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Assessment of glycosylated hemoglobin (HbA1c) in type 2 diabetics before and after non-surgical periodontal treatment. A short-term follow-up study

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Aim: To evaluate glycosylated hemoglobin (HbA1c) before and after non-surgical periodontal treatment in patients with type 2 diabetes mellitus (DM-2). **Methods:** Twenty subjects diagnosed with periodontitis and DM-2 were treated using an NSPT protocol. Periodontal examination and blood measurements were performed at baseline and after three months. Patients with DM-2 treated for at least a year, with at least 10 teeth and with probing depths between 4-6 mm in more than three regions were included. The variables evaluated were HbA1c in blood and periodontal measures (probing depths, insertion level, gingival bleeding on probing, dental plaque, calculus, inflammation, clinical attachment and mobility). All patients were informed of the conditions of the therapy used. Scaling and root planning (SRP) of the full mouth was performed using an ultrasonic scaler and hand instrument under local anesthesia, supragingival prophylaxis and oral hygiene instruction. Also, 0.12% chlorhexidine digluconate was formulated twice a day for two weeks. Statistical analyses were performed using StataIC 14. The values are shown as the mean, median and standard deviation (SD) or interquartile rank (IR), and $p<0.05$ was considered significant. **Results:** Twenty subjects completed the three-month follow-up and were included in the analysis. Three months after the non-surgical periodontal treatment, most periodontal parameters had a meaningful reduction ($p< 0.05$) and a large effect size >0.8. Clinical attachment level showed no improvement. The HbA1c values were not significantly decreased ($p=0.94$). **Conclusions:** Although non-surgical periodontal therapy eliminates local inflammation, it is insufficient to significantly reduce HbA1c levels in a short time period.

Keywords: Diabetes mellitus. Glycosylated hemoglobin. Chronic periodontitis.

Introduction

Diabetes mellitus (DM) is a chronic degenerative disease characterized by the presence of hyperglycemia due to deficits in insulin action or production that affect carbohydrate, protein and lipid metabolism, which leads to long-term development of other systemic complications[1,2]. To determine glycemic control, glycosylated hemoglobin (HbA1C) measurement is used, which is a good indicator of glycemic control. The results are presented as a percentage and are considered normal when they are between 5% and 6%. When HbA1c is 6.5% or higher, it is considered abnormal, and values up to 7% are indicative of poor control[3]. The most frequent oral pathology in diabetics is periodontal disease (PD), with a reported prevalence of up to 60%, that results from poor immune response, especially in those with poor control or uncontrolled diabetes. They can have severe PD with bone loss, a probing depth greater than 4 mm, and loss of clinical attachment[4-7]. In addition, in a poorly controlled patient, saliva and gingival crevicular fluid may contain increased amounts of glucose, which alters the microbiota and dental biofilm. Those changes are related to qualitative modification of subgingival microbiota. Among them, *Actinomyces* and *Aggregatibacter* were associated with periodontitis in diabetic patients.[8,9] Moreover phylotypes such as *Fusobacterium nucleatum, Veillonella parvula, V. dispar* and *Eikenella corrodens* were detected more often in diabetics[1]. Therefore, glucose levels in gingival crevicular fluid alter the oral environment and induce oxidative stress in the gingiva through Advanced Glycation Endproducts (AGEs), a potential mechanism for accelerated tissue injury, which potentiates the proteolytic effect of the periodontopathic bacteria of the subgingival plaque in diabetics[10-13] and triggers local and systemic inflammatory responses.

On the other hand, hyperglycemia associated with diabetes leads to micro- and macrovascular complications that influence the pathophysiology of periodontitis, which causes high levels of inflammatory cytokines such as TNF-alpha, activated C-reactive protein, interleukin-17, -23, and -1B, interferon-y and osteo-regulators associated with bone resorption, causing oxidative stress that impairs insulin sensitivity over time[6,10,13].

It has been proposed that PD plays an important role as a component of the pathogenesis of DM. The two diseases have a bidirectional relationship as poorly controlled DM has an adverse effect on periodontal health. There are studies that suggest that there is an association between the improvement in glycemic control in type 2 diabetic patients and periodontitis after periodontal treatment [4,6,14-18].

In this way, diabetes is considered to be associated with an increase in the incidence and progression of periodontitis, which can worsen the diabetic state. It is possible to confirm that effective control of PD in diabetic patients is possible with changes in lifestyle. The serum levels of AGEs can be reduced, which could reduce insulin resistance and facilitate metabolic control of diabetes[4,5,8,16]. Accordingly, this article tries to answer the question of whether non-surgical periodontal treatment improves the periodontal inflammatory state and glycemic control (HbA1C) in type II diabetic patients in a short time period.

Material and methods

This study was a quasi-experimental study. In the present analysis, 20 patients with DM-2 and periodontal disease were evaluated. The patients were recruited from the metabolic disease center of FOSCAL Bucaramanga-Colombia.

Accepting an alpha risk of 0.05 and a beta risk of 0.1 for a unilateral contrast, 20 subjects are required to detect a difference equal to or greater than 0.6 units of HbA1c[33] assuming a standard deviation of 0.8. The rate of follow-up losses was estimated to be 20%. The type of sampling was incidental until all patients completed the three-month follow-up without delay in May 2017.

The patients were contacted by telephone (583 phone calls). Once inclusion criteria were verified, appointments were assigned for assessment at the Santo Tomás University Bucaramanga-Colombia (96 appointments), and clinical inclusion criteria were applied. Forty patients were included, and nineteen of them had a delay of fifteen days for the baseline or three-month follow-up visit, and one was lost to follow-up. Twenty patients completed the three-month visit and were analyzed without including adherence to periodontal hygiene criteria, as shown in the flowchart (Figure 1).

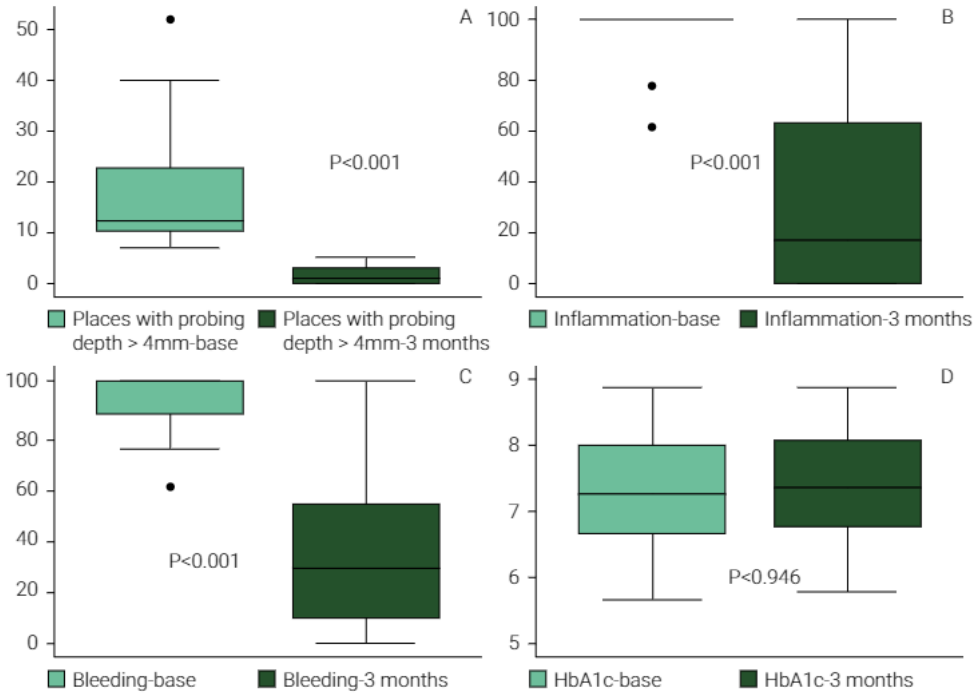

Figure. Baseline and three months values of places with probing depth >4mm (A), Inflammation (B), bleeding (C), and HbA1c (D)

Inclusion and exclusion criteria

Subjects who had been diagnosed with diabetes mellitus type 2 for at least 10 years were included. In addition, subjects had to have an Hba1c between 6.5% and 10%, be aged over 18 years, have a minimum of 10 teeth present, and have a probing depth >4 mm and <6 mm at more than three sites.

Exclusion criteria were anemia; pregnancy; lactation; patients using antibiotic, anti-inflammatory, or immunosuppressive treatment in the last 6 months; those who received periodontal treatment in the last year; and patients with valvulopathy, orthodontic treatment or diagnosed infectious foci.

The variables evaluated were sociodemographic characteristics (sex, age, origin, educational level, body mass index (BMI)) and clinical examination findings including periodontal parameters (calculus (C), gingival bleeding (GB), plaque index (PI), probing depth (PPD), clinical attachment level (CAL), dental mobility (DM) and Hba1c).

The study was reviewed and approved by the CEI-FOSCAL committee # 54-2-19082016

Clinical evaluation

Periodontal parameters were evaluated with a North Caroline periodontal probe.

Dental plaque, calculus and bleeding on probing (POB) were registered for each tooth to calculate percentages. Clinical attachment level (CAL) was calculated by place (6 per tooth) and is presented as an average.

An appointment was made for non-surgical periodontal treatment (NSPT). One operator, different from the person who evaluated the patient, developed the protocol.

NSPT consisted of disinfection of the oral cavity with 0.12% chlorhexidine for 1 minute. Scaling and root planning (SRP) of the full mouth was performed using an ultrasonic scaler and hand instrument under local anesthesia with an ultrasonic scaler with a P-10 long insert tip with a power of 25 Khz. The scaling began with the right sextant and then the left and ended with the anterior sector. The treatment ended with root planning with Gracey curettes, and the periodontal pockets were irrigated with 0.12% chlorhexidine, finishing with supragingival prophylaxis and oral hygiene instructions. All places that needed treatment were treated the same day without restriction on time. The 0.12% chlorhexidine digluconate was formulated twice a day for two weeks.

One week later, a telephone follow-up was carried out to ensure adherence to dental hygiene protocols, and at the 15-day visit, supportive periodontal care, supragingival intervention and SRP were used if necessary.

Metabolic parameters

Blood measures of HbA1c were taken a day before periodontal therapy and a day before the three-month evaluation. Samples were obtained from an antecubital vein. Biochemical assessment of HbA1c was performed in the Clinical Laboratory of Higuera Escalante using the turbidimetric inhibition immunoassay (TINA) technique for hemolyzed whole blood.

Statistical analysis

A descriptive analysis was carried out to estimate the central tendency and dispersion according to the frequency distribution of the data. Categorical variables were summarized with absolute values and proportions. We evaluated HbA1c using the paired sign test or paired Student`s t-test according of the distribution of data. Cohen's kappa coefficient and the interclass correlation coefficient (ICC) were calculated to analyze

the agreement between periodontal measurements. Intraoperative kappa was 0.93 for probing depth >4 mm, and it was 0.781 for bleeding and 0.88 for mobility, and the ICC was 0.855, CI (0.71-0.93) for probing depth.

Data were analyzed using STATA IC/14 software (StataCorp. Stata Statistical Software, TX: StataCorp LP) with a significance level set at 5%.

Results

Ninety-six DM2 subjects were examined. Forty patients were included, and 20 completed the three-month evaluation without delay (Figure 1).

The analyses were conducted with 20 subjects who completed the three-month visit. All patients were from an urban area, and there were 10 men and 10 women, with a median age of 61.6 ±7.4 years old. In all, 40% had a high school level of education, and 50% had a healthy BMI (18.5 – 24.9 kg/m^2). Additionally, 75% had other chronic diseases besides DM-2. Hypertension was the most common at 55% (Table 1).

Table 1. General characteristics of the population

Variables	N(%)
Sex	
Male	10(50)
Female	10(50)
Origin	
Urban	20(100)
Body mass index	
18.5-24.9	10(50)
25-29.9	5(25)
>30	5(25)
Educational level	
Primary	11(55)
High school	8(40)
College	1(5)
Comorbidities	
Yes	15(75)
No	5(25)
Hypertension	
Yes	11(55)
No	9(45)
Cardiac disease	
Yes	4(20)
No	16(80)
Thyroid diseases	
Yes	3(15)
No	17(85)
Gastric diseases	
Yes	2(10)
No	18(90)
Triglycerides	
Yes	1(5)
No	19(95)
Other diseases	
Yes	4(20)
No	16(80)

For medications, 80% of participants used insulin. The most common medicines besides hypoglycemic agents were antihypertensive drugs at 50%. A high percentage of patients had good adherence to diabetes treatment, and 95% were considered adherent to the periodontal treatment (Table 2).

Table 2. Medication use and adherence to treatment

Variables	N (%)	
Medication consumption		
Hypoglycemic agents		
Insulin	16 (80)	
Oral Hypoglycemic agents	4(20)	
Antihypertensive	10(50)	
Cholesterol Medication	6(30)	
Thyroid Medication	3(15)	
Cardiac Medication	9(45)	
Other medicines	6(30)	
Adherence to treatment	**Base**	**3 months**
	N (%)	**N (%)**
Forgot to take medicines		
Yes	7(35)	7(35)
No	13(65)	13(65)
Took medications at specified times		
Yes	16(80)	15(75)
No	4(20)	5(25)
Stopped taking medications if feeling well		
Yes	5(25)	-------
No	15(75)	20(100)
Stopped taking medications if feeling bad		
Yes	19(95)	1(5)
No	1(5)	19(95)
Changed the dose of medication		
Yes	-	6(30)
No	20(100)	14(70)
Used the recommended toothpaste		
Yes	-	20(100)
No		----
Used the recommended mouthwash		
Yes	-	19(95)
No		1(5)
Followed oral hygiene instructions		
Yes	-	19(95)
No		1(5)

Clinical periodontal baseline parameters are presented in Table 3.

Three months after the non-surgical periodontal treatment, periodontal parameters had meaningfully changed in most patients ($p<0.02$), and only CAL was not statistically significantly different, but there was evidence of an increase in the mean (Table 3).

Table 3. Comparison of Periodontal Parameters Before and After Non-Surgical Periodontal Intervention

	Base		3 months		P Value	*d* (IC)
	M(SD)	M(IR)	M(SD)	m(IR)		
Calculus %		82.8(58-100)		24.8(0-54)	<0.001*	1.4(0.77-2.18)
Inflammation %	96.6(10.5)		32.7(37.7)		<0.001+	2.3(1.49-3.1)
Bleeding BOP %		100(88-100)		28.3(10.5-53)	<0.001*	2.2(1.47-3.07)
CAL	3.24(0.99)		3.45(1.21)		0.20+	-0.18(-0.8-0.4)
Plaque %	96.7(9.9)		49.5(32.4)		<0.001+	1.97(1.2-2.7)
Probing depth mean	2.6(0.31)		2.34(0.29)		0.002+	0.86(0.21-1.5)
Probing depth >4 mm mean	4.1(0.12)		2.84(2.31)		0.023+	0.77(0.12-1.4)
Probing depth P >4 mm%		11.8(8.8-21)		1.03(0-2.7)	<0.001*	1.72(0.98-2.4)
Extension %	44.9(21.6)		5.6(7.0)		<0.001+	2.4(1.61-3.2)
Tooth with probing depth >4 mm	8.4(4.2)		1.2(1.23)		<0.001+	2.3(1.50-3.1)
N° of places with probing depth >4 mm	17.3(12.1)		1.65(1.81)		<0.001+	1.8(1.06-2.5)

M: Mean. SD: Standard Deviation. m: median. IR: interquartile rank. + Paired T-test *Paired sign test d: Effect size Cohen´s d. IC confidence interval.

Cohen´s effect size calculation showed a large effect on periodontal clinical measurements except CAL, which showed a negative effect due to the baseline mean being lower than the mean at the three-month evaluation. The effect size on CAL was 0.18, which means a loss of clinical attachment of 0.18 standard deviations after NPST (Table 3).

Table 4 shows the effects of periodontal therapy on glycemic parameters. The mean at baseline was 7.38, SD 0.91, and at three months, the mean was 7.39, SD 0.88 (p= 0.94) (Table 4).

Table 4. Blood tests and changes in Hba1c

HbA1c	M	(SD)	CI	p value	*d* (IC)
Delta Hba1c	-0.01	0.657			
Hba1c base	7.38	0.916	6.95-7.8	0.946*	-0.01(-0.63-0.60)
Hba1c 3 m	7.39	0.887	6.97-7.8		

M: Mean, SD: Standard Deviation, *T test d: Effect size, Cohen´s d. IC: confidence interval.

The clinical effect of periodontal therapy showed significant changes in periodontal parameters such as BOP, inflammation and places with a probing depth >4 mm (all p values <0.001). However, there was no evidence of reduced HbA1c p=0.94 (Graphic 1).

Discussion

Diabetes mellitus is considered a risk factor for periodontal disease, for which the prevalence and severity are higher in poorly controlled diabetic patients[17]. The idea that periodontitis influences glycemic control has been examined in several studies. Due to the mediators released in inflammatory processes that alter sensitivity to insulin, several authors have linked both pathologies in a bidirectional way[21-23].

Different authors, who presented contradictory results [6,22-24,26], analyzed the changes in Hba1c levels among type II diabetic patients who received periodontal treatment. This

study evaluated glycosylated hemoglobin values before and after non-surgical periodontal treatment in patients with DM2 and PD. No additional antibiotic treatments were used, and no evidence of a reduction in HbA1c was found.

These results are in contrast to a meta-analysis[27] that concluded that periodontal therapy for type 2 diabetic patients with periodontitis is favorable and may reduce HbA1c levels 0.40% or more compared to non-intervened subjects. Similarly, Teshome and Yitahe[28] (2016), in a meta-analysis, found a moderate reduction in HbA1c levels in the intervention group, with a random effect of 0.53% in HbA1c after 3-4 months. Other review papers, such as that by Simpson et al.[23], suggested a mean percentage reduction in HbA1c of 0.29% at 3-4 months.

On the other hand, different clinical trials, longitudinal studies and quasi-experimental studies[21,24,29,30] showed reductions in HbA1c at 3, 6, 9 and 12 months after periodontal treatment.

The results of this study are consistent with the ones reported by Engebretson et al.[32] They stated that non-surgical periodontal therapy improves periodontal parameters but does not improve glycemic control in DM-2 patients with moderate or advanced periodontitis, as found by many other authors. [3,13,33-36,]

In the same way, a cohort study developed by Aueyeung et al, in similar conditions to this work, did not find statistical differences in HbA1c changes before and after NSPT.[37]

Many others studies evaluated different strategies to reduce inflammatory effects: oral hygiene, healthy lifestyles and self-control instructions for periodontitis,[31] antibiotics plus periodontal therapy and SRP,[22,39,40,41] topical antibiotics [25,18,44-47] and propolis. [18,48] Some authors found a reduction in HbA1c, and some authors did not find significant changes. [44-46]

These different results could be due to the fact that patients with poor glycemic control improved less than those with better HbA1c control.[34,38] Other researchers have suggested that medication changes for the treatment of diabetes could lead to changes in glycemic control. Nevertheless, Gelato et al.[49] showed that patients with poor glycemic control, HbA1c >8%, may be more susceptible to changes in medication. However, variation in HbA1c values is low during periodontal treatment and therefore should not be considered an influential factor. In the present research, all study participants were taking medication to treat their medical condition, and six had increased medication or dosages of hypoglycemic agents. Nineteen of the participants followed oral hygiene instructions. However, there was no evidence of reduced HbA1c.

It is important to consider which glycosylated hemoglobin reduction values may be clinically significant in the management of diabetic patients and to recognize that any improvement, even if it is not statistically significant, may be favorable for patient treatment. Also, promoting adherence to periodontal treatment with hygiene and adequate habits and the use of chlorhexidine-type mouthwashes, which favor periodontal health and healthy lifestyles, will positively change other metabolic parameters, such as cholesterol and triglycerides, that could interfere with glycemic control.

The limitations of this study include the lack of a control group for analysis for ethical reasons because diabetic subjects with PD experience cardiovascular or cerebrovascular events more frequently[50]. In addition, the strict inclusion and exclusion criteria limited

the patient sample, which does not allow generalization of the results. Also, periodontal treatment did not include topical or systemic antibiotic treatment, and surgical periodontal treatment was not considered because of the difficulty in standardizing protocols. However, the results allow us to broaden the horizon for future research.

Finally, although non-surgical periodontal therapy eliminates local inflammation, it is insufficient to significantly reduce HbA1c levels in a short time period. It is necessary to carry out new studies that include evaluation of other known factors in periodontal management that interfere with glycemic control.

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