Effect of periodontal treatment on glycemic control of patients with diabetes: A systematic review and meta-analysis

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ABSTRACT

Aims/Introduction: The aim of the present study was to investigate whether non-surgical periodontal treatment reduces glycated hemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) levels in diabetic patients.

Materials and Methods: An electronic search was carried out on MEDLINE (through PubMed interface), EMBASE and the Cochrane Central Register of Controlled Trials. Randomized controlled trials with a minimum of 3 months follow up were included. The risk of bias was assessed for each study. A meta-analysis was carried out to evaluate the effect of non-surgical periodontal treatment on HbA_{1c} and FPG levels. The effect of the adjunctive use of antimicrobials was also assessed.

Results: A total of 15 studies were included. A reduction of −0.38% (95% confidence interval [CI] −0.23 to −0.53) after 3–4 months ($P < 0.001$) and of −0.31% (95% CI 0.11 to −0.74) after 6 months ($P = 0.15$) of follow-up was found for HbA_{1c}, favoring the treatment group. Similarly, in treated patients, a significantly greater decrease in FPG was observed in respect to control participants. Such difference amounted to −9.01 mg/dL (95% CI −2.24 to −15.78) after 3–4 months ($P = 0.009$) and −13.62 mg/dL (95% CI 0.45 to −27.69) after 6 months ($P = 0.06$) from treatment, respectively. In participants treated with adjunctive antimicrobials, a non-significant increase of HbA_{1c} was observed 3 months after treatment, whereas FPG decreased by 0.27 mg/dL (95% CI 39.56 to −40.11; $P = 0.99$).

Conclusions: The meta-analysis showed that non-surgical periodontal treatment improves metabolic control in patients with both periodontitis and diabetes. (J Diabetes Invest, doi: 10.1111/jdi.12088, 2013)

KEY WORDS: Diabetes, Metabolic control, Periodontal diseases

INTRODUCTION

Type 2 diabetes mellitus is a highly prevalent metabolic disease that causes an impairment in glycemic control[1]. Such impairment can cause a decrease of polymorphonucleate leukocytes activity and damage to microvascular endothelium, either of which can increase the susceptibility to periodontal disease[2–4].

The presence of a chronic infection, such as periodontitis, might induce an increase of circulating cytokines and soluble factors (such as C-reactive protein [CRP], interleukin-1β [IL-1β], interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α] and prostaglandin-E_2 [PGE_2]), which in turn increases the general inflammatory burden in the organism[5–8]. These events, as a result of low-grade chronic infection, might alter the insulin activity, impairing glycemic control[9,10]. Furthermore, recent epidemiological studies have correlated the presence of periodontal diseases to poor glycemic control in patients with diabetes[11,12].

Since 1960, it has been hypothesized that periodontal treatment can have beneficial effects on glycemic control in diabetic patients with severe periodontal conditions[13]. Both surgical and non-surgical periodontal treatment can decrease the systemic inflammatory burden, allowing better glycemic control[8,14], even if some studies did not report a significant improvement[15,16].

Some systematic reviews described a significant positive effect of periodontal non-surgical treatment on glycemic control despite a lack of robustness and homogeneity among studies[17–19].

The present study aimed at evaluating the effect of non-surgical periodontal treatment (NSPT) on glycemic control in patients affected by diabetes and periodontal diseases.

MATERIALS AND METHODS

Search Strategy

The electronic search was carried out on MEDLINE (through PubMed interface), EMBASE and the Cochrane Central Register of Controlled Trials. A search string was created *ad hoc* combining keywords with the use of boolean operators 'AND' and 'OR'. The search string was (periodont*) AND (diabet* OR 'non insulin dependent diabetes' OR 'niddm' OR 'insulin dependent diabetes' OR 'iddm' OR 'type 1 diabetes' OR 't1dm'

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OR 'type 2 diabetes' OR 't2dm') AND ('therapy' OR 'treatment' OR 'intervention'). Results were limited by the year of publication (from 1970), and the last search was carried out in October 2012. In addition, a manual search was carried out considering the reference lists of the selected articles and articles published in the *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Dental Research, Journal of Dentistry*, *Journal of Periodontal Research*, *International Journal of Periodontics and Restorative Dentistry*, *Periodontology 2000*, *Odontology*, *Clinical Oral Investigations*, *Annals of Periodontology*, *Journal of American Dental Association*, *British Dental Journal, Community Dentistry and Oral Epidemiology*, *Diabetes*, *Diabetes Care*, *Diabetes & Metabolic Syndrome*, *Diabetes & Metabolism* and *Annals of Internal Medicine.* No language restriction was placed.

Study Selection Criteria

The following inclusion criteria had to be met:

- randomized controlled studies on human subjects;
- intervention studies on diabetic patients with periodontal diseases;
- a minimum of 3 months of follow up after intervention;
- reporting data about glycated hemoglobin (HbA_{1c}) and/or fasting plasma glucose (FPG) modification after treatment; and
- clear presentation of population demographic characteristics.

A first screening was based on title and abstract.

Study Quality Assessment

Study quality was assessed independently by two authors (SC and MDF) according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Library, http://www.cochrane-handbook.org, Chapter 8). The following parameters were considered: (i) random sequence generation; (ii) allocation concealment; (iii) blinding of participants and personnel; (iv) incomplete data outcome; and (v) selective reporting. If no random sequence generation was present (high risk of bias), the study was excluded. In cases of randomization method not reported, allocation concealment control or blinding, such parameters were considered at unclear risk of bias. If two or more parameters were evaluated at unclear or high risk of bias, the study was considered at moderate risk and included in the review. Otherwise, the studies were considered at low risk of bias.

Data Extraction and Statistical Analysis

The following parameters were extracted from each selected study and recorded by two authors (SC and MDF) independently: (i) demographics (age, country, sex); (ii) definition of periodontal disease and of diabetes; (iii) sample group size; (iv) characteristics of periodontal treatment; (v) follow-up duration; and (vi) evaluated parameters (HbA_{1c} and FPG) chosen accordingly with previous systematic reviews[18].

Data regarding modifications of HbA_{1c} and FPG between follow up and baseline examination were included in the meta-analysis. The meta-analysis was made using Review Manager 5.1 (Cochrane Library, http://ims.cochrane.org/revman). Non-surgical periodontal treatment (NSPT) was compared with no treatment. A further comparison was made between NSPT alone vs NSPT with any adjunctive antimicrobial substance. Two time frames were considered: (i) 3–4 months of follow up; and (ii) 6 months.

According to a previous systematic review[18]; if not reported, the absolute difference of the selected parameters (ΔP) between baseline (t_0) and the end (t_1) of the study was estimated as follows:

$$-\Delta P = Pt_0 - Pt_1$$

where P represented the chosen parameter.

The variance (and consequently the standard deviation) of ΔP, if not reported, was estimated as follows[18]:

$$S\,\Delta P^2 = St_0{}^2 + St_1{}^2 - 2r \times St_0 \times St_1$$

where $S\,\Delta P^2$ is the variance of ΔP, $St_0{}^2$ is the variance of P at baseline, $St_1{}^2$ is the variance of P at follow-up visit and r is the correlation between St_0 and St_1 ($r = 0.5$ as described in previous studies[18,20]).

When two or more treatment or control groups had to be pooled to be included in the comparison, the weighted mean was computed and the variance of the pooled group was computed as follows[21]:

$$S_C{}^2 = (n_1 \times [S_1{}^2 + (X_1 - X_C)^2] + n_2 \times [S_2{}^2 + (X_2 - X_C)^2])/(n_1 + n_2)$$

where n is the number of observations, $S_C{}^2$ is the combined variance, $S_1{}^2$ and $S_2{}^2$ are the variance of the two groups, X_1 and X_2 are the mean values of the two groups and X_C is the mean value of the combined group.

The meta-analysis was carried out using an inverse variance statistical method and random effects model comparing weighted mean difference.

RESULTS

The flowchart of the article selection process is shown in Figure 1. The initial research retrieved 803 articles. After title and abstract screening, 23 articles were identified as potentially relevant. The full text of these articles was obtained and evaluated for inclusion. Six articles were excluded, because they were not coherent with the methods of the present study. The risk of bias evaluation of the included articles is shown in Figure 2. One article was then excluded after the risk of bias evaluation, because no random allocation was described[22]. Another study was excluded because of the impossibility of the calculation of standard deviations in the meta-analysis[23]. A total of 15 articles

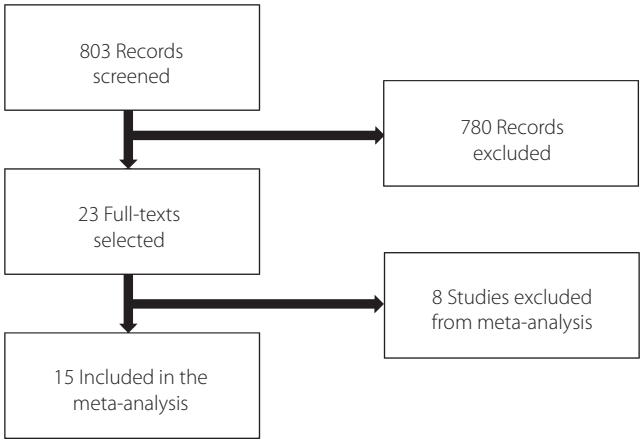

Figure 1 | Flow chart of article selection process.

were finally considered for the meta-analysis[24–38]. The main characteristics of the selected studies are summarized in Table 1.

Periodontal Treatment and HbA_{1c}

Periodontal non-surgical treatment was compared with no treatment in eight studies. Seven of them (accounting for a total of 678 participants)[25,27,28,31,34,36–38] presented data at 3–4 months follow up after treatment, and three studies (235 participants)[33,34,36] presented data at 6 months follow up. At the 3–4 months follow up, the computed weighted mean difference was −0.38% (95% confidence interval [CI] −0.23 to −0.53; Figure 3), and at 6 months it was −0.31% (95% CI 0.11 to −0.74; Figure 4), favoring the treatment groups. Considering the meta-analysis, heterogeneity of the study outcomes was statistically significant for both comparisons.

The comparison between periodontal non-surgical treatment alone vs treatment with adjunctive antimicrobial devices was made in five studies (208 participants)[26,29,30,32,35], which presented data at 3–4 months follow up. One study presented data for this comparison at 6 months follow up, showing $2.3 \pm 2.69\%$ increase of HbA_{1c} in the control group and $2.5 \pm 2.77\%$ increase in the test group without significant difference[24]. After 3–4 months follow up, the computed weighted mean difference was 0.13% (95% CI 0.35 to −0.10; Figure 5), favoring the control group. The heterogeneity was not significant ($P = 0.47$).

Periodontal Treatment and FPG

Periodontal non-surgical treatment was compared with no treatment in six studies. Five of these studies (412 participants)[27,31,34,37,38] presented data at 3–4 months follow up, and two studies (175 participants)[33,34] presented data at 6 months follow up. At 3–4 months, the computed weighted mean difference was −9.01 mg/dL (95% CI −2.24 to −15.78; Figure 6), and at 6 months it was −13.62 mg/dL (95% CI 0.45 to −27.69; Figure 7), favoring the treatment groups. The heterogeneity

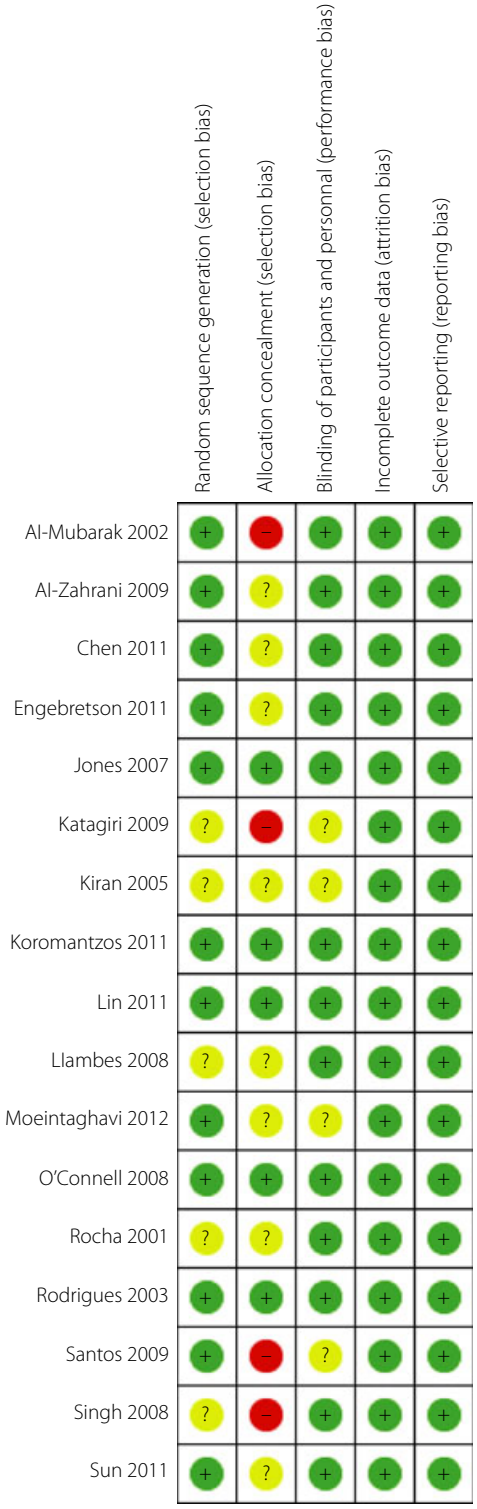

Figure 2 | Risk of bias evaluation graph.

calculated in the meta-analysis was not significant in both comparisons ($P = 0.09$ comparing no treatment vs treatment at 3–4 months and $P = 0.50$ at 6 months).

Table 1 | Main characteristics of the study

Study	Year	Population	Definition of diabetes	Definition of periodontal disease
Rocha *et al.*[23]	2001	Type 2 diabetes mellitus	Type 2 diabetes mellitus diagnosis 'confirmed'	More than one tooth with PD ≥3 mm
Al-Mubarak *et al.*[24]	2002	Type 1 and type 2 diabetes mellitus	Type 1 or type 2 diabetes mellitus for more than 1 year	At least 14 teeth; with calculus in at least four teeth in two different quadrants. PD ≥5 mm, but <8 mm in at least one site in four teeth in at least two different quadrants
Rodrigues *et al.*[25]	2003	Type 2 diabetes mellitus	Type 2 diabetes mellitus diagnosis 'confirmed'	More than one site with PD ≥5 mm and more than two teeth with CAL ≥6 mm
Kiran *et al.*[26]	2005	Type 2 diabetes mellitus	6% < HbA_{1c} < 8%	NR
Jones *et al.*[27]	2007	Poorly controlled diabetes	HbA_{1c} > 8.5% within the last 6 months	CPITN scores of ≥3 in at least two sextants
Singh *et al.*[30]	2008	Type 2 diabetes mellitus	Type 2 diabetes mellitus diagnosis 'confirmed'	More than 30% teeth with PD ≥4 mm
Llambes *et al.*[28]	2008	Type 1 diabetes	Definition of American Diabetes Association (1994)	More five sites with PD ≥5 mm and CAL ≥3 mm
O'Connell *et al.*[29]	2008	Type 2 diabetes mellitus	HbA_{1c} > 8%	More than one tooth with PD ≥5 mm and more than 2 teeth with CAL ≥6 mm
Katagiri *et al.*[32]	2009	Type 2 diabetes mellitus	6.5% < HbA_{1c} < 10%	More than 11 remaining teeth; more than 2 sites with PD ≥4 mm
Al-Zahrani *et al.*[31]	2011	Type 2 diabetes mellitus	Type 2 diabetes mellitus diagnosis 'confirmed'	CAL ≥3 mm at 30% sites: ≥20 remaining teeth
Koromantzos *et al.*[35]	2011	Type 2 diabetes mellitus	Type 2 diabetes mellitus diagnosis 'confirmed'	More than eight sites with PD ≥6 mm and more than four sites with CAL ≥5 mm
Chen *et al.*[33]	2011	Type 2 diabetes mellitus	NR	Mean CAL ≥1 mm
Sun *et al.*[36]	2011	Type 2 diabetes mellitus	7.5% ≤ HbA_{1c} ≤ 9.5%	More than 30% teeth with AL >4 mm or more than 60% teeth with PD >4 mm and AL >3 mm
Engebretson *et al.*[34]	2011	Type 2 diabetes mellitus	Type 2 diabetes mellitus diagnosis 'confirmed'	Loss of clinical attachment greater than 5 mm in at least one site in each jaw quadrant
Moeintaghavi *et al.*[37]	2012	Type 2 diabetes mellitus	HbA_{1c} > 7%	Armitage[49]; American Academy of Periodontology

AL, attachment loss; CAL, clinical attachment loss; CPITN, Community Peridontal Index of Treatment Needs; Hba_{1c}, glycated hemoglobin; NR, not reported; PD: probing depth.

Two studies (60 participants)[26,30] with a 3 to 4-month follow up evaluated the effect of adjunctive antimicrobial devices on periodontal treatment. No studies presented data for this comparison at 6 months follow up. After 3–4 months, the computed weighted mean difference was −0.27 mg/dL (95% CI 39.56 to −40.11; Figure 8), favoring the control group (heterogeneity $P = 0.46$).

DISCUSSION

The present study aimed at evaluating if non-surgical periodontal treatment alone or with the adjunctive use of antimicrobials had an influence on clinical parameters related with glycemic control in patients affected by both diabetes and periodontitis.

As compared with previous reviews, a higher number of articles could be included and different comparisons were carried out (NSPT vs no treatment and NSPT + antimicrobials vs NSPT) for the two clinical parameters considered.

In the included studies, the majority of patients were affected by uncontrolled type 2 diabetes mellitus, whereas only one of the studies involved patients with type 1 diabetes[29].

The meta-analysis showed that periodontal treatment significantly reduces the levels of HbA_{1c} and FPG in patients with diabetes. Though, it is difficult to quantify the clinical relevance of such findings in terms of improved glycemic control. The mean decrease of HbA_{1c} after periodontal treatment (−0.38% after 3 months and −0.31% after 6 months) can be hypothesized to have a clinical relevance. Considering that the decrease of such a parameter after the therapeutic administration of some antidiabetes agents can range from 0.4% to more than 3.0%[39], the effect estimated in the present study can be considered relevant, as its order of magnitude is similar.

Other systematic reviews have investigated the effects of periodontal treatment on glycemic control in patients with diabetes and periodontitis[17–19,40]. Although most of these reviews

Study or subgroup	Treatment Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
1.1.1 Moderate risk of bias									
Kiran 2005	−0.86	0.77	22	0.31	1.83	22	3.0%	−1.17 [−2.00, −0.34]	2005
Singh 2008	−0.7	0.66	30	0.06	0.72	15	8.9%	−0.76 [−1.19, −0.33]	2008
Moeintaghavi 2012	−0.74	1.18	20	−0.25	2.05	20	2.0%	−0.49 [−1.53, 0.55]	2012
Subtotal (95% CI)			72			57	13.9%	−0.80 [−1.17, −0.44]	
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (*P* = 0.57); I^2 = 0%									
Test for overall effect: Z = 4.37 (*P* < 0.0001)									
1.1.2 Low risk of bias									
Al-Mubarak 2002	−0.36	0.33	26	−0.2	0.34	26	22.8%	−0.16 [−0.34, 0.02]	2002
Jones 2007	−0.65	1.21	74	−0.49	1.22	80	10.6%	−0.16 [−0.54, 0.22]	2007
Sun 2011	−0.5	0.18	82	−0.14	0.12	75	33.1%	−0.36 [−0.41, −0.31]	2011
Koromantzos 2011	−0.73	0.66	30	−0.18	0.59	30	13.6%	−0.55 [−0.87, −0.23]	2011
Chen 2011	−0.07	1.46	85	0.34	1.52	41	6.0%	−0.41 [−0.97, 0.15]	2011
Subtotal (95% CI)			297			252	86.1%	−0.32 [−0.44, −0.19]	
Heterogeneity: Tau² = 0.01; Chi² = 6.87, df = 4 (*P* = 0.14); I^2 = 42%									
Test for overall effect: Z = 4.89 (*P* < 0.00001)									
Total (95% CI)			369			309	100.0%	−0.38 [−0.53, −0.23]	
Heterogeneity: Tau² = 0.02; Chi² = 14.04, df = 7 (*P* = 0.05); I^2 = 50%									
Test for overall effect: Z = 5.01 (*P* < 0.00001)									
Test for subgroup differences: Chi² = 6.25, df = 1 (*P* = 0.01); I^2 = 84.0%									

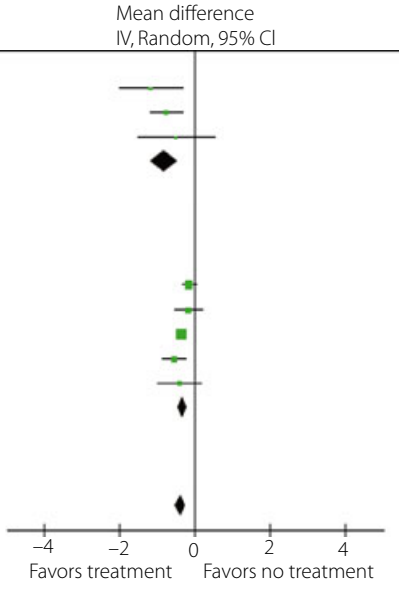

Figure 3 | Non-surgical periodontal treatment vs no treatment: 3-month glycated hemoglobin (%) difference between baseline and end of treatment. CI, confidence interval; df, degrees of freedom; SD, standard deviation.

Study or subgroup	Treatment Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
Katagiri 2009	0.14	0.63	32	0.09	0.57	17	36.7%	0.05 [−0.30, 0.40]	2009
Koromantzos 2011	−0.71	0.72	30	−0.13	0.69	30	36.3%	−0.58 [−0.94, −0.22]	2011
Chen 2011	−0.32	1.33	85	0.13	1.53	41	27.0%	−0.45 [−1.00, 0.10]	2011
Total (95% CI)			147			88	100.0%	−0.31 [−0.74, 0.11]	
Heterogeneity: Tau² = 0.10; Chi² = 6.53, df = 2 (*P* = 0.04); I^2 = 69%									
Test for overall effect: Z = 1.44 (P = 0.15)									

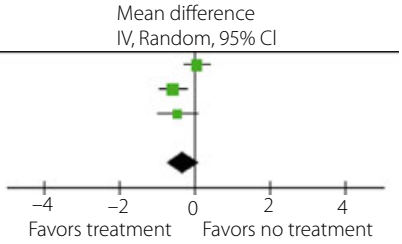

Figure 4 | Non-surgical periodontal treatment vs no treatment: 6-month glycated hemoglobin (%) difference between baseline and end of treatment. CI, confidence interval; df, degrees of freedom; SD, standard deviation.

Study or subgroup	Treatment Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
1.3.1 Moderate risk of bias									
Kiran 2005	3.96	30.58	22	−1.22	37.49	22	9.0%	5.18 [−15.04, 25.40]	2005
Singh 2008	−4.05	14.5	30	1.9	12.35	15	27.9%	−5.95 [−14.07, 2.17]	2008
Moeintaghavi 2012	−17.5	48.91	20	9.78	38.02	20	5.5%	−27.28 [−54.43, −0.13]	2012
Subtotal (95% CI)			72			57	42.4%	−6.75 [−19.82, 6.32]	
Heterogeneity: Tau² = 62.13; Chi² = 3.53, df = 2 (*P* = 0.17); I^2 = 43%									
Test for overall effect: Z = 1.01 (*P* = 0.31)									
1.3.2 Low risk of bias									
Chen 2011	0.14	34.25	85	3.61	46.37	41	13.0%	−3.47 [−19.42, 12.48]	2011
Sun 2011	−21.1	8.84	82	−7.93	4.32	75	44.6%	−13.17 [−15.32, −11.02]	2011
Subtotal (95% CI)			167			116	57.6%	−11.67 [−18.54, −4.80]	
Heterogeneity: Tau² = 13.32; Chi² = 1.40, df = 1 (*P* = 0.24); I^2 = 28%									
Test for overall effect: Z = 3.33 (*P* = 0.0009)									
Total (95% CI)			239			173	100.0%	−9.01 [−15.78, −2.24]	
Heterogeneity: Tau² = 25.56; Chi² = 8.18, df = 4 (*P* = 0.09); I^2 = 51%									
Test for overall effect: Z = 2.61 (*P* = 0.009)									
Test for subgroup differences: Chi² = 0.43, df = 1 (*P* = 0.51), I^2 = 0%									

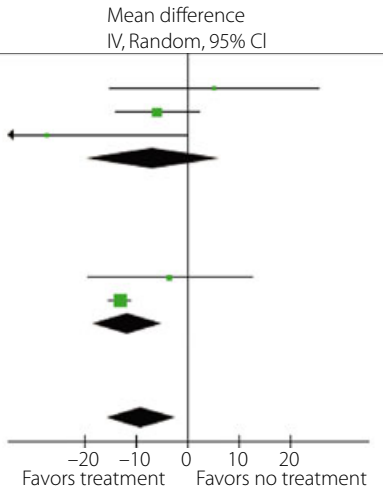

Figure 5 | Non-surgical periodontal treatment and adjunctive antimicrobials vs non-surgical periodontal treatment: 3-month glycated hemoglobin (%) difference between baseline and end of treatment. Study heterogeneity cannot be observed (*P* = 0.47). CI, confidence interval; df, degrees of freedom; SD, standard deviation.

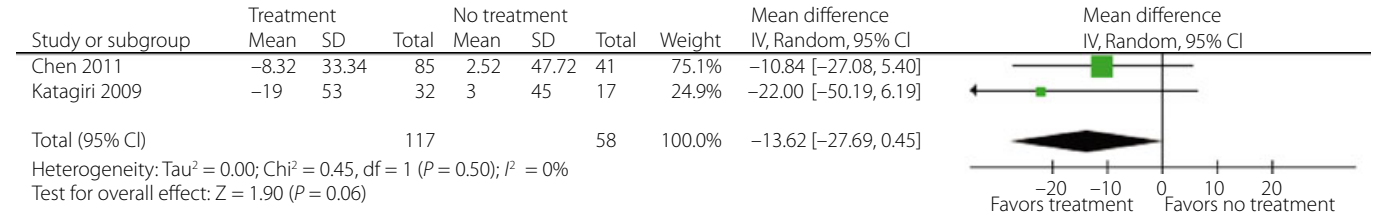

Figure 6 | Non-surgical periodontal treatment vs no treatment: 3-month fasting plasma glucose (mg/dL) difference between baseline and end of treatment. CI, confidence interval; df, degrees of freedom; SD, standard deviation.

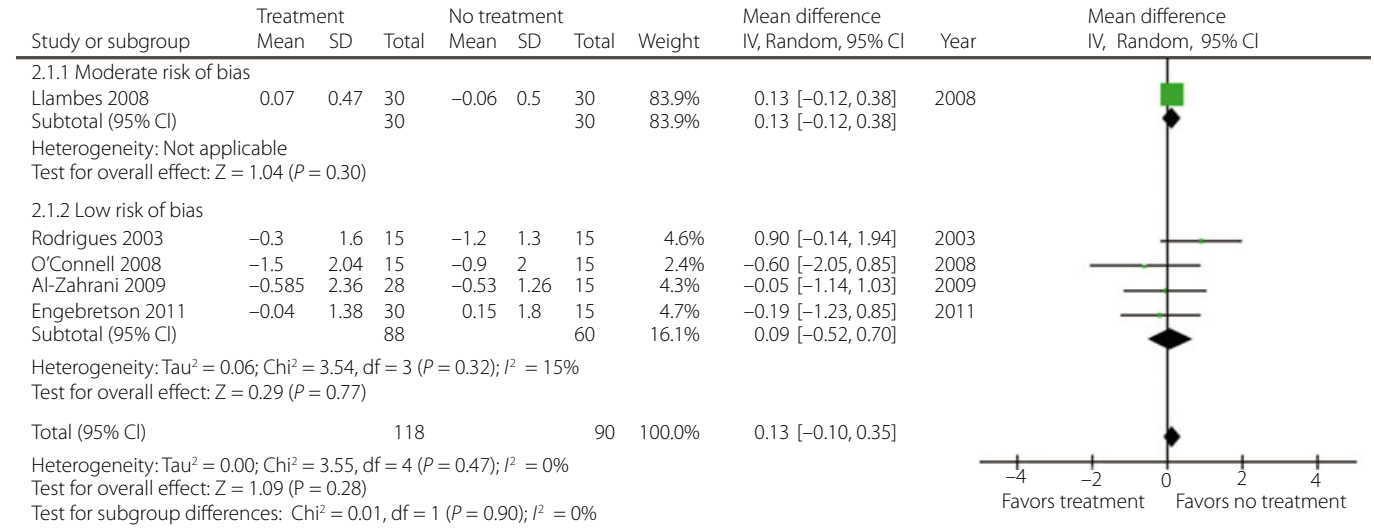

Figure 7 | Non-surgical periodontal treatment vs no treatment: 6-month glycated hemoglobin (%) difference between baseline and end of treatment. Study heterogeneity cannot be observed (*P* = 0.50). CI, confidence interval; df, degrees of freedom; SD, standard deviation.

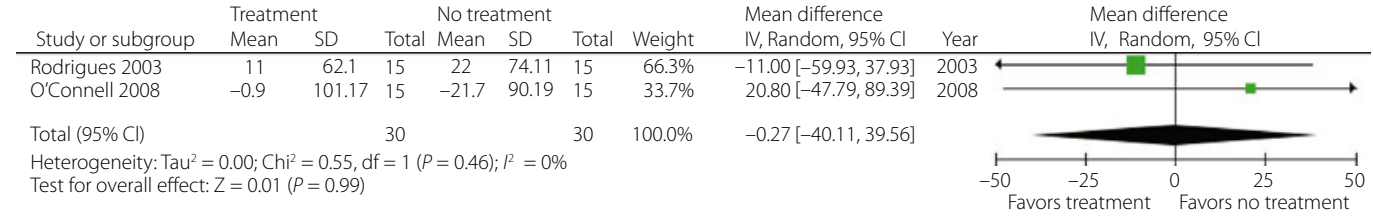

Figure 8 | Non-surgical periodontal treatment and adjunctive vs Non-surgical periodontal treatment: 3-month fasting plasma glucose (mg/dL) difference between baseline and end of treatment. Study heterogeneity cannot be observed (*P* = 0.46). CI, confidence interval; df, degrees of freedom; SD, standard deviation.

concluded that periodontal therapy causes a statistically significant improvement of glycemic control[18,40], some authors reported that the significance is low and does not allow for generalization of the results to the entire population[17]. One review reported a positive effect of the use of adjunctive antimicrobials, which was not observed in the present meta-analysis[19]. The authors, however, stated that such an effect was not statistically significant[19].

Some novel aspects emerged from the present article. First, in relation to previous reviews, a higher number of articles could be considered. Then, different comparisons were carried out (NSPT vs no treatment and NSPT + antimicrobials vs NSPT) for two clinical parameters, which were not carried out in the previous published systematic reviews.

In the present study, some studies that did not fulfill the inclusion criteria reported positive effects of periodontal treatment on glycemic control[41–43].

Conversely, other studies failed to show that periodontal treatment might improve glycemic control, despite an improvement in clinical periodontal parameters in patients with type 1 diabetes mellitus[44–46].

Other studies reported that extraction of 'hopeless' teeth might be beneficial to glycemic control, because it might guarantee a complete elimination of periodontal infection, which is difficult to obtain with either non-surgical or surgical periodontal treatment alone[47,48].

Some limitations should be recognized in the present study. First, the estimation of standard deviations using the cited methods could be valid from a mathematical point of view, but it might not correspond to actual values. Furthermore, no distinction was made in outcomes analysis between controlled and uncontrolled diabetes, and between studies carried out in developing countries where other major risk factors could have acted as confounding factors. Finally, it has to be underlined that the robustness of results of some comparisons could be weakened by the heterogeneity among the studies, as described in the literature[18].

In order to clarify the effect of non-surgical periodontal treatment on glycemic control in patients affected by diabetes, it is important that further randomized controlled trials with a large sample size report detailed information about initial and final parameters. Finally, as shown in a previous review[19], the positive effect of periodontal treatment must be clearly demonstrated.

Despite the limitations of the present study, it can be concluded that periodontal treatment might be effective in improving metabolic control in terms of reduction of HbA_{1c} and FPG concentrations in patients with diabetes. However, the significance of this improvement is questionable and should be further investigated.

Periodontal non-surgical treatment is important in periodontal patients affected by diabetes because, in addition to the negligible side-effects, it leads to the reduction of one potential factor impairing glycemic control, while preserving dental and periodontal health.

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