CONCISE REVIEW

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Efficacy of systemic antibiotics in nonsurgical periodontal therapy for diabetic subjects: a systematic review and meta-analysis

Maria Luisa S. Souto[1], Emanuel S. Rovai[1], Juliana A. Ganhito[1], Marinella Holzhausen[1], Leandro Chambrone[2] and Cláudio M. Pannuti[1]

[1]*Division of Periodontics, School of Dentistry, University of São Paulo, São Paulo, Brazil;* [2]*Unit of Basic Oral Investigations, El Bosque University, Bogota, Colombia.*

Objectives: To evaluate the effects of systemic antibiotics as adjuncts to nonsurgical periodontal treatment (NSPT), as opposed to using NSPT alone, on periodontal clinical parameters of diabetic patients with periodontitis. **Materials and methods:** Randomised controlled trials with a follow-up of 3 months or more, assessing the effects of NSPT in combination with antibiotics, in diabetic patients with periodontitis were included. Trials published up to August 2016 were identified from MEDLINE, EMBASE and LILACS databases. Meta-analyses were conducted to determine changes in clinical attachment level (CAL), probing pocket depth (PPD), bleeding on probing (BOP) and gingival index (GI). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this review. **Results:** Of the 164 papers potentially admissible to this systematic review, 15 articles on 11 randomised clinical trials were considered as eligible. The results of the meta-analyses presented a modest additional benefit of 0.14 mm (95% confidence interval: 0.08–0.20) in reducing PPD but no further benefit in CAL gain. **Conclusion:** When the data for all antibiotic protocols were considered together for the treatment of periodontitis patients with DM, a significant, albeit small, reduction of PPD and no improvement in CAL gain was observed. When the antibiotic protocols were analysed separately, the combination of amoxicillin plus metronidazole yielded the best results for PPD.

Key words: *Diabetes mellitus, periodontal diseases, anti-infective agents, root planing, systematic review*

INTRODUCTION

Diabetes mellitus (DM) is a complex, chronic disease that requires continuous treatment and multifactorial strategies to control glycaemic levels. There are two principal types of DM: type 1 and type 2. Type 1 DM is characterised by insulin deficiency caused by autoimmune destruction of pancreatic β-cells, and type 2 DM is a result of resistance to insulin action[1].

DM is considered to be a risk factor for periodontitis[2]. It has been demonstrated that diabetic patients have a greater prevalence and severity of periodontal disease than nondiabetic patients[3–9]. Moreover, periodontal infection may lead to poorer glycaemic control in patients with diabetes[10] and periodontal treatment can help with glycaemic control[11], indicating a bidirectional relationship between DM and periodontitis[10].

As a result of the severity of periodontal disease in diabetic patients, some clinical studies have evaluated the adjunctive effect of antibiotics in nonsurgical periodontal treatment for these patients[12–15]. A recent systematic review (SR)[16] has shown that local antimicrobials are effective in reducing probing pocket depth (PPD) and increasing clinical attachment level (CAL) in diabetic patients. Two recent SRs have addressed the effect of systemic antimicrobials in diabetic patients with periodontitis[17,18]. However, both included studies that used doxycycline at subantimicrobial doses. Furthermore, different antibiotics may have different efficacy against periodontal infection. When analysed together, antimicrobials' effectiveness

may be underestimated. Thus, this SR aimed to evaluate the adjunctive effects of systemic antibiotics used in nonsurgical periodontal treatment (NSPT), compared with NSPT alone, on the periodontal clinical parameters of diabetic patients with periodontitis. Moreover, this review aimed to analyse the individual effect of different antibiotics, in order to identify which one provides an additional effect on periodontal therapy.

METHODOLOGY

The following focussed question was addressed: 'In periodontitis patients with diabetes, is the use of systemic antimicrobials adjunct to NSPT more effective than NSPT alone in reducing PPD and improving CAL?' We have registered the protocol of this SR at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO, registration number CRD42016032831). Guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[19], the *Cochrane Handbook of Systematic Reviews of Interverstions*[20] and Check Review checklist[20] were used to structure the review text.

Eligibility criteria

We included randomised trials of 3 months or longer with follow-up that evaluated the effects of systemic antibiotics adjunctive to NSPT, compared with NSPT alone, in DM (type 1 and/or type 2) patients with periodontitis. We excluded studies with pregnant women, patients with gestational diabetes or patients who had received systemic antimicrobials 3 months before the study. In addition, trials that used local antimicrobials, antibiotics in sub-antimicrobial doses or that presented inadequate information about the antibacterial agent or the therapy protocol, were not included in this review. The primary outcomes were change in CAL and change in PPD.

Information source and search strategy

We searched MEDLINE via PubMed, EMBASE and LILACS databases to identify relevant publications up to August 2016. MeSH terms and keywords were combined with Boolean operators and used to search the databases. There was no restriction regarding language or publication year. Search strategies are presented in *Data S1*. In addition, reference lists of the selected studies were handsearched, and unpublished studies were searched at OpenGray[21].

Study selection

Initially, titles and abstracts of the studies were screened independently by two reviewers (E.S.R. and M.L.S.). After this phase, the same reviewers conducted a full-text screening of those trials apparently meeting the inclusion criteria, as well as any papers without available abstracts. In both phases, a third reviewer (C.M.P.) resolved any disagreement between the two reviewers. Data extraction and validity assessment were performed on the publications that met the inclusion criteria. Moreover, the reasons for excluding publications were recorded.

Data collection

Two reviewers (E.S.R. and M.L.S.) performed the data extraction independently using extraction forms[22]. A third reviewer (C.M.P.) solved any disagreements in the data extraction. Also, if needed, the authors of the included trials were contacted to elucidate questions or missing data.

The reviewers collected the following data from the eligible studies: (i) citation; (ii) country of the study; (iii) participants' characteristics; (iv) definition of periodontitis and diabetes; (v) follow-up duration; (vi) intervention characteristics (active principle, concentration and dose interval); (vii) sample size; (viii) outcome variables; and (ix) financial support and conflict of interest.

Risk of bias in individual studies

Risk of bias was assessed using the Cochrane Collaboration's Tool for Assessing Risk of Bias[20]. Two reviewers (E.S.R. and M.L.S.) independently performed the quality assessment, and any disagreement was solved by a third investigator (C.M.P.). The following domains were classified as adequate (+), inadequate (−) or unclear (?): sequence generation; allocation concealment; blinding of patients, personnel and examiners; incomplete outcome data; selective reporting; and other biases. Each trial was rated as being at low, unclear or high risk of bias.

Summary measures and synthesis of results

We used a software package (Review Manager software, version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to conduct a random-effects meta-analyses for CAL gain, PPD reduction, bleeding on probing (BOP) change and gingival index (GI) change. Weighted mean differences (WMDs) between groups were calculated.

Cochran's Q statistic and I^2 were used to assess heterogeneity among trials.

RESULTS

Study selection

The search in the databases resulted in the identification of 164 publications, 143 of which were excluded after reviewing titles and abstracts. The complete texts of 21 publications were analysed[13,15,23–41], and of these, six[32,33,35–37,40] were excluded (*Figure 1*).

Included studies

Fifteen articles, regarding 11 RCTs, were included in this review (*Tables 1* and *2*). Three RCTs[13,15,25] had their data reported in more than one article each (i.e. according to the follow-up period or type analysis). Consequently, the articles were included under one study name. *Table 1* presents the characteristics of the included trials. Overall, 541 patients with chronic periodontitis and diabetes were included in the trials, and 496 (91.68%) completed the follow-up period. Six studies[15,19,23,26,28,31] excluded smokers, two[13,24]

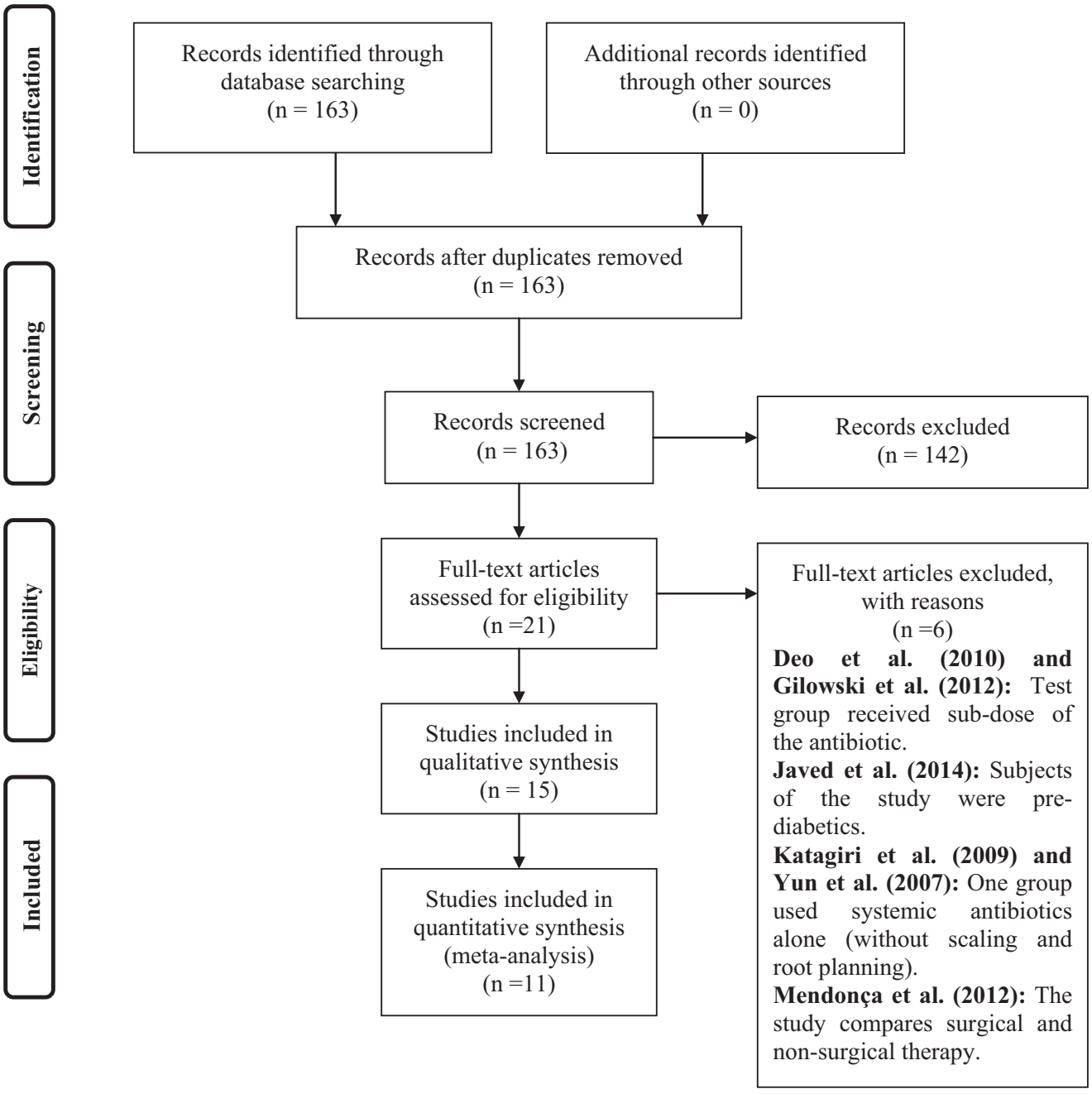

Figure 1. Flow-chart.

Table 1 Characteristics of the studies

Study[ref.no.] (country)	Study design	Follow-up	Sample size (baseline)	Peridontitis definition/clinical examination	Diabetes definition	Funding
Al-Nowaiser *et al.* (2014)[23] (Saudi Arabia)	Parallel RCT	6 months	*N* = 76 (47 male and 29 female subjects) Age mean: 42 ± 6.41 years	Severe chronic periodontitis. Presence of at least 16 teeth, and a minimum of 8 sites with probing depth >5 mm and CAL >5 mm Florida probe®	Type 2, diagnosed for ≥1 year and good physical condition with no additional serious medical conditions	No
Al-Zahrani *et al.* (2009)[24] (Saudi Arabia)	Parallel RCT	3 months	*N* = 45 (17 male and 26 female subjects; gender distribution is reported at the end of the study only) Age Mean: 52.21 ± 8.35 years	Moderate to severe chronic periodontitis; ≥20 remaining teeth; CAL ≥3 mm at ≥30% of sites Probe not reported	Type 2 diabetes No diabetes criteria reported	No
Botero *et al.* (2013)[25]/Hincapié *et al.* (2014)[34] (Colombia)	Parallel RCT	9 months	*N* = 105 (74 male and 31 female subjects)	Moderate periodontitis. Two or more interproximal sites with CAL ≥4 mm, not on the same tooth, or two or more interproximal sites with probing depth ≥5 mm, not on the same tooth UNC-15 probe	Diabetes types 1 or 2 Patients >18 years of age, confirmed diagnosis of type 1 and 2 diabetes with ≥2 years duration	Partially supported by a grant from Colgate-Palmolive (020-2009) and the Universidad de Antioquia. Azithromycin was provided by Tecnoquimicas (Cali, Colombia). Placebo tablets were provided by the Faculty of Pharmaceutical Chemistry (Universidad de Antioquia, Medellin, Colombia)
Gaikwad *et al.* (2013)[26] (India)	Parallel RCT	4 months	*N* = 50 (34 male and 16 female subjects) Age Range: 30–70 years (mean not mentioned)	No periodontitis definition reported UNC-15 probe	Diabetes type 2 No diabetes criteria reported	No
Grossi *et al.* (1997)[27] (USA)	Parallel RCT	6 months	*N* = 113 (81 male and 32 female subjects) Age Range: 25–65 years (mean not mentioned)	Moderate to severe periodontitis. No criteria definition reported Constant force probe	Diabetes type 2 World Health Organization, Expert Committee on Diabetes (1980)	Eastman Kodak, Rochester, NY and National Institute of Dental Research
Llambés *et al.* (2005[13], 2008[38], 2012)[39] (Spain)	Parallel RCT	3 months	*N* = 60 (30 male and 30 female subjects) Age Mean: 35.3 ± 9 years	Moderate to severe periodontitis, minimum of 14 natural teeth with at least five areas with probing depth of ≥5 mm and CAL ≥3 mm Probe not reported	Diabetes type 1 Diabetic patients for more than 1 year. Diabetic control was measured by HbA1c	No
O'Connel *et al.* (2008)[28] (Brazil)	Parallel RCT	3 months	*N* = 35 (14 male and 16 female subjects; gender distribution is reported at the end of the study only) Age Mean: 52.9 years	At least one site with probing depth of ≥5 mm and two teeth with CAL ≥6 mm Florida probe®	Diabetes type 2 Diabetic patients for more than 5 years and HbA1c >8%	The State of São Paulo Research Foundation, São Paulo, SP, Brazil (grant 04/09844-8 to Dr Taba) and the National Council for Scientific and Technological Development, Brasilia, DF, Brazil (grant 470638/2006 to Drs Novaes and Taba)

(continued)

Table 1 continued

Study[ref.no.] (country)	Study design	Follow-up	Sample size (baseline)	Peridontitis definition/clinical examination	Diabetes definition	Funding
Rodrigues *et al.* (2003)[29] (Brazil)	Parallel RCT	3 months	*N* = 30 (gender distribution not mentioned) Age Mean and range not mentioned	Chronic periodontal disease. At least one site with probing depth ≥5 mm and two teeth with CAL ≥6 mm Florida probe® and customised acrylic stent	Diabetes type 2 Diagnosis in the past 5 years	Capes (Edducacional Support Center, São Paulo, Brazil) and Fapesp (São Paulo State Research Foundation, Brazil)
Singh *et al.* (2008)[30] (India)	Parallel RCT	3 months	*N* = 45 (gender distribution not mentioned) Age Mean and range not mentioned	No periodontitis definition reported. Willian's probe and customised acrylic Stent	Diabetes type 2 No diabetes criteria reported	No
Miranda *et al.* (2014)[41]/ Tamashiro *et al.* (2016)[15] (Brazil)	Parallel RCT	24 months	*N* = 58 (30 male and 26 female subjects; gender distribution are reported at the end of the study only) Age Mean: 54.0 ± 8.2 (test) and 53.7 ± 8.0 (control)	Generalised chronic periodontitis. At least 15 teeth, more than 30% of the sites with probing depth and CAL ≥4 mm and a minimum of six teeth with at least one site with probing depth and CAL ≥5 mm and BOP at baseline. UNC-15 probe	Diabetes type 2 Diabetic patients for more than 5 years, diabetes treatment with diet and insulin supplementation or oral hypoglycaemic agents and HbA1c ≥6.5% and ≤11%	São Paulo State Research Foundation (São Paulo, Brazil)
Tsalikis *et al.* (2014)[31] (Greece)	Parallel RCT	6 months	*N* = 70 (38 male and 28 female subjects; gender distribution are reported at the end of the study only) Age Mean: 62.9 ± 10 (test) and 57.94 ± 8.22 (control)	Moderate or advanced periodontitis. Six pockets with probing depth >5 mm and CAL >3 mm with radiographic bone loss >10% in more than 30% of teeth. Florida probe®	Diabetes type 2 Diagnosed at least 1 year before baseline examination. At least two consecutive values of HbA1c <7.5%	Procter and Gamble Hellas through the Koulourides 2011 Award for Dental Research in Greece

BOP, bleeding on probing; HbA1c, glycated haemoglobin; RCT, randomised controlled trial.

Table 2 Participants, interventions, outcomes and results

Study[ref. no.]	Participants	Interventions	Outcomes measures of interest for the review
Al-Nowaiser *et al.* (2014)[23]	Test group: *N* baseline = 38 *N* end of trial = 35	Test group: 6–8 sessions of SRP. After 45 days, re-evaluation and subgingival debridement + antimicrobial dose of systemic DOXY 100 mg once a day for 14 days with a loading dose of 200 mg on the first day	Test Overall CAL gain: 0.74 ± 0.17 mm Overall probing depth reduction: 1.5 ± 0.38 mm
	Control group: *N* baseline = 38 *N* end of trial = 33	Control group: 6–8 sessions of SRP. After 45 days, re-evaluation and subgingival debridement	Control Overall CAL gain: 0.96 ± 0.22 mm Overall probing depth reduction: 1.4 ± 0.28 mm
Al-Zahrani *et al.* (2009)[24]	Test group: *N* baseline = 15 *N* end of trial = 14	Test group: 1–4 sessions of SRP + DOXY 200 mg on the first day and DOXY 100 mg once daily for 13 days	Test Overall CAL gain: 0.49 ± 0.64 mm Overall probing depth reduction: 0.44 ± 0.38 mm Reduction of sites with probing depth ≥5: 0.1
	Control group: *N* baseline = 15 *N* end of trial = 15 Note: PDT group = 15	Control group: 1–4 sessions of SRP only	Control Overall CAL gain: 0.56 ± 1.14 mm Overall probing depth reduction: 0.6 ± 0.67 mm Reduction of sites with probing depth ≥5: 0.06
Botero *et al.* (2013)[25]/ Hincapié *et al.* (2014)[34]	Test group: *N* baseline = 33 *N* end of trial = 28	Test group: subgingival scaling in a single session + systemic AZT 500 mg/day for 3 days	Test Overall CAL gain: 0.2 ± 0.75 mm Overall probing depth reduction: 0.6 ± 0.51 mm
	Control group: *N* baseline = 37 *N* end of trial = 31	Control group: subgingival scaling in a single session + placebo	Control Overall CAL gain: 0.3 ± 1.08 mm Overall probing depth reduction: 0.4 ± 0.62 mm
Gaikwad *et al.* (2013)[26]	Test group: *N* baseline = 25 *N* end of trial = not reported	Test group: full-mouth SRP + systemic DOXY 100 mg once a day for 15 days	Test Overall CAL gain: 0.93 ± 0.45 mm Overall probing depth reduction: 0.69 ± 0.11 mm
	Control group: *N* baseline = 25 *N* end of trial = not reported	Control group: full-mouth SRP only	Control Overall CAL gain: 0.47 ± 0.52 mm Overall probing depth reduction: 0.52 ± 0.34 mm
Grossi *et al.* (1997)[27]	Test group: *N* baseline = not reported *N* end of trial = not reported	Test group: SRP + water irrigation + systemic DOXY 100 mg	Test Overall CAL gain: 0.54 ± 0.3 mm Overall probing depth reduction: 0.72 ± 0.2 mm
	Control group: *N* baseline = not reported *N* end of trial = not reported	Control group: SRP + water irrigation + placebo SRP in two sessions (half of the mouth in each session) and irrigation with water. Doxycycline 100 mg or placebo per day for 2 weeks starting in the first session of SRP	Control Overall CAL gain: 0.4 ± 0.2 mm Overall probing depth reduction: 0.56 ± 0.1 mm
Llambés *et al.* (2005[13], 2008[38], 2012[39])	Test group: *N* baseline = 30 *N* end of trial = 30	Test group: SRP in one or two sessions plus chlorhexidine 0.2% rinses (20 ml for 30 s, twice daily) for 12 weeks plus systemic DOXY 100 mg (twice daily for the first day and then one capsule/day thereafter) for 15 days	Test Overall CAL gain: 0.45 ± 0.55 mm Overall probing depth reduction: 0.74 ± 0.46 mm
	Control group: *N* baseline = 30 *N* end of trial = 30	Control group: SRP in one or two sessions plus chlorhexidine 0.2% rinses (20 ml for 30 s, twice daily)	Control Overall CAL gain: 0.42 ± 0.37 mm Overall probing depth reduction: 0.65 ± 0.33 mm

(continued)

Table 2 continued

Study[ref. no.]	Participants	Interventions	Outcomes measures of interest for the review
O'Connel *et al.* (2008)[28]	Test group: *N* baseline: not reported *N* end of trial: 15	Test group: full-mouth SRP + systemic DOXY 100 mg	Test Overall CAL gain: 0.9 ± 1.6 mm Overall probing depth reduction: 1.1 ± 0.4 mm Reduction of sites with probing depth 4–5 mm: 21.8 Reduction of sites with probing depth ≥6 mm: 5.0
	Control group: *N* baseline: not reported *N* end of trial: 15	Control group: full-mouth SRP + placebo 2–4 sessions of SRP within 24 to 36 hours plus systemic DOXY 100 mg or placebo for 14 days after an initial dose of 200 mg (the antibiotic or placebo therapy started the day before SRP was performed)	Control Overall CAL gain: 0.5 ± 1.35 mm Overall probing depth reduction: 0.8 ± 0.7 mm Reduction of sites with probing depth 4–5 mm: 18.7 Reduction of sites with probing depth ≥6 mm: 8.9
Rodrigues *et al.* (2003)[29]	Test group: *N* baseline: 15 *N* end of trial: not reported	Test group: full-mouth SRP in two sessions within 24–6 hours. One day before the first session, AMOX/clavulanic acid 875 mg was systemically administered twice daily for 2 weeks	Test Overall CAL gain: 0.0 ± 1.2 mm Overall probing depth reduction: 0.8 ± 0.6 mm
	Control group: *N* baseline: 15 *N* end of trial: not reported	Control group: full-mouth SRP in two sessions within 24–36 hours only	Control Overall CAL gain: 0.0 ± 1.35 mm Overall probing depth reduction: 0.9 ± 0.7 mm
Singh *et al.* (2008)[30]	Test group: *N* baseline: 15 *N* end of trial: not mentioned	Test group: full-mouth SRP plus systemic DOXY 100 mg daily for 14 days (200 mg in the first day)	Test Overall CAL gain: 0.34 ± 0.61 mm Overall probing depth reduction: 0.38 ± 0.47 mm
	Control group: *N* baseline: 15 *N* end of trial: not mentioned	Control group: full-mouth SRP only	Control Overall CAL gain: 0.3 ± 0.45 mm Overall probing depth reduction: 0.34 ± 0.35 mm
Miranda *et al.* (2014)[41]/ Tamashiro *et al.* (2016)[15]	Test group: *N* baseline: 29 *N* end of trial: 16	Test group: SRP + systemic MTZ 400 mg and AMOX 500 mg	Test Overall CAL gain: 0.9 ± 1.08 mm Moderate sites (probing depth 4–6 mm) CAL gain: 1.42 ± 0.10 mm Deep sites (probing depth ≥7 mm) CAL gain: 3.35 ± 0.26 mm Overall probing depth reduction: 1.1 ± 0.43 mm Moderate sites (probing depth 4–6 mm) probing depth reduction: 1.89 ± 0.10 mm Deep sites (probing depth ≥7 mm) probing depth reduction: 4.32 ± 0.24 mm Reduction of sites with probing depth ≥5 mm: 29.14 ± 1.68 Reduction of sites with probing depth ≥6 mm: 14.85 ± 1.12
	Control group: *N* baseline: 29 *N* end of trial: 17	Control group: SRP + placebo After the first session of SRP, the antibiotics (MTZ 400 mg and AMOX 500 mg) or placebo were administered three times daily for 14 days	Control Overall CAL gain: 0.5 ± 0.85 mm Moderate sites (probing depth 4–6 mm) CAL gain: 0.88 ± 0.10 mm Deep sites (probing depth ≥7 mm) CAL gain: 2.39 ± 0.25 mm Overall probing depth reduction: 0.7 ± 0.6 mm Moderate sites (probing depth 4–6 mm) probing depth reduction: 1.19 ± 0.10 mm Deep sites (probing depth ≥7 mm) probing depth reduction: 2.82 ± 0.24 mm Reduction of sites with probing depth ≥5 mm: 18.69 ± 1.74 Reduction of sites with probing depth ≥6 mm: 10.49 ± 1.16

(continued)

Table 2 continued

Study[ref. no.]	Participants	Interventions	Outcomes measures of interest for the review
Tsalikis *et al.* (2014)[31]	Test group: *N* baseline: 35 *N* end of trial: 31	Test group: SRP + systemic DOXY 100 mg	Test Overall CAL gain: 0.71 ± 0.78 mm Overall probing depth reduction: 0.84 ± 0.74 mm Reduction of sites with probing depth ≥5 mm: 178
	Control group: *N* baseline: 35 *N* end of trial: 35	Control group: SRP + placebo SRP in two sessions plus systemic DOXY 100 mg (200 mg as loading dose and 100 mg for 20 days) or placebo	Control Overall CAL gain: 0.9 ± 1.1 mm Overall probing depth reduction: 0.76 ± 0.66 mm Reduction of sites with probing depth ≥5 mm: 198

AMOX, amoxicillin; AZT, azithromycin; CAL, clinical attachment level; DOXY, doxycycline; HbA1c, glycated haemoglobin; MTZ, metronidazole; PDT, photodynamic therapy; SRP, scaling and root planing.

included smokers and three[25,27,30] did not report participants' smoking status.

Methodological quality of included studies

Three trials[15,25,31] were judged to have low risk of bias, seven[13,23,24,26,27,29,30] to have high risk of bias and one[28] to have unclear risk of bias (*Table 3*).

Results of individual studies

Eleven trials assessed the use of systemic antibiotics as adjunct to scaling and root planing (SRP) (doxycycline[13,23,24,26–28,30,31], azithromycin[25], amoxicillin + metronidazole[15], and amoxicillin + clavulanic acid[29]). Of these studies, three[15,26,27] presented a significant PPD reduction/CAL gain associated with the use of systemic antibiotics when compared with the placebo group (*Table 2*).

Synthesis of results

Meta-analyses of the studies were conducted with data from 11 trials. Significant differences between groups for overall PPD reduction were observed [WMD = 0.14; 95% confidence interval (95% CI): 0.08–0.20; $P < 0.00001$, $I^2 = 0\%$] (*Figure 2*). Subgroup analysis revealed a significant effect of systemic antibiotics for PPD reduction only in subjects with type 2 diabetes (WMD = 0.15; 95% CI: 0.08–0.21; $P < 0.0001$, $I^2 = 3\%$) (*Figure 2*). However, there was no significant difference between groups in CAL gain (*Figure 3*). Moreover, studies considered to have low (WMD = 0.27; 95% CI: 0.07–0.41; $P = 0.005$, $I^2 = 7\%$) and high (WMD = 0.12; 95% CI: 0.06–0.19; $P = 0.002$, $I^2 = 0\%$) risk of bias showed a significant PPD reduction favouring the test group (*Figure 4*). The risk of bias of the trials did not influence CAL gain (*Figure 5*). Regarding antibiotic type, meta-analyses showed that only doxycycline and the combination of amoxicillin + metronidazole resulted in significant PPD reduction (WMD = 0.13; 95% CI: 0.07–0.20; $P < 0.0001$, $I^2 = 0\%$; WMD = 0.39; 95% CI: 0.12–0.66; $P = 0.004$, respectively (*Figure 6*). Furthermore, none of the antimicrobials provided CAL gain (*Figure 7*).

Adverse effects

One trial[25] mentioned that one participant in the placebo group reported gastrointestinal discomfort with the

Table 3 Summary of risk of bias (low/high/? unclear) in selected studies

Systemic antimicrobials	Random sequence generation	Allocation concealment	Masking patient	Masking operator	Masking examiner	Attrition bias	Selective reporting	Sample size calculation	Overall risk of bias
Al-Nowaiser *et al.* (2014)[23]	+	?	–	?	?	?	+	?	High
AL-Zahrani *et al.* (2009)[24]	+	?	–	?	+	+	+	+	High
Botero *et al.* (2013)[25]	+	+	+	+	+	+	+	+	Low
Gaikwad *et al.* (2013)[26]	?	?	–	?	?	?	+	?	High
Grossi *et al.* (1997)[27]	?	?	+	–	+	?	+	?	High
Llambés *et al.* (2005)[13]	–	?	–	?	?	–	+	?	High
Tamashiro *et al.* (2014)[15]	+	+	+	+	+	+	+	+	Low
O'Connell *et al.* (2008)[28]	?	?	+	+	+	?	+	?	?
Rodrigues *et al.* (2003)[29]	?	?	–	–	–	?	+	?	High
Singh *et al.* (2008)[30]	?	?	–	?	?	?	+	?	High
Tsalikis *et al.* (2014)[31]	+	+	+	+	+	+	+	+	High

+, adequate; –, inadequate; ?, unclear.

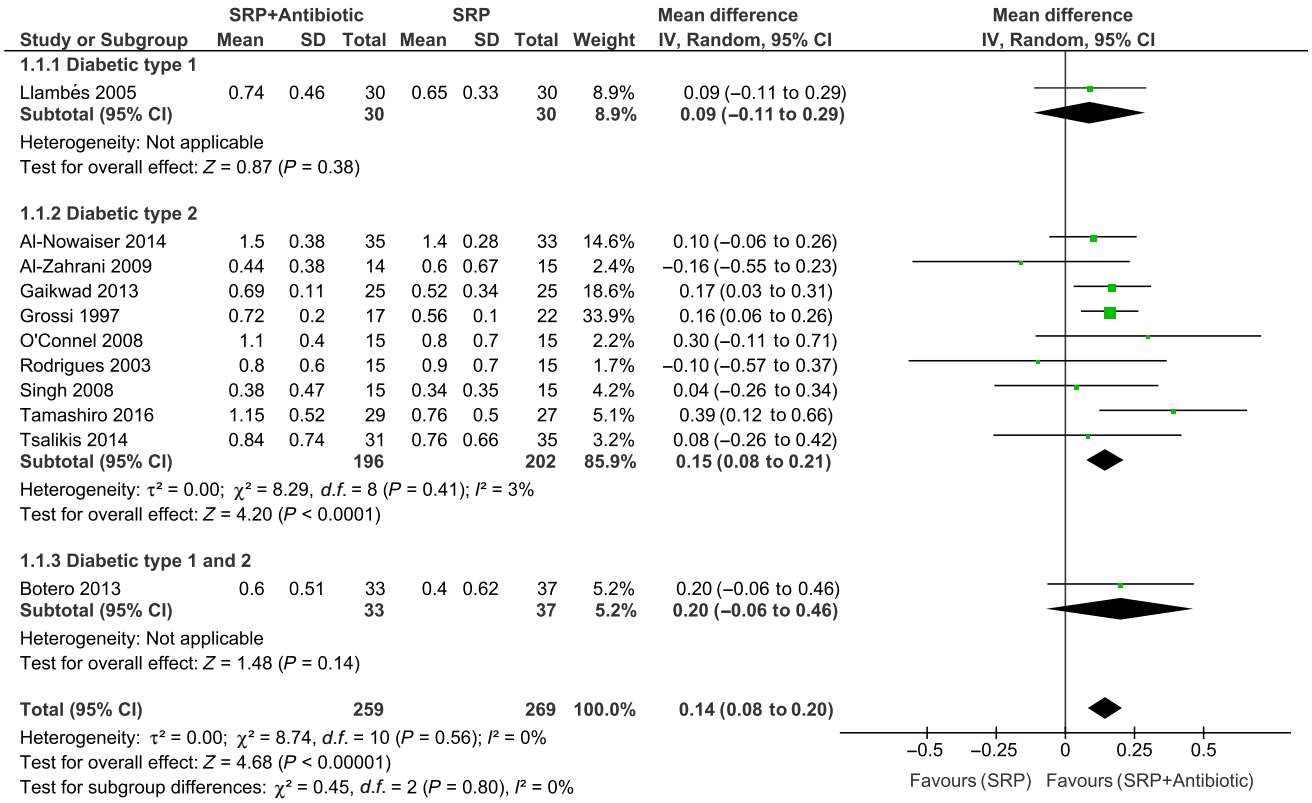

Figure 2. Forest-plot probing pocket depth (PPD) reduction. 95% CI, 95% confidence interval; SD, standard deviation; SRP, scaling and root planing.

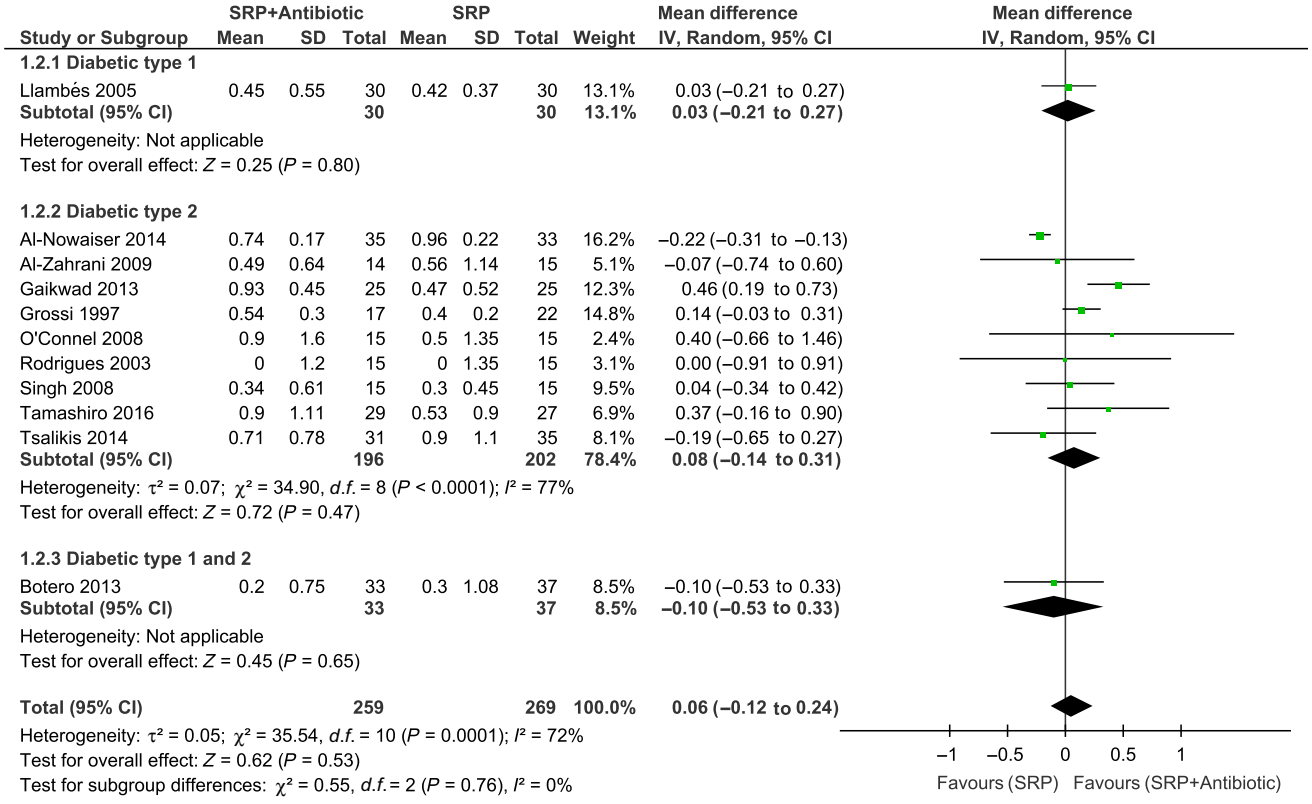

Figure 3. Forest-plot of clinical attachment level (CAL) gain. 95% CI, 95% confidence interval; SD, standard deviation; SRP, scaling and root planing.

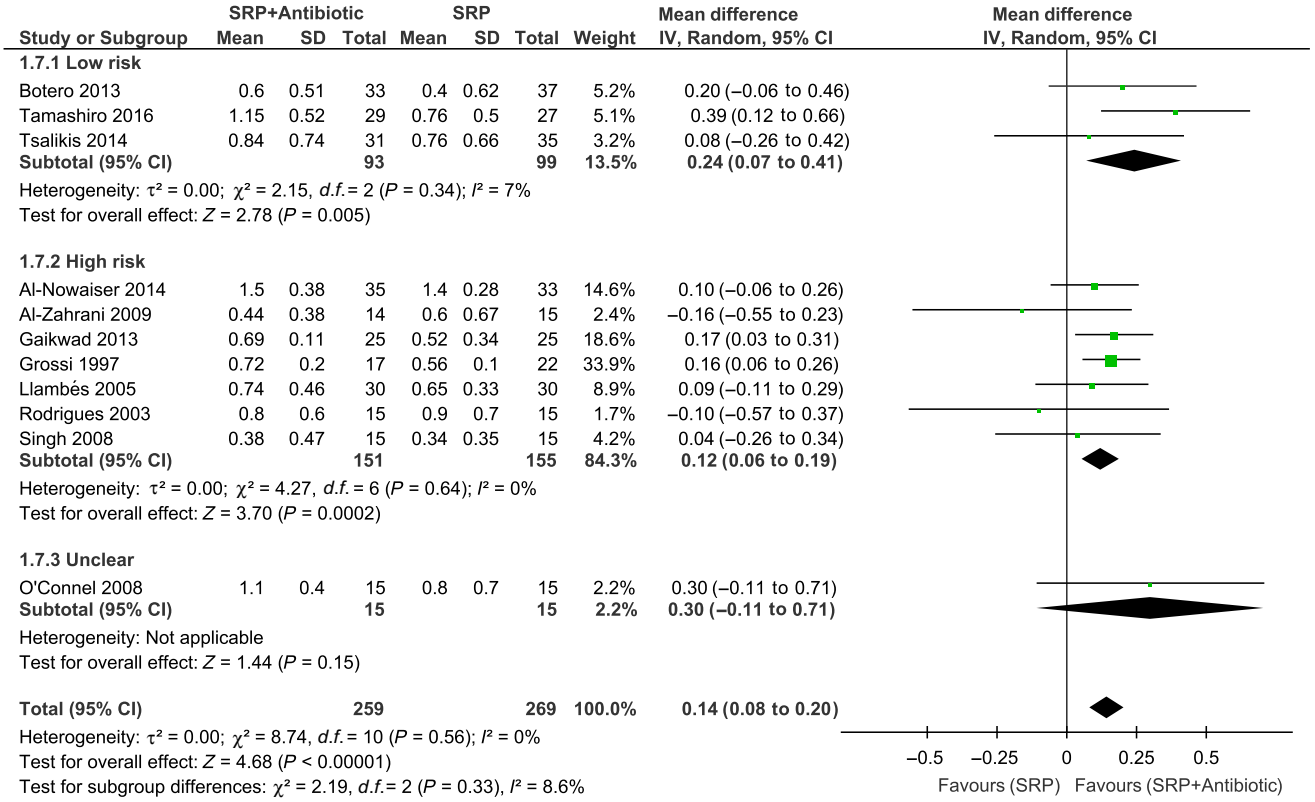

Figure 4. Forest-plot of probing pocket depth (PPD) reduction and risk of bias. 95% CI, 95% confidence interval; SD, standard deviation; SRP, scaling and root planing.

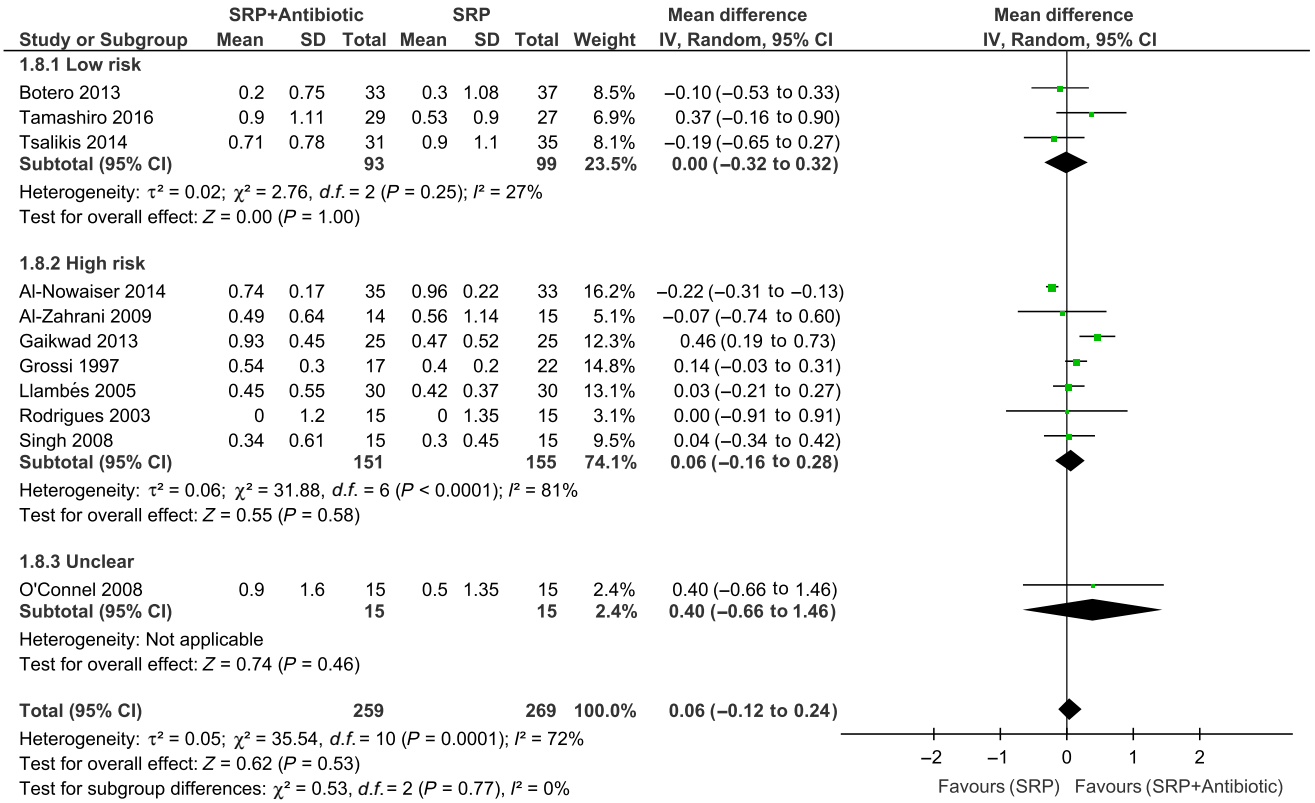

Figure 5. Forest-plot of clinical attachment level (CAL) gain and risk of bias. 95% CI, 95% confidence interval; SD, standard deviation; SRP, scaling and root planing.

last tablet. One study[15] reported that diarrhoea (three subjects in the control group and seven in the test group), headache (one patient in the control group and four in the test group), metallic taste (two patients in the control group and four in the test group) and nausea/vomiting (two participants in the control group and five in the test group) were adverse effects informed by the participants. Another study[31] reported that one female patient in the control group reported dizziness and difficulty in swallowing. Only one trial[26] reported that there were no adverse events. The other seven papers[13,23,24,27–30] included in this meta-analysis did not mention adverse effects or complications in the paper.

DISCUSSION

Main results

Overall, meta-analysis showed a modest additional benefit of 0.14 mm in PPD reduction in subjects treated with SRP + antimicrobial in comparison with SRP + placebo/alone. Conversely, no further benefit was found in CAL gain. Only three[15,26,27] of the 11 investigations showed significant CAL gain and PPD reduction when adjunctive systemic antimicrobials were used. Two of these studies investigated the effect of doxycycline 100 mg[26,27] and one study assessed the effects of the association of metronidazole 400 mg + amoxicillin 500 mg[15].

Doxycyline was the antimicrobial most commonly studied[13,23,24,26–28,30,31,38,39]. However, subgroup analysis showed a modest additional benefit of 0.13 mm in PPD reduction and no further benefit in CAL gain compared with SRP alone. These findings are similar to those found in the use of doxycycline as adjunct to SRP in healthy subjects[42]. Thus, the findings of the present SR do not support the use of doxycycline in combination with SRP for the treatment of periodontitis in diabetic subjects. Furthermore, also based on one study, subanalyses revealed no additional benefits regarding the use of azithromycin or amoxicillin + clavulanic acid as adjuncts to SRP. Only one trial[15] included in the present review assessed the effect of amoxicillin + metronidazole as adjuncts to SRP, which is the combination with more evidence of efficacy[43]. Subgroup analysis revealed an additional

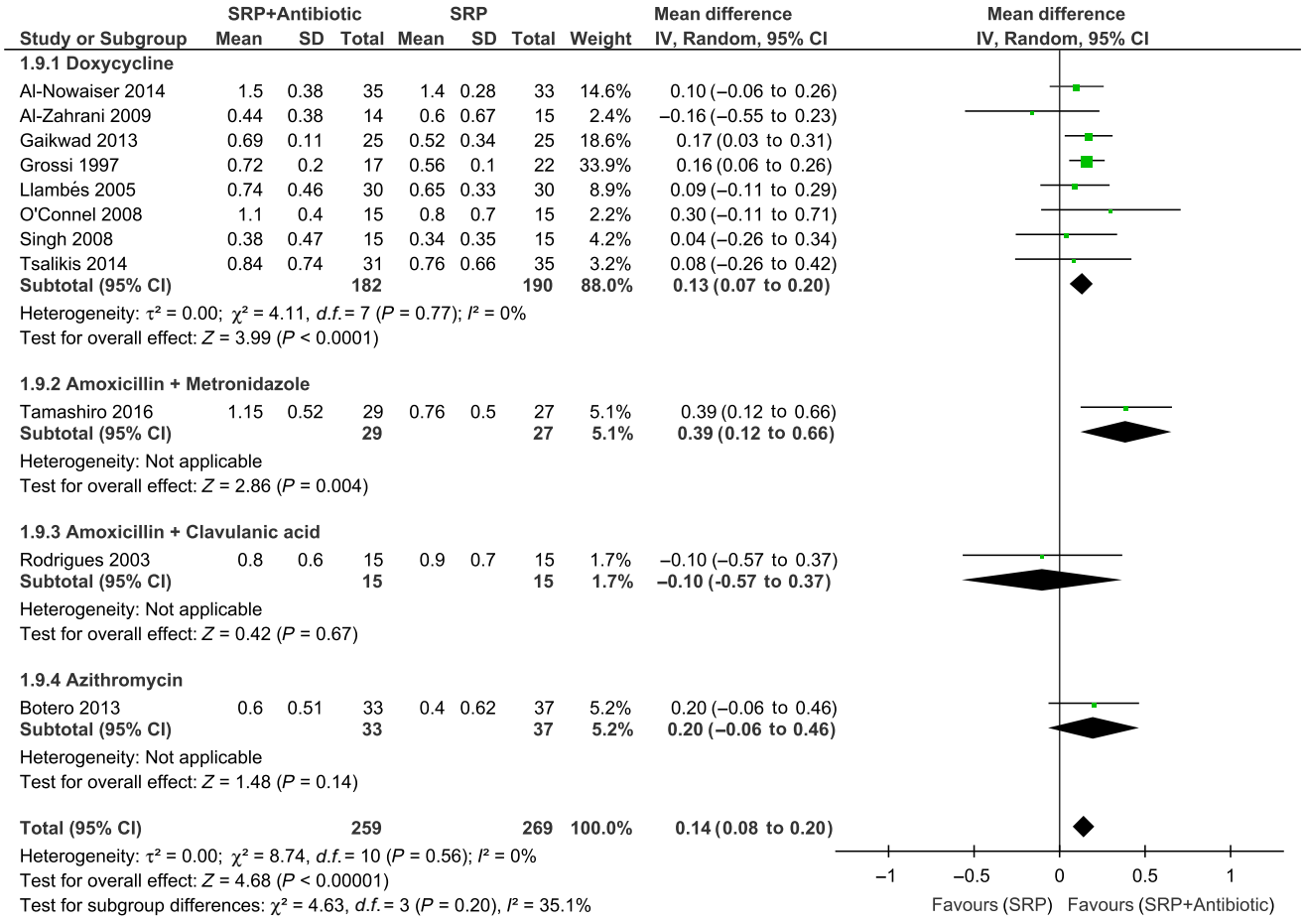

Figure 6. Forest-plot of probing pocket depth (PPD) reduction according to antibiotic type. 95% CI, 95% confidence interval; SD, standard deviation; SRP, scaling and root planing.

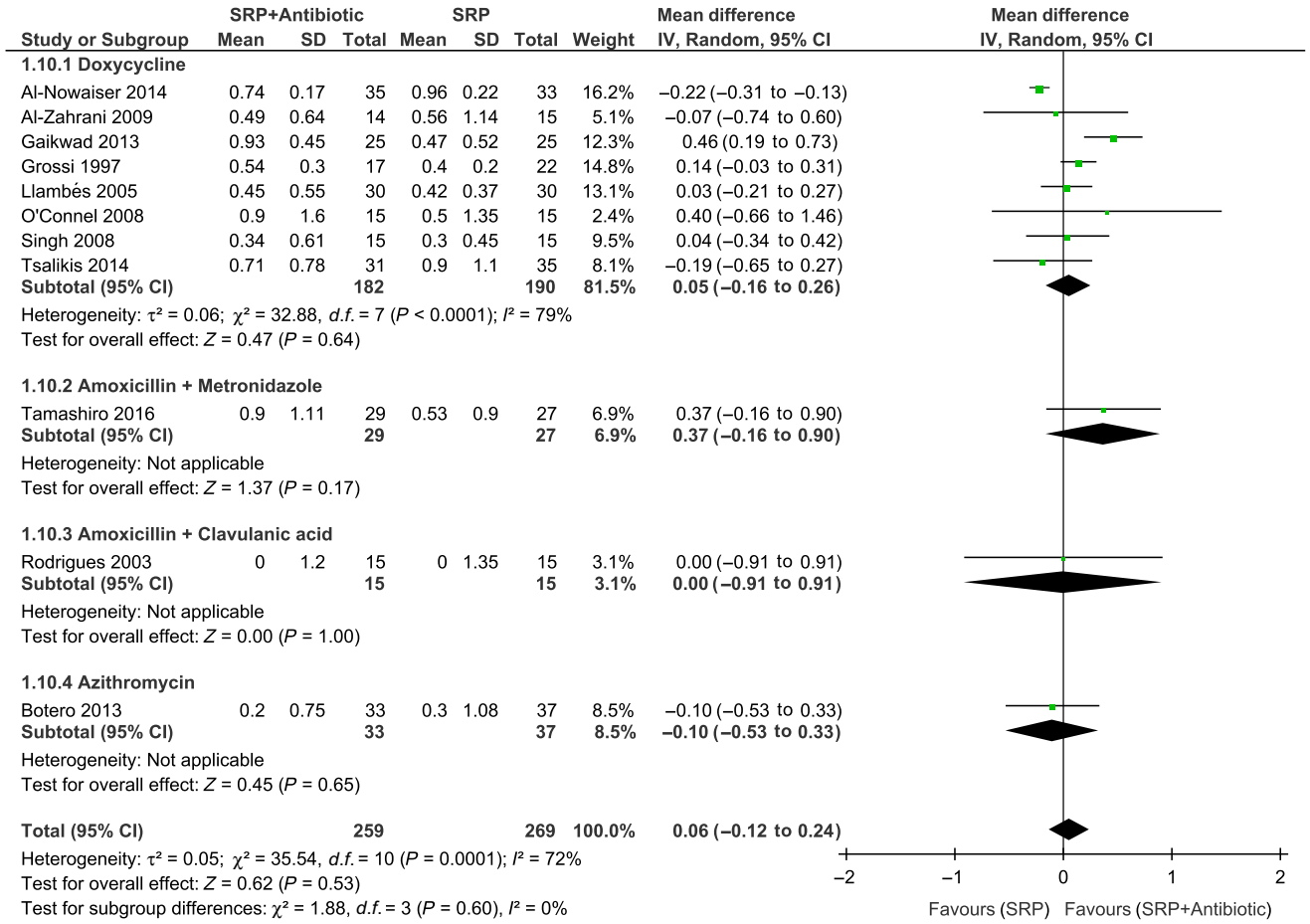

Figure 7. Forest-plot of clinical attachment level (CAL) gain according to antibiotic type. 95% CI, 95% confidence interval; SD, standard deviation; SRP, scaling and root planing.

benefit of 0.39 mm in PPD reduction when compared with SRP alone. Noteworthy, this trial presented low risk of bias and was the study with the longest follow-up period (2 years). Thus, the results favouring the antibiotic therapy observed by these authors, such as the significant reduction of sites with ≥5 mm of CAL gain and PPD reduction must be highlighted. A larger number of well-conducted clinical trials, which assess the effects of amoxicillin plus metronidazole in combination with SRP in the treatment of chronic periodontitis in diabetic patients, should be conducted to corroborate these findings.

Quality assessment and limitations

According to Cochrane Collaboration's tool[20], the risk of bias analyses showed that among the 11 trials, only three[15,25,31] (27.27%) were considered to have low risk of bias. In SRs, qualitative assessments of the studies represent a pivotal tool for evaluating methodological weakness that may influence the results of the trials. In the present SR, most of the studies[13,24,26,28,29] included chose reduction of glycated haemoglobin as the primary outcome, and were conducted with short-term follow-up periods. Although the follow-up of 3 and 4 months may be sufficient to evaluate this outcome, the short follow-up might not have been sufficient to detect improvement in clinical parameters (PPD reduction and CAL gain). Furthermore, although smoking has a negative influence in the periodontal therapy[42–44], some of the trials[24,25,27,30] included in the present SR did not exclude smokers or report participant's smoking status.

High heterogeneity (>70%) was observed in pooled estimates of CAL gain (*Figure 3*), whereas no heterogeneity was found in the assessment of PPD (*Figure 2*). This could be a result of the different definitions of periodontitis used in the studies, different baseline periodontal status (mainly initial PPD) and different treatment protocols (including the various agents and concentrations). Furthermore, risk of bias of the studies (high/unclear) may have influenced the pooled estimates (*Figures 4 and 5*). However, despite these differences and the limitations of most of the studies included in this review, the outcomes of

these trials could be considered as in agreement in terms of PPD reduction, in view of the lack of significant heterogeneity detected ($I^2 = 0\%$). Still, the findings of the present review should be interpreted with caution.

Comparison with the literature

The meta-analyses of this review demonstrated a limited advantage in PPD reduction and no further advantage in CAL gain in subjects treated with SRP plus systemic antimicrobials in comparison with SRP alone or placebo. These main findings are in agreement with the other two SRs[17,18]. One of the SRs[18] excluded one trial[26] that was included in our review. The reason was that the final number of participants in the groups was not reported in the article. Moreover, the same authors excluded two studies[28,29] from the global meta-analyses because the CAL was measured using customised acrylic stents. In our review, we chose to include both because we analysed CAL change from baseline. In addition, another difference from our study is that Grellmann *et al.*[18] opted to include a study[32] with subantimicrobial dose doxycycline, even though the literature shows that the administration in the long-term administration of this kind of therapy does not present antibacterial effects[44]. The main differences between our SR and the one conducted by Santos *et al.*[17] are the inclusion of a study with subantimicrobial dose doxycycline[32] and studies with at least 6 months of follow-up. Thus, the number of trials included in their meta-analyses was restricted to four.

Suggestion for future studies

Future trials on the use of systemic antibiotics in DM subjects with chronic periodontitis should present: (i) at least 12 months of follow-up; (ii) well-defined inclusion criteria on diabetes status; and (iii) exclusion of smokers or randomisation stratified according to smoking status.

In conclusion, when the data for all antibiotic protocols were considered together for the treatment of periodontitis patients with DM, a significant, albeit small, PPD reduction and no improvement in CAL gain were observed. When the antibiotic protocols were analysed separately, the combination of amoxicillin + metronidazole yielded the best results for PPD reduction.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Search strategy.

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Correspondence to:
Dr Cláudio Mendes Pannuti
Division of Periodontics,
University of São Paulo,
Avenida Prof. Lineu Prestes,
2227, São Paulo 05508-000,
SP, Brazil.
Email: pannuti@usp.br