $p < 0.05$) in HbA1C was observed in the AZ-Sca at 9 mo as compared to the PB-Sca group in which the reduction was from 7.9% to 7.6% (Δ0.3%). There was no decrease in HbA1C in the AZ-Pro group over time. Mean glycemia values decreased from 195 mg/dL to 159.2 mg/dL (Δ35.8 mg/dL; $p < 0.05$) in the AZ-Sca group whereas a decrease from 194 mg/dL to 174.8 mg/dL (Δ19.2 mg/dL) in the PB-Sca group at 9 mo was observed. There were no differences between the AZ-Sca and PB-Sca groups for glycemic parameters. No improvement in glycemic values in the AZ-Pro group was observed.

Conclusions: A modest improvement in glycemic control was detected with a trend towards the use of non-surgical therapy plus AZ as compared to the placebo.

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A bidirectional association between periodontal disease and diabetes has been proposed (1). First, the prevalence of periodontitis is higher in individuals with diabetes than in healthy subjects and with increased risk of worsening the periodontal condition over time (2–4). Secondly, studies have shown that the control of glycemia could be affected by the establishment and severity of periodontitis (5,6). Higher and sustained hyperglycemia leads to production of advanced glycation end products that are implicated in the production of matrix metalloproteinase-1 and inflammatory cytokines in patients with diabetes and periodontitis (7,8).

Initial studies reported a reduction in the use of insulin and glycated hemoglobin (HbA1C) after periodontal therapy in patients with type 1 and 2 diabetes (9–11). Recent comparative and randomized controlled clinical studies have helped confirm the benefits of good periodontal care in the control of glycemia in patients with diabetes (12–14). A meta-analysis (15) demonstrated a weighted mean difference of ΔHbA1C before and after therapy of −0.40% (95% CI −0.77 to −0.04%, $p = 0.03$) favoring periodontal intervention in patients with type 2 diabetes suggesting an improvement in glycemic control.

The use of systemic antibiotics has been suggested as a co-adjuvant to non-surgical debridement for the treatment of periodontitis but use in patients with diabetes has not been fully studied. Rodrigues *et al.* (12) found no benefits of using amoxicillin/clavulanic acid on the glycemic control in patients with type 2 diabetes. On the contrary, O'Connell *et al.* (16) observed a reduction of 1.5% HbA1C levels with the use of systemic doxycycline plus scaling and root planning as compared to the placebo group (0.9%).

Azithromycin (AZ) is a macrolide that has been used in medicine for the treatment of several types of infections such as middle ear and respiratory tract infections. It is accumulated in macrophages and polymorphonuclear neutrophils and has an anti-inflammatory effect (17,18). There are studies that support the use of AZ for the treatment of periodontitis with good clinical results (19–21). A recent study (22) over a 9 mo follow-up period reported a significant reduction in clinical outcome with the adjunctive use of 0.5% AZ as a controlled drug delivery system. To our knowledge, there are no available controlled clinical trials that use adjunctive systemic AZ and glycemic control in patients with diabetes.

Considering that both patients with type 1 and 2 diabetes are equally susceptible to periodontal disease (23–25) and as the main etiopathogenic mechanism associated with periodontitis are the high levels of blood glucose (8,26), this study aimed to determine the quantifiable changes in HbA1C after periodontal non-surgical therapy plus AZ in a mixed population of patients with poorly controlled diabetes.

Material and methods

A three-group, double blind, randomized clinical trial was designed (Clinical Trial identifier NCT01271231). Patients attending the diabetes program at the San Vicente de Paul Hospital (Medellin, Colombia) were invited to participate in the study between January 2011 and July 2012. The Institutional Review Board (Faculty of Dentistry – IRB-020-2009) approved the study protocol following the guidelines of the Helsinki declaration. Each patient signed an informed written consent at enrolment.

Patients were examined for the following inclusion criteria: > 18 years of age, confirmed diagnosis of type 1 and 2 diabetes with $\geq$ 2 years duration (27) and having a minimum of 10 teeth present. Moderate periodontitis was defined as two or more interproximal sites with clinical attachment level (CAL) $\geq$ 4 mm, not on the same tooth, or two or more interproximal sites with probing depth (PD) $\geq$ 5 mm, not on the same tooth (28). Participants were excluded if they received periodontal treatment and antibiotic therapy in the previous 3 mo, presented with malignant diseases, rheumatoid arthritis, treatment with bisphosphonates or cyclosporine, had coronary heart disease, HIV and were pregnant. The treatment of diabetes was in charge of the consulting physician and patients took several medications, including those directed for glucose control (insulin, metformin, glibenclamide) and other medications for hypertension (enalapril, captopril, losartan) and cholesterol control (statins). The mean duration of diabetes was 13 years.

A sample of 90 patients for the study was calculated to detect a 0.7% (0.7 units) in HbA1C difference between treatments with a 0.05 level of significance (two-tailed) and 85% power. A 10% increase in the samples was estimated to compensate for dropouts. To achieve a balance between groups at baseline regarding sex, a restricted randomization was performed by use of a computer-generated table with permutations in blocks of four and with stratification by gender by one of the authors independent of the clinical part of the study (JEB).

Clinical examination and interventions

A full periodontal examination was carried out by two clinicians (CAO, SPO) and periodontal interventions by three clinicians (FLY, NR, MAB), which were previously standardized and calibrated (intraclass and interclass > 0.80). Six sites were examined around each tooth, excluding third molars using a marked UNC-15 probe (USA Delta, Chicago, IL, USA). Gingival margin, PD (mm), CAL(mm), bleeding on probing (% sites) and plaque index (% surfaces) were recorded. HbA1C (%) and fasting glycemia (mg/dL) were measured at baseline in all patients.

Patients were randomized to the following groups:

1. Azithromycin 500mg/day for 3 days plus subgingival scaling (AZ-Sca).
2. Placebo 500mg/day for 3 days plus subgingival scaling (PB-Sca).
3. Azithromycin 500mg/day for 3 days plus supragingival prophylaxis (AZ-Pro).

Subgingival scaling was performed in a single session with an ultrasonic

device (Cavitron; Dentsply, York, PA, USA) at medium intensity until the root surface was smooth. Supragingival prophylaxis was completed with polishing paste and rubber cups and was repeated in the AZ-Pro group 1 wk later. Patients were instructed to take one AZ or placebo tablet daily for three consecutive days starting the day of intervention and to report any side effects or failure to adhere to the therapy.

AZ and placebo tablets were identical and were given to patients in an opaque sealed and coded envelope that resulted from the randomization process. Both patients and clinicians performing therapy and examination were blind to the type of pharmacological treatment. All periodontal and diabetic parameters were measured at 3, 6 and 9 mo and received supragingival prophylaxis at each post-treatment appointment. All patients in the AZ-Pro group received subgingival scaling at the end of the study.

Statistical analysis

Intention-to-treat analysis was performed. Demographic information and periodontal clinical parameters are presented as the mean ± SD. The primary outcomes were the average reduction (Δ) in HbA1C and glycemia values at 3, 6 and 9 mo. HbA1C and glycemia are presented as the mean ± SD. The difference (Δ) for PD and CAL between baseline and 9 mo examinations between groups are presented as the median (IQ range) and assessed with the Mann–Whitney test. Differences for repeated measurements and between groups were determined using the two-tailed paired *t*-test and the unpaired *t*-test, respectively. A non-parametrical test was used when appropriate. Statistical software (GraphPad Prism version 5.00 for Windows; GraphPad Software, San Diego, CA, USA) was used to analyze all data. Statistical differences were assumed when $p < 0.05$.

Results

Figure 1 shows the flow chart of patient inclusion and examination. A total of 105 patients were randomized to the AZ-Sca ($n = 33$), PB-Sca ($n = 37$) and AZ-Pro ($n = 35$) groups. Groups were balanced with more female patients than male participants with a mean age of 57 years old (Table 1). The proportion of patients with type 2 diabetes was higher than type 1 diabetes in all groups but difference was non-significant. Patients had mean diabetes duration of 14 years. Only one patient reported gastrointestinal discomfort in the placebo group with the last tablet. Mean baseline HbA1C values were similar between patients with types 1 and 2 diabetes (Table 2).

Clinical periodontal parameters are presented in Table 3. Mean bleeding on probing, PD and CAL were improved in the AZ-Sca and PB-Sca as compared to the AZ-Pro group. However, a greater reduction in PD (median Δ0.71 mm; $p < 0.05$) and number of sites with PD $\geq$ 4 mm was observed in the AZ-Sca group as compared to the PB-Sca (median Δ0.39 mm) group at 9 mo. Improvement in CAL was similar between AZ-Sca and PB-Sca groups. The reduction in plaque scores was minimal in all groups at 9 mo. The AZ-Pro group did not present any improvement in PD and CAL over time.

Figures 2 and 3 show the effects of periodontal therapy on glycemic parameters. Overall, patients had a regular/poor control of glycemia. A reduction from 8.0% to 7.2% (Δ0.8%; $p < 0.05$) in HbA1C was observed in the AZ-Sca at 9 mo as compared to the PB-Sca group in which the reduction was from 7.9% to 7.6% (Δ0.3%). There was no decrease in HbA1C in the AZ-Pro group over time (Fig. 2). Mean glycemia values decreased from 195 mg/dL to 159.2 mg/dL (Δ35.8 mg/dL; $p < 0.05$) in the AZ-Sca group whereas a decrease from 194 mg/dL to 174.8 mg/dL (Δ19.2 mg/dL) in the PB-Sca group at 9 mo was observed. There

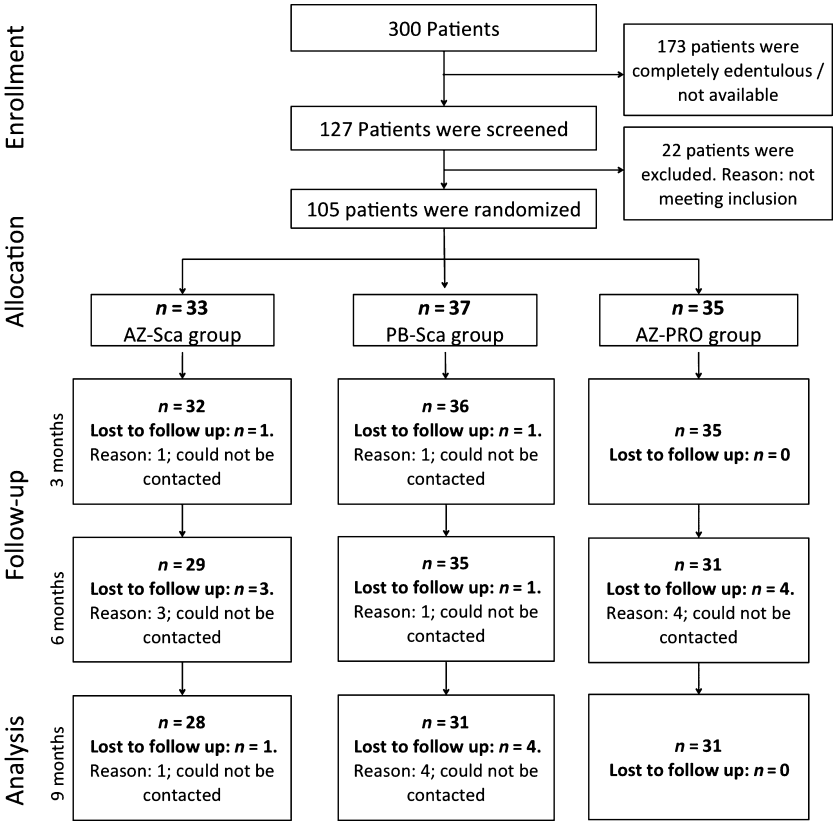

Fig. 1. Flow chart of patient inclusion and assessment. AZ-Sca, azithromycin 500 mg plus subgingival scaling; PB-Sca, placebo 500 mg plus subgingival scaling; AZ-Pro, azithromycin 500 mg plus supragingival prophylaxis.

Table 1. Demographic characteristics of patients according to intervention group

	AZ-Sca	PB-Sca	AZ-Pro	p^a
No. of patients	33	37	35	NS
Sex F/M	22/11	27/10	25/10	0.57
Age (mean ± SD)	55.9 ± 12.6	58.2 ± 11.1	56.14 ± 11.32	0.54
No. patients with type 1 diabetes (%)	10 (30.3)	17 (45.9)	12 (34.2)	NS[b]
No. of patients with type 2 diabetes (%)	23 (69.7)	20 (54.1)	23 (65.8)	NS[b]
Diabetes duration (mean ± SD)	14.0 ± 10.5	13.6 ± 9.3	14.8 ± 13.1	0.53
Number of teeth (mean ± SD)	20.9 ± 5.0	21.1 ± 4.7	19.7 ± 6.6	0.52

AZ-Sca, azithromycin 500 mg plus subgingival scaling; PB-Sca, placebo 500 mg plus subgingival scaling; AZ-Pro, azithromycin 500 mg plus supragingival prophylaxis; NS, non-significant.
[a]One-way ANOVA.
[b]Chi-squared test.

Table 2. Baseline glycated hemoglobin values according to each group

Group	Type 1 diabetes	Type 2 diabetes	p^a
AZ-Sca (mean ± SEM)	8.2 ± 0.8	7.8 ± 0.2	0.80
PB-Sca (mean ± SEM)	8.2 ± 0.8	7.8 ± 0.4	0.88
AZ-Pro (mean ± SEM)	7.8 ± 0.5	7.9 ± 0.4	0.89
Total (mean ± SEM)	8.0 ± 0.4	7.8 ± 0.2	0.80

AZ-Sca, azithromycin 500 mg plus subgingival scaling; PB-Sca, placebo 500 mg plus subgingival scaling; AZ-Pro, azithromycin 500 mg plus supragingival prophylaxis.
[a]Two tailed Student's *t*-test.

were no statistical differences between the AZ-Sca and PB-Sca groups for glycemic parameters. No improvement in glycemic values in the AZ-Pro group was observed (Fig. 3).

Discussion

This study showed that non-surgical therapy results in a modest improvement in glycemic control in patients with diabetes. Nonetheless, a greater reduction in HbA1C values was observed with the use of AZ as co-adjuvant to periodontal therapy as well as a reduction in periodontal parameters (PD, CAL) at 9 mo. The greatest reduction in glycemic parameters were observed at 3 mo in the groups receiving non-surgical therapy and maintained at 9 mo. We did not find any differences with regards of the type and duration of diabetes in this study.

Periodontal disease is an infectious and chronic inflammatory process that has an impact on the systemic health of individuals (29). Periodontitis has been associated with increased levels of inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-17 and IL-23 in patients with diabetes (30,31). This increased production of inflammatory cytokines for long periods of time, results in insulin resistance as demonstrated in studies in animals (32) and humans (3,33,34). Consequently, periodontal disease could interfere with the glycemic control in patients with impaired fasting glucose or with established diabetes. The resulting hyperglycemia in patients with diabetes and periodontitis produces increased levels of advanced glycation end products (26,35), which are associated with the biological mechanisms of periodontal breakdown. This in turns leads to a vicious cycle where the two diseases are connected in a two-way relationship (36).

Non-surgical periodontal therapy may influence the systemic conditions of patients with diabetes through the reduction of periodontal inflammation and infection. A recent randomized clinical trial showed that non-surgical periodontal therapy was effective in reducing circulation and periodontal clinical markers of inflammation in patients with type 2 diabetes. A trend in improved glycemic control after periodontal treatment was observed (14). Another study found that serum levels of C-reactive protein, tumor necrosis factor-α, IL-6, fasting plasma glucose, HbA1C, fasting insulin and homeostasis model of assessment-insulin resistance index decreased after periodontal treatment in patients with poorly controlled diabetes (37). To date, this is the first randomized clinical trial to assess the clinical effects of non-surgical therapy with adjunctive AZ. The primary outcome was HbA1C because it reflects the glycemic control over a 3 mo period. Although non-surgical therapy helped in reducing HbA1C values and periodontal clinical parameters, the improvement was better with the use of adjunctive AZ in our study population, which was characterized by the long duration of diabetes and moderate periodontitis. In contrast, the AZ-Pro group did not present improvement in any of the clinical parameters. This difference highlights the adjunctive effects of antibiotics when used simultaneously with the removal of the subgingival biofilm to reduce periodontal parameters.

The reduction in HbA1C in the AZ-Sca group (Δ0.8%) as compared to the PB-Sca group (Δ0.3%) is consistent with the results from the only meta-analysis performed in this field (Δ0.40%) (15). This supports the concept that reducing periodontal parameters could help improve glycemic control in patients with diabetes. But the results should be considered carefully, as the observed improvement in glycemic control could also be due to diet, physical exercise, motivation of patients and other variables. Differences in initial glycemic values, therapeutic approach and severity of periodontal destruction may also have to be considered. A concern in this clinical trial is the ability to apply findings to the general population with diabetes. Our study sample was certainly small and therefore may express some variability and selection bias. In addition, confounders such as body mass index, central adiposity,

Table 3. Periodontal clinical parameters from baseline to 9 mo in each study group

	AZ-Sca				PB-Sca				AZ-Pro			
	Baseline	3 mo	6 mo	9 mo	Baseline	3 mo	6 mo	9 mo	Baseline	3 mo	6 mo	9 mo
No. of patients	33	32	29	28	37	36	35	31	35	35	31	31
BOP (mean ± SD)	52.4 ± 26.0	29.2 ± 17.1	25.5 ± 16.5	28.8 ± 19.7	45.7 ± 27.8	34.1 ± 20.4	27.8 ± 18.3	24.8 ± 20.4	43.8 ± 24.1	29.1 ± 17.1	30.8 ± 17.8	29.6 ± 15.7
Mean ± SD no. of sites with PD ≤ 3 mm (%)	103 ± 35.1 (85.8%)	119 ± 36.8 (91.4%)	120.3 ± 32.7 (95.2%)	120.5 ± 31.2 (96.1%)	107.3 ± 38.9 (83.3%)	111.9 ± 35.2 (87.2%)	112 ± 35.3 (88.1%)	117 ± 34.2 (91.4%)	106.4 ± 42 (88.0%)	112.8 ± 41.6 (94.3%)	116.1 ± 39.9 (94.4%)	116.1 ± 39.1 (94.2%)
Mean ± SD no. of sites with PD ≥ 4 mm (%)	22.0 ± 15.4 (19.2%)	4.3 ± 7.8 (4.0%)	2.6 ± 4.5 (2.1%)	3.5 ± 5.2 (3.7%)	19.9 ± 15.3 (18.4%)	7.5 ± 12.7 (6.4%)	6.7 ± 11.7 (5.9%)	4.6 ± 10.3 (4.8%)	13.7 ± 12.3 (15.4%)	13.1 ± 6 (15.1%)	13.2 ± 5.8 (15.1%)	13.4 ± 5.9 (15.2%)
PD (mean ± SD)	2.7 ± 0.6	2.3 ± 0.6	2.1 ± 0.3	2.1 ± 0.3	2.6 ± 0.7	2.5 ± 0.5	2.3 ± 0.5	2.2 ± 0.5	2.4 ± 0.6	2.2 ± 0.4	2.2 ± 0.3	2.1 ± 0.3
ΔPD Baseline-9 mo (median (IQ range))	0.71 (0.08–0.94)[a]				0.39 (−0.20–0.62)				0.20 (−0.14–0.51)			
CAL (mean ± SD)	2.8 ± 0.8	2.5 ± 0.8	2.6 ± 0.7	2.6 ± 0.7	3.1 ± 1.16	3.0 ± 1.1	3.0 ± 1.25	2.8 ± 1.0	2.9 ± 1.1	2.8 ± 0.9	2.8 ± 0.9	2.7 ± 1.0
ΔCAL Baseline-9 mo (median (IQ range))	0.17 (−0.19–0.39)				0.14 (−0.14–0.58)				0.11 (−0.36–0.35)			
Plaque (mean ± SD)	55.1 ± 14.6	42 ± 18.6	40.4 ± 18.6	45.5 ± 16.9	54.4 ± 19.1	39.53 ± 16.7	40.3 ± 20.9	39.9 ± 20.8	58.6 ± 19.5	45.0 ± 20.0	41.1 ± 16.4	47.2 ± 18.7

AZ-Sca, azithromycin 500 mg plus subgingival scaling; PB-Sca, placebo 500 mg plus subgingival scaling; AZ-Pro, azithromycin 500 mg plus supragingival prophylaxis; BOP, bleeding on probing; CAL, clinical attachment level; PD, probing depth.

[a]Mann–Whitney test, $p = 0.036$ (Δ).

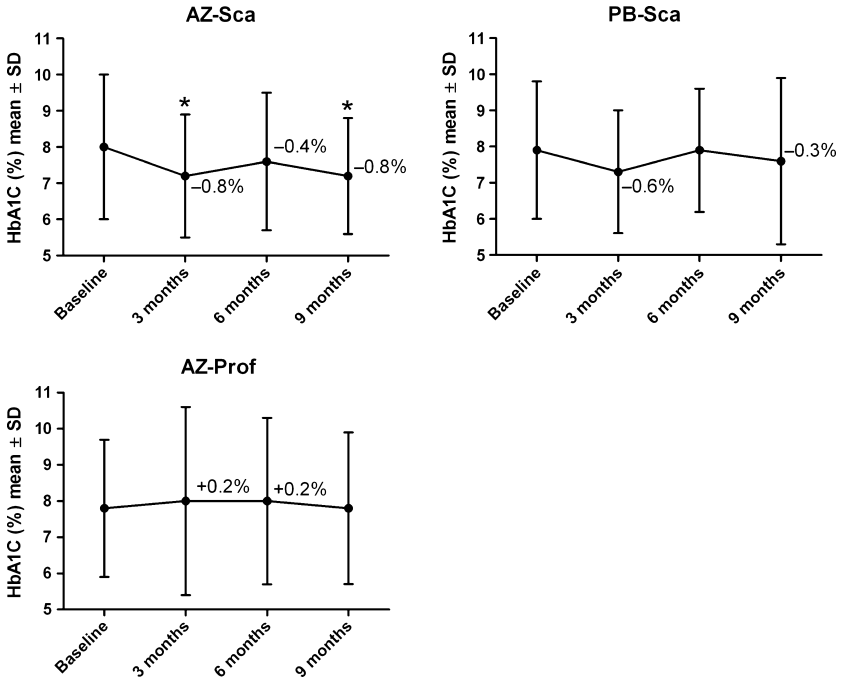

Fig. 2. Changes in HbA1C after treatment from baseline to 9 mo. Values are presented as the mean (SD). *Two-tailed paired *t*-test $p < 0.05$. AZ-Sca, azithromycin 500 mg plus subgingival scaling; PB-Sca, placebo 500 mg plus subgingival scaling; AZ-Pro, azithromycin 500 mg plus supragingival prophylaxis; HbA1C, glycated hemoglobin.

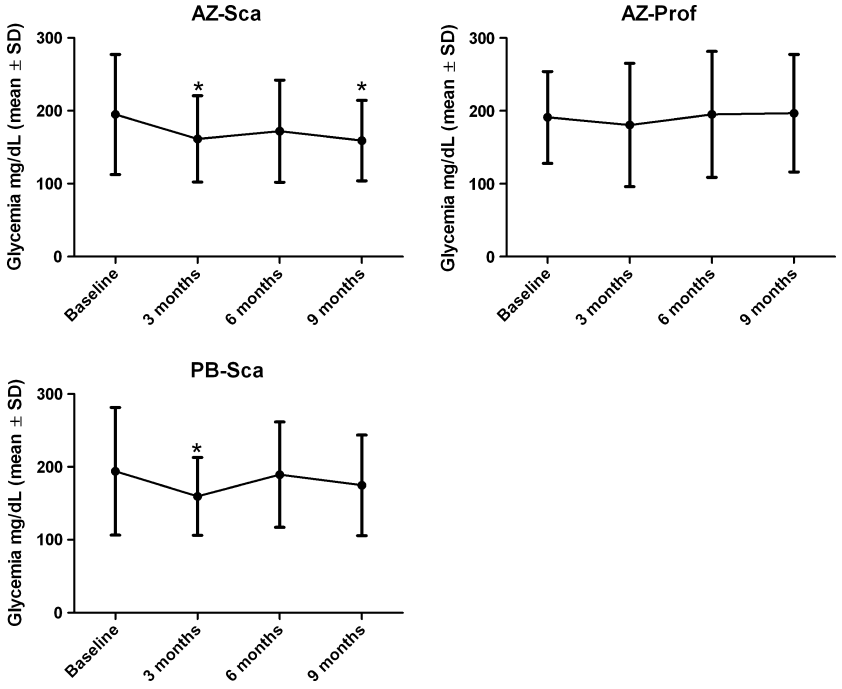

Fig. 3. Changes in glycemia after treatment from baseline to 9 mo. Values are presented as the mean (SD). *Two-tailed paired *t*-test $p < 0.05$. AZ-Sca, azithromycin 500 mg plus subgingival scaling; PB-Sca, placebo 500 mg plus subgingival scaling; AZ-Pro, azithromycin 500 mg plus supragingival prophylaxis.

smoking and serum triglycerides were not assessed. Additional large sample studies with the assessment of potential confounders are necessary to support if the treatment of periodontal disease could help in the control of glycemia and the prevention of complications of diabetes in adults.

In conclusion, a modest improvement in glycemic control was detected with a trend towards the use of non-surgical therapy plus AZ as compared to the placebo. Nonetheless, improving and maintaining periodontal health are important objectives by themselves and confirmatory studies in patients with diabetes and severe generalized periodontitis are still warranted.

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