Clinical Oral Investigations (2018) 22:2413–2430
https://doi.org/10.1007/s00784-018-2507-x

REVIEW

Locally applied statins as adjuvants to non-surgical periodontal treatment for chronic periodontitis: a systematic review and meta-analysis

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Received: 22 September 2017 / Accepted: 30 May 2018 / Published online: 12 June 2018

Abstract

Objective This review aimed at evaluating the effects of chronic periodontitis (CP) treatment with local statins as adjuncts to scaling and root planing (SRP), compared with SRP alone or with placebo.

Methods Electronic and hand searches were conducted in three databases to select randomized controlled trials (RCTs) comparing SRP + statins versus SRP alone. Random effects models were conducted to determine the clinical attachment level (CAL) gain as the primary outcome variable, and probing pocket depth (PPD) reduction, modified sulcus bleeding index (mSBI), and intrabony defect depth (IBD) as the secondary outcomes.

Results Of the 526 papers identified, 15 articles met the criteria for inclusion in this systematic review, and 13 in the meta-analysis. The meta-analysis showed a statistically significant CAL gain (mean differences [MD] = 1.84 mm, 95% confidence interval [CI] = 1.45 to 2.23; $p = 0.000$), PPD reduction (MD = 1.69 mm, 95% CI = 1.37 to 2.04; $p = 0.000$), mSBI change (MD = 0.70, 95% CI = 0.57 to 0.84; $p = 0.000$), and IBD (MD = 1.48, 95% CI = 1.30 to 1.67; $p = 0.000$) attributed to SRP + statin treatment (6 months).

Conclusion Within the limitations of this study, the collective evidence emerging from this systematic review and meta-analysis may support the use of locally applied statins as adjuncts to SRP in CP treatment, based on being an easy, low-cost alternative, with lesser adverse effects on bacterial resistance. These results should be interpreted with caution.

Clinical relevance Clinicians might consider the use of SRP + statins as an adjunct over other alternative approaches, based on the results of the present review. The informed decision should be taken, considering the patient's values and preferences, and the intervention to be implemented by the clinician.

Keywords Hydroxymethylglutaryl CoA reductases · Root planing · Chronic periodontitis · Meta-analysis

Introduction

Scaling and root planing (SRP) remains an essential part of successful periodontal disease therapy [1]. Evidence from numerous randomized clinical trials (RCTs) reveals a consistency in the clinical responses to chronic periodontitis (CP) treatment by SRP, which is considered the "gold standard."

The clinical changes after SRP include periodontal pockets depth (PPD) reductions and clinical attachment level (CAL) gains [2]. However, SRP may not sufficiently reduce the periodontal pocket (PPD < 4 mm) in some cases, for example, deeper pockets, tooth type, and tooth location [3]. Adjuvant procedures have been proposed to enhance non-surgical periodontal treatment efficacy, including antibiotics [4], antiseptic agents [5], and photodynamic therapy [6, 7].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00784-018-2507-x) contains supplementary material, which is available to authorized users.

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Statins are inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), which is an important enzyme related to the synthesis of cholesterol [8]. Statins are the most widely used hypolipidemic agents (as inhibitors of cholesterol biosynthesis), due to their effectiveness in reducing the concentration of blood cholesterol and their excellent tolerability, safety, and low cost [9].

These drugs prevent the synthesis of mevalonate but also of isoprenoid precursors (geranyl and farnesyl pyrophosphates), which are substrates for prenylation (addition of hydrophobic molecule to proteins) of small GTP-binding proteins (Rho, Rac, Rab) [10]. This decrease in prenylation inhibits osteoclast activity because these small proteins cannot anchor to the membrane of osteoclasts by lack of a lipid chain [11]. Mevalonate deprivation suppresses the expression of the receptor for activation of nuclear factor kappa B (NFκB) ligand (RANKL) and activation of NFκB that inhibits osteoclast differentiation and induces osteoclast apoptosis [12],

Both in vitro and in vivo studies demonstrate that statins show convincing anabolic and anti-resorptive bone effects [13, 14], and share these effects on cholesterol pathway downstream to mevalonate with nitrogen-containing bisphosphonates (pamidronate, risedronate, ibandronate, and zoledronate), which inhibit specifically farnesyl pyrophosphate synthase and act as bone anti-resorptive agents [11].

In this sense, statins were considered an almost ideal candidate family of anti-osteoporotic drugs, due to their potential dual anabolic and anti-resorptive effects on bone, and to the extremely large and reassuring experience with these drugs in cardiology (excellent risks to benefits ratio and very low incidence of side effects) [15].

Also, it is reported that use of statins gives rise also to the so-called pleiotropic effects, on the expression of bone morphogenetic protein-2 (BMP-2) gen in bone cells [13], indicating an anabolic effect on bone [8]. Some studies have shown that statins are able to modulate inflammation and alveolar bone loss [16]. Various animal studies reported favorable effects on bone regeneration when statins were applied locally or orally [17–19] and a positive effect around dental implants, increasing osteogenesis [20, 21].

Their immunoregulatory effects in human epithelial cells is well-known in vitro studies [22], as well as their antibacterial properties inhibiting oral and perioral microorganisms, in vitro [23]. The pleiotropic effects were observed clinically, where CP patients on statin medication expressed lower IL-1 levels [24]; and a downregulation of IL-1β, myeloperoxidase levels, and higher anti-inflammatory IL-10 levels in gingival crevicular fluid compared to patients without statin treatment [25].

A series of studies in humans have shown that local delivery of statins may result in additional benefits to non-surgical periodontal treatment, when compared to SRP alone [26–29]. Thereafter, numerous studies were published, investigating the effect of locally applied statins in periodontology. Hence, the aim of the current systematic review is to determine if the adjunctive local use of statins could provide additional benefits for periodontal disease treatment.

Material and methods

The present systematic review was conducted in accordance with the Transparent Reporting of Systematic Reviews and Meta-Analysis—PRISMA Statement [30] and AMSTAR [31] guidelines.

Focus question

This systematic review and meta-analysis aimed to answer the following focus question developed in accordance with the recognized Population, Intervention, Comparison, Outcome (PICO) format: "Can the local application of statins improve clinical periodontal parameters, in terms of CAL gain, PPD reduction, modified sulcus bleeding index (mSBI), and IBD reduction, when used as an adjuvant to SRP versus SRP alone (or placebo) in the treatment of patients with CP?"

Population is classified with chronic periodontitis when PPD ≥ 5 mm, CAL ≥ 3 mm, and angular bone loss ≥ 3 mm [32]. Its classification also depends on additional measurements of bleeding on probing (BOP) [33].

Inclusion and exclusion criteria for studies to be considered for inclusion in this review

The studies had to meet the following criteria to be eligible:

i. Randomized controlled trials (RCTs) and split-mouth studies in human individuals (≥ 18 years old).
ii. Studies that assessed the local use of statins as adjuvants to SRP non-surgical treatment (SRP + statins) in CP patients.
iii. Control patients that received the same SRP non-surgical treatment either alone or plus placebo (SRP + placebo).
iv. Studies that quantitatively reported clinical periodontal parameters, such as CAL, PPD, mSBI, and IBD, with at least 6 months of follow-up after randomization.
v. Studies that included individuals with systemic diseases or risk factors (e.g., diabetes or smoking).

Exclusion criteria

The excluded studies comprised prospective, controlled clinical trials without randomization; case-control, cross-sectional case series and case report studies; literature or narrative reviews; animal and in vitro studies; studies that included aggressive periodontitis patients, or in which an adjunct was

administered more than 1 week after SRP, or was reapplied to progressively worsening tooth sites.

Search strategy

The electronic search was performed by two authors (J.M.M. and D.S.P.) for articles in English, up to March 2017. The search strategy combined MeSH and EMTREE terms. Other terms not indexed as MeSH were also used. A hand search of relevant primary sources was performed. Finally, the references of the included studies were explored to capture any potential additional records [34].

In addition, the gray literature in the System for Information on Grey Literature in Europe (http://www.opengrey.eu), The New York Academy of Medicine Grey Literature Report (http://www.greylit.org), and Google Scholar databases were screened electronically, as recommended by the high standards for systematic reviews (AMSTAR guideline) [31]. Furthermore, a hand search of relevant primary sources related to the topic was made in *Journal of Dental Research*, *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research*, *Clinical Oral Investigations*, and *Archives of Oral Biology*. Finally, the references of included studies were explored to capture any potential additional records, as suggested by Greenhalgh and Peacock [34]. The search details tailored for each database are depicted in Appendix-S1.

Data collection, extraction, and management

Screening and selection of papers

Titles and abstracts were screened by two reviewers independently (D.S.P. and D.P.O.). Full-text reports were obtained and reviewed independently for studies that seemed to meet the inclusion criteria (Appendix-S2); kappa scores (Cohen's κ coefficient) were employed during full-text assessment to ensure eligibility and level of agreement between the reviewers. Disagreements were resolved by discussion and consulting a third reviewer (J.M.C.).

Search outcomes and evaluation

Two independent researchers (J.M.M. and D.C.P.) extracted the variables of interest in duplicate, using predefined spreadsheets; disagreements were resolved by discussion with a third reviewer (J.M.C.). In the event of missing data, a request was sent to the authors.

Chronic periodontitis is so classified when PPD $\geq$ 5 mm, clinical attachment CAL $\geq$ 3 mm, and angular bone loss $\geq$ 3 mm [32]. Its classification also depends on additional measurements of bleeding on probing (BOP) [33].

Primary outcome

CAL is used as the main outcome, because PPD fails to capture the effect of non-surgical treatment, and has a predictability of about 50% in probing depths of 7 mm [35–38].

CAL gain CAL gain is considered as the mean changes in millimeters between baseline and follow-up. CAL is defined as the extent of the periodontal support that has been destroyed around a tooth. It is estimated by calculating the arithmetic difference between the PPD and the position of the gingival margin (distance from the gingival margin to the cement-enamel junction (CEJ)/recession). If CEJ is not detected, it can be estimated according to the apical margin of restoration.

Secondary outcomes

PPD reduction PPD reduction is considered as the mean changes in millimeters between baseline and follow-up. PPD is defined as the distance from the free gingival margin to the bottom of the periodontal pocket, measured with a calibrated periodontal probe.

mSBI changes mSBI changes is considered as the mean changes between baseline and follow-up. The modified sulcus bleeding index (mSBI) quantifies the bleeding on probing (BOP). Individual patients can be monitored for their response to initial therapy and during maintenance by using mSBI with three recommended bleeding scores [39], as well as mean BOP values (with standard deviation) [40].

IBD reduction IBD reduction is considered as the mean changes in millimeters between baseline and follow-up of the vertical distance from the crest of the alveolar bone to the base of the defect, detected by standardized periapical radiographs. In addition, the Glossary of Periodontal Terms of the American Academy of Periodontology considers an osseous defect as the reduction in or deficiency of the bony architecture around the teeth and implants, caused by disease or trauma; it may be intrabony or interradicular in nature.

Risk of bias in individual studies

Quality assessment was performed by two independent reviewers (J.M.M. and D.S.P.), according to the Cochrane Collaboration tool for assessing risk of bias in randomized trials [41], and using the following assessment criteria: low risk of bias (all domains were met); high risk of bias (when $\geq$ 1 domain was not met); and unclear (when $\geq$ 1 domain was partially met). The interexaminer agreement was ascertained by a kappa test; disagreements were resolved by discussion, consulting a third advisor (D.C.P.). A summary of bias appraisal is depicted in Appendix-S3.

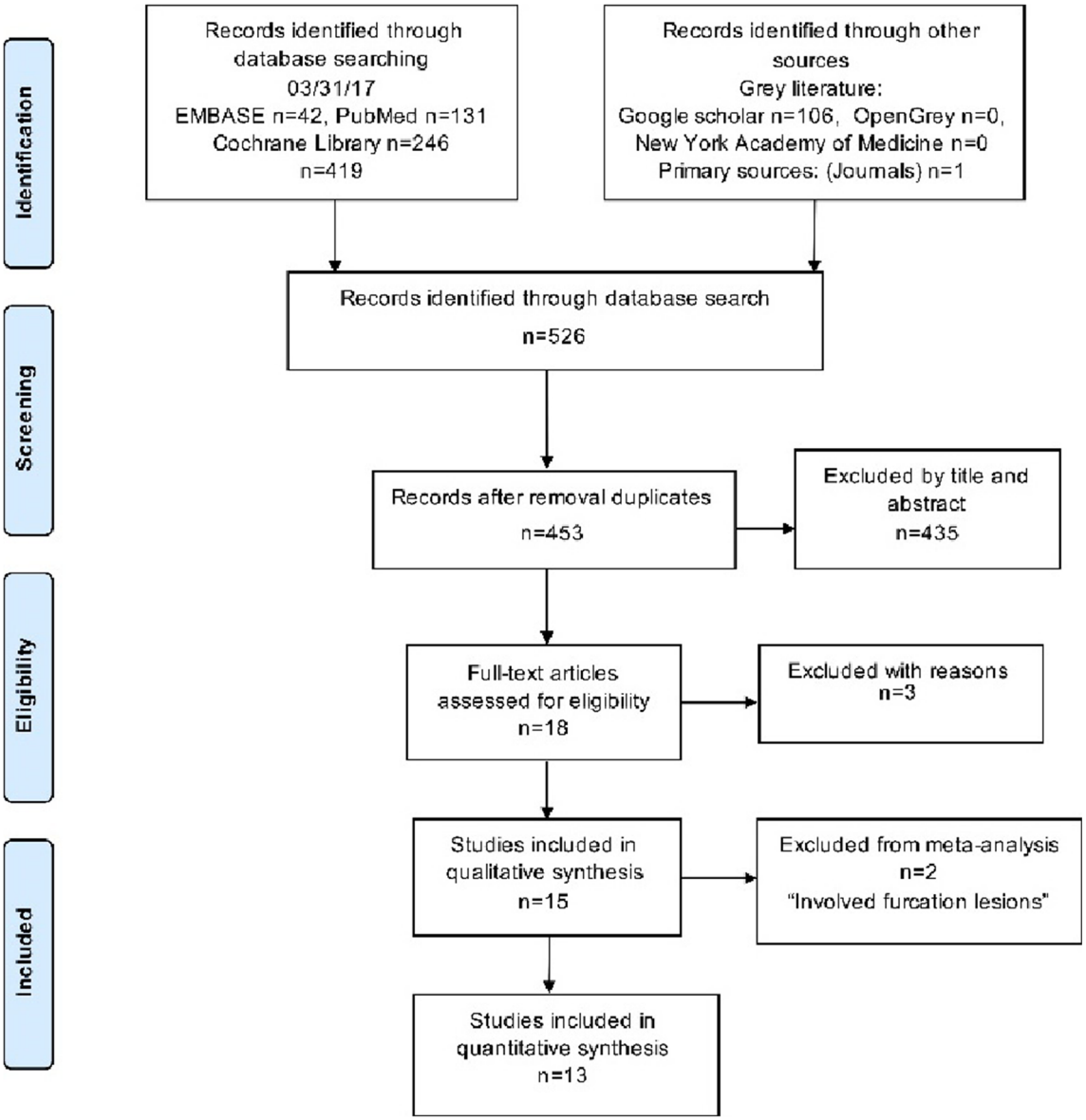

Fig. 1 PRISMA flow chart of manuscripts screened through the review process

Summary of measures and synthesis of results

Statistical data handling was performed by one author (J.M.C.). Random effects meta-analyses were conducted at 3 and 6 months of follow-up. Pooled outcomes were expressed as mean differences (MD) with a 95% confidence interval (CI). Forest plots were created to illustrate the effects of the meta-analysis results. Studies involving furcation lesions were excluded from the meta-analysis, because the prognosis differs in terms of defect composition and healing.

Subgroup analyses were conducted according to different statin types. If the analysis failed to detect any significant difference, the locally applied statins were considered as a sole group in the meta-analysis. In studies with multiple treatment arms, in which data from the control group were compared with data from more than one other group, the number (n) of subjects in the control group was divided by the number of comparisons. The I^2 statistics and corresponding nullity Q test were employed [42]; I^2 values of 25, 50, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. The potential for publication bias was determined using Egger's test [43]. In addition, the classic fail-safe number was used to test data robustness regarding publication bias and average effect size of the intervention. This test estimates the number of additional "negative" studies (studies in which the effect of the intervention was zero) that would be needed to increase the P value of the meta-analysis above 0.05. A sensitivity meta-analysis was planned to determine the main outcome, based on the inclusion or exclusion of trials that include

Table 1 Characteristics of the included studies

Author (year) country/region	Study design	Diagnosis	Clinical parameters	N M/F age	Dropouts	CP definition	Treatment/ scaffold	Risk populations	Follow-up	Summary of findings
Pradeep & Throat (2010) India/Asia	RCT (single blind)	Chronic Periodontitis	PPD, CAL, mSBI and IBD evaluated by periapical Rx with a parallel-angle technique	60 33/31 25–45	0	Patients with PPD 5 to 6 mm CAL 4 to 6 mm *N* 24 or PPD ≥ 7 mm, CAL of 6 to 9 mm *N* 36 and vertical bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 30 sites SRP + SMV 1.2% (test) in 30 sites methylcellulose gel		6 months (months 1, 2, 4, 6)	There was greater decrease in PPD and more CAL gain with significant IBD fill with locally delivered SMV in patients with CP.
Pradeep et al. (2012) India/Asia	RCT (single blind)	Chronic periodontitis with mandibular class II furcation defects	PPD, RAL, mSBI and IBD evaluated by periapical Rx with a parallel-angle technique	72 38/34 30–50	6	Patients with PPD ≥ 5 mm with a radiolucency in the furcation area on an intraoral (periapical radiographs)	SRP + placebo (control) in 33 sites SRP + SMV 1.2% (test) in 33 sites methylcellulose gel		6 months (months 3, 6)	There was greater decrease in PPD, mSBI and more RAL gain with significant bone fill with locally delivered SMV in patients with class II furcation defects.
Rath et al. (2012) India/Asia	RCT (single blind)	Generalized chronic periodontitis	PPD, CAL, mSBI and IBD evaluated by periapical Rx with a parallel-angle technique	60 33/27 25–45	0	Patients with PPD ≥ 5 mm and vertical bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 30 sites SRP + SMV 1.2% (test) in 30 sites methylcellulose gel		180 days (days 60, 90, 180)	There was greater decrease in PPD, mSBI and improved bone fill with locally delivered SMV in patients with CP.
Rao et al. (2013) India and Asia	RCT (single blind)	Chronic periodontitis	PPD, CAL, mSBI, and IBD evaluated by periapical Rx with a parallel-angle technique	40 40/0 30–50	5	Patients with PPD ≥ 5 mm or CAL ≥ 4 mm and vertical bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 34 sites SRP + SMV 1.2% (test) in 33 sites methylcellulose gel	Smokers (more than 10 cigarettes/day for a minimum of 5 years.)	9 months (months 3, 6, 9)	There was a greater decrease in mSBI and PD and more CAL gain with significant IBD fill at sites treated with SRP plus locally delivered SMV in smokers with chronic periodontitis
Pradeep et al. (2013a) India/Asia	RCT (double blind)	Chronic periodontitis	PPD, CAL, mSBI, and IBD evaluated by periapical Rx with a parallel-angle technique	38 20/18 30–50	3	Patients with PPD ≥ 5 mm, CAL ≥ 4 mm and vertical bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 29 sites, SRP + SMV 1.2% (test) in 29 sites methylcellulose gel	Type 2 diabetes	9 months (months 3, 6, 9)	There was a greater decrease in mSBI and PD and more CAL gain with significant IBD fill at sites treated with SRP plus locally delivered SMV in patients with type 2 diabetes and CP.
Pradeep et al. (2013b) India/Asia	RCT (single blind)	Severe chronic periodontitis	PPD, CAL, mSBI, and IBD evaluated by periapical Rx with a parallel-angle technique	67 35/32 30–50	7	Patients with PPD ≥ 5 mm, CAL ≥ 4 mm and vertical bone loss ≥ 3	SRP + placebo (control) in 30 sites, SRP + ATV 1.2% (test) in 30 sites methylcellulose gel		9 months (months 3, 6, 9)	Local delivery of 1.2% ATV into IBD in individuals with CP stimulates a significant increase in PPD

Table 1 (continued)

Author (year) country/region	Study design	Diagnosis	Clinical parameters	N M/F age	Dropouts	CP definition	Treatment/ scaffold	Risk populations	Follow-up	Summary of findings
						mm (periapical radiographs)				reduction, CAL gain, and improved bone fill as an adjunct to SRP compared with placebo gel.
Gaekwad et al. (2015) India/Asia	RCT/split-mouth (single blind)	Chronic periodontitis	PPD, CAL, and bleeding index	20 0/20 45–55	0	Patients with PPD ≥ 4 mm, CAL ≥ 3 mm and bleeding on probing	SRP + placebo (control) in 20 sites, SRP + SMV 1.2% (test) in 20 sites	Post-menopausal	6 months (months 3, 6)	The results of the study showed predictable clinical improvements with the subgingival delivery of SMV adjunctively to SRP.
Pradeep et al. (2015) India/Asia	RCT (single blind)	Moderate chronic periodontitis	PPD, CAL, mSBI and IBD evaluated by periapical Rx with a parallel-angle technique	70 33/37 25–50	5	Patients with PPD 5 to 6 mm, CAL 4 to 6 mm, and vertical bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 33 sites SRP + RSV 1.2% (test) in 32 sites methylcellulose gel		6 months (months 1, 3,4,6)	The results of the study concluded that 1.2% RSV in situ gel, when delivered subgingival/locally, showed bone formation in IBD sites, thereby reducing PPD and increasing CAL gain.
Agarwal et al. (2016) India/Asia	RCT/split-mouth (single blind)	Chronic periodontitis	PPD, CAL, and IBD evaluated by periapical Rx with a parallel-angle technique	30 −/− 25–50	11	Patients with PPD ≥ 5 mm and vertical bone loss ≥ 2 mm (periapical radiographs)	SRP + placebo (control) in 19 sites SRP + SMV 1.2% (test) in 19 sites methylcellulose gel		6 months (months 1, 3, 6)	Local drug delivery of SMV enhanced the beneficial effect of SRP, in pocket reduction, gain in CAL and bone fill
Pradeep et al. (2016a) India/Asia	RCT (triple blind)	Chronic periodontitis	PPD, CAL, mSBI, and IBD evaluated by periapical Rx with a parallel-angle technique	90 45/45 25–45	9	Patients with PPD ≥ 5 mm, CAL ≥ 3 mm, and angular bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 27 sites, SRP + RSV 1.2% (test) in 27 sites, SRP + ATV 1.2% (test) in 27 site methylcellulose gel.		9 months (months 6, 9)	Adjunctive subgingival administration of statins is superior to mechanical periodontal therapy alone, with of 1.2% RSV resulting in significantly greater clinical and radiographic improvements compared with 1.2% ATV.
Pradeep et al. (2016b) India/Asia	RCT (doubled blind)	Chronic generalized periodontitis	PPD, CAL, mSBI, and IBD evaluated by periapical Rx with a parallel-angle technique	66 −/− 30–50	6	Patients with PPD ≥ 5 mm, CAL 4 to 6 mm, and vertical bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 30 sites SRP + ATV 1.2% (test) in 30 sites		9 months (months 3,6,9)	There was greater decrease in PPD and more CAL gain with significant IBD fill with locally delivered ATV in patients with CP.
Kumari et al. (2016a) India/Asia	RCT (single blind)	Chronic periodontitis	PPD, CAL, mSBI, and IBD evaluated	71 −/− 30–50	5	Patients with PPD ≥ 5 mm,	SRP + placebo (control) in 33 sites SRP + ATV	Smokers (more than 10 cigarettes/day	9 months (months 3, 6, 9)	Local delivery of 1.2% ATV into periodontal pockets

Table 1 (continued)

Author (year) country/region	Study design	Diagnosis	Clinical parameters	N M/F age	Dropouts	CP definition	Treatment/ scaffold	Risk populations	Follow-up	Summary of findings
			by periapical Rx with a parallel-angle technique			CAL ≥ 4 mm, and vertical bone loss ≥ 3 mm (periapical radiographs)	1.2% (test) in 33 sites Methylcellulose gel	for a minimum of 5 years.)		in smokers with CP stimulated a significant improvement in clinical parameters compared with placebo gel as an adjunct to SRP.
Kumari et al. (2016b) India/Asia	RCT (single blind)	Chronic periodontitis	PPD, RAL, mSBI, and IBD evaluated by periapical Rx with a parallel-angle technique	75 38/37 40–50	15	Patients with PPD ≥ 5 mm, RAL ≥ 4 mm, and vertical bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 30 sites SRP + ATV 1.2% (test) in 30 sites methylcellulose gel	Type 2 diabetes	9 months (months 3, 6, 9)	Local delivery of 1.2% ATV into periodontal pockets of patients with t2DM stimulated significant improvement in clinical and radiographic parameters compared with placebo gel in adjunct to SRP.
Martande et al. (2017) India/Asia	RCT (single blind)	Moderate to severe chronic periodontitis	PPD, CAL, mSBI, and IBD evaluated by periapical Rx with a parallel-angle technique	96 50/46 25–45	8	Patients with PPD ≥ 5 mm, CAL ≥ 4 mm, and vertical bone loss ≥ 3 mm (periapical radiographs)	SRP + placebo (control) in 28 sites, SRP + ATV 1.2% (test) in 30 sites, SRP + SMV 1.2% (test)* in 30 sites. methylcellulose gel		9 months (months 6, 9)	ATV resulted in greater improvements in clinical parameters with higher percentage of radiographic defect depth reduction as compared to SMV in the treatment of intrabony defects in CP subjects.
Garg & Pradeep (2017) India/Asia	RCT (single blind)	Chronic periodontitis with mandibular class II furcation defects	PPD, RAL, mSBI, and IBD evaluated by periapical Rx with a parallel-angle technique	90 40/50 –/–	0	Patients with PPD ≥ 5 mm with a radiolucency in the furcation area on an intraoral (periapical radiographs)	SRP + placebo (control) in 30 sites, SRP + RSV 1.2% (test) in 30 sites, SRP + ATV 1.2% (test)* in 30 sites. methylcellulose gel		9 months (months 3, 6, 9)	RSV group showed significant improvement in all clinical parameters along with significantly greater defect depth reduction as compared to ATV group in treatment of mandibular class II furcation defects as an adjunct to SRP.

N population, *M/F* male/female, *RCT* randomized clinical trial, *CP* chronic periodontitis, *mSBI* modified sulcus bleeding, *PPD* periodontal probing depth, *CAL* clinical attachment level, *RAL* relative attachment level, *IBD* intrabony defect, *Rx* = radiograph, *SRP* scaling and root planing, *SMV* simvastatin, *ATV* atorvastatin, *RSV* rosuvastatin

patients with systemic diseases or risk factors that may exert effects, such as confounders or effect size modifiers. The analysis was performed using the Comprehensive Meta-Analysis Ver. 3 software package, Biostat Inc. Englewood, NJ, USA.

Grading the evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was employed to assess the quality of the body of evidence related to the primary outcome. The GRADEpro Guideline Development Tool https://gradepro.org was used to create a "summary-of-findings" (SoF) table [44, 45], considering that the RCTs begin the appraisal process as high-quality studies "⊕⊕⊕⊕," and base their final score on the limitations or strengths of the studies.

Results

Study selection

The search strategy identified 526 potentially eligible papers. After removal of duplicates and screening of titles/abstracts, the full texts of 18 titles were selected and assessed; the reviewers showed excellent agreement ($K = 0.84$). Three studies were excluded because they did not fulfill the eligibility criteria [46–48], and two studies were excluded from the meta-analysis, because they involved furcation lesions [49, 50]. At the end, 15 articles met the criteria for inclusion in the systematic review, and 13, in the meta-analysis (Fig. 1). One title [29] was retrieved by gray literature search.

Study characteristics

The included reports were conducted between 2010 and 2017; all were RCT with a placebo control group (Table 1). Data from 864 individuals with CP were collected and analyzed at 3 and 6 months. Five studies involved patients with systemic or local risk factors, smokers [51, 52], diabetics [53, 54], and post-menopausal women [29], called risk populations in this study. Furthermore, only two studies involved sites with furcation lesions, which were included only in the qualitative synthesis and not in the meta-analysis [49, 50]. Critical changes were established from baseline up to 6 months in the parameters assessed. The gel was applied locally by subgingival injection with a blunt cannula; three types of statins were described across the available literature in the present study: simvastatin (SMV) [29, 49, 51, 55–58], atorvastatin (ATV) [28, 30, 37–39], and rosuvastatin (RSV) [38, 40].

The CAL gain changes were measured from the cement-enamel junction to the base of the pocket, except in three studies [49, 50, 54] that evaluated the relative attachment level (RAL). This parameter was calculated by measuring the distance from the stent (a custom-made acrylic guide that serves

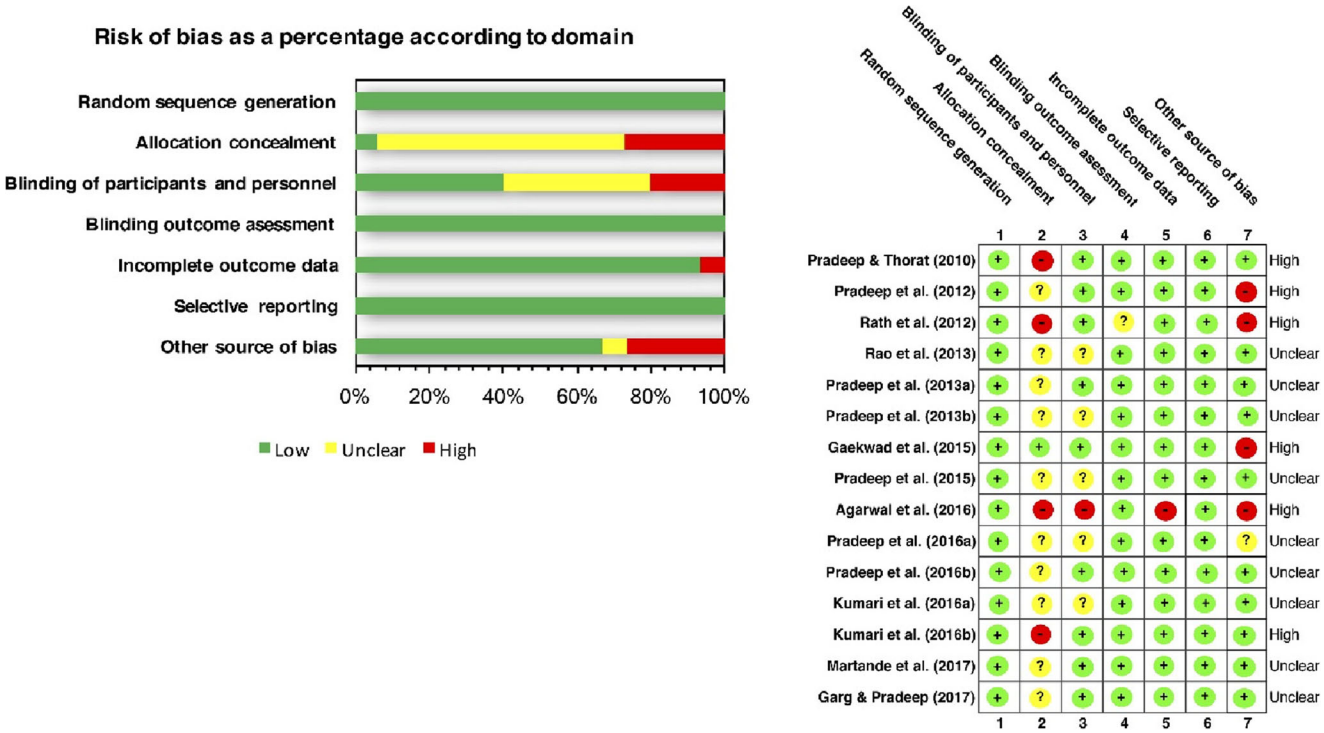

Fig. 2 Summary of the risk of bias of the trials included in the systematic review, according to the Cochrane Collaboration's tool, [41]. Plus sign indicates yes; minus sign indicates no; question mark indicates not specified/unclear

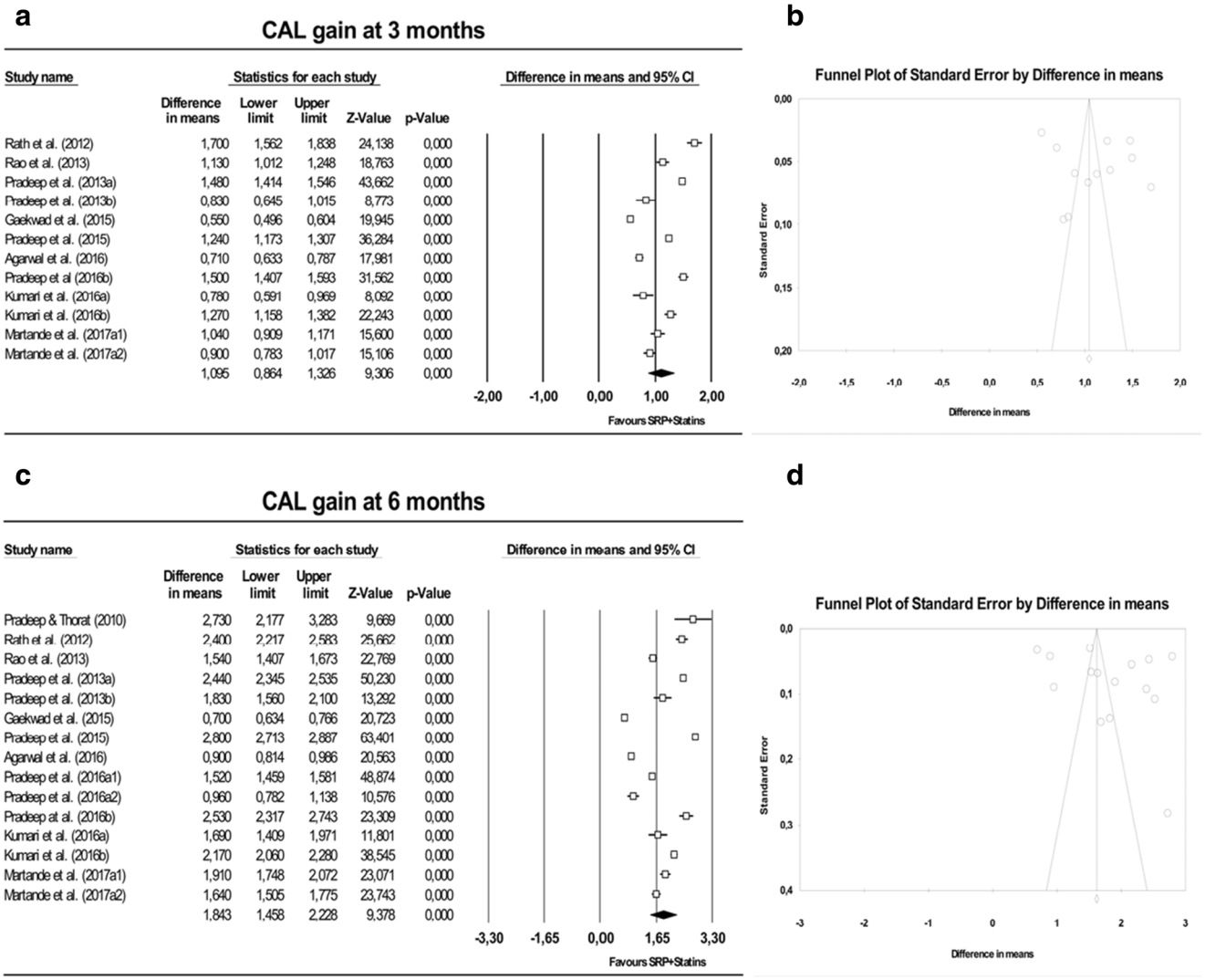

Fig. 3 Forest plot of random effects meta-analyses evaluating CAL reduction, and the funnel plot for publication bias at 3 months (**a**, **b**) and 6 months (**c**, **d**), between SRP + statins versus SRP + placebo; *Z* value, *Z* test; CI, confidence interval

as a standardized reference point) to the base of the pocket, minus the distance from the stent to the cement-enamel junction. All the studies evaluated the mSBI according to Mombelli et al. [59], except two reports [29, 57], which were excluded from the analysis due to incompatible data. Only two reports offered no data regarding intrabony defects [29, 57], and two studies [49, 50] evaluated the change in furcation lesions, but were excluded from the meta-analysis, as mentioned above. These lesion changes were evaluated radiographically by an image analyzer and a periapical radiograph with a parallel-angle technique for assessment. The radiographs were scanned with a digital scanner, at different resolutions across the studies.

Risk of bias in individual studies

The interexaminer agreement was substantial ($K = 0.80$), according to the Landis and Koch scale [42]. The allocation concealment is not clearly reported in most studies. The second less reported item was the blinding of participants. Only one study had a "high" risk of bias for the incomplete data item. Finally, four studies were judged as "high" risk for other sources of bias (Fig. 2).

Synthesis of meta-analysis results

At 9 months, there was no clinical effect on the outcomes assessed in the intervention group, compared with the control (data not shown). Interstudy heterogeneity appears significant for parameters of interest at 3 and 6 months; moreover, in regard to IBD reduction, only 6-month data were included in the meta-analysis. Although subgroup and sensitivity analyses were performed, the I^2 values remain high. The results of the subgroup analyses according to statin type are depicted in Appendix S5.

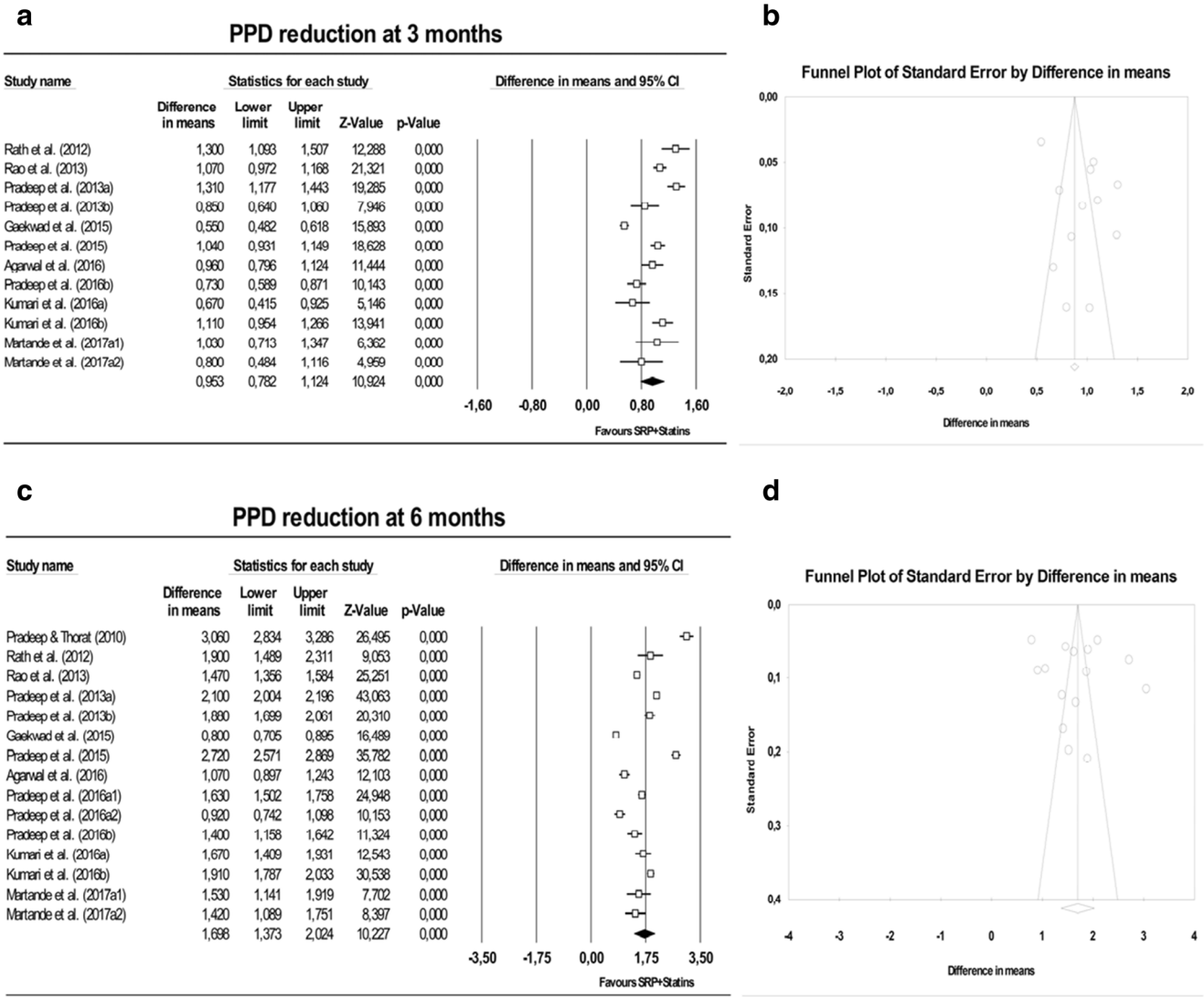

Fig. 4 Forest plot of random effects meta-analyses evaluating PPD reduction, and the funnel plot for publication bias at 3 months (**a**, **b**) and 6 months (**c**, **d**), between SRP + statins versus SRP + placebo; Z value, *Z* test; CI, confidence interval

Clinical attachment level gain

At 3 months, the random effects meta-analyses showed a CAL gain favoring SRP + statins (MD = 1.09; 95% CI 0.86–1.33) (Fig. 3a), showing high heterogeneity (*Q* test *p* value < 0.000; I^2 = 98.6%). The same trend and high heterogeneity was maintained at 6 months for SRP + statins (MD = 1.84; 95% CI 1.45–2.23) (Fig. 3c), showing high heterogeneity (*Q* test *p* value < 0.000; I^2 = 99.4%). The subgroup analysis at 3 and 6 months failed to detect significant differences; all subgroups showed high heterogeneity with I^2 values over 90%.

Periodontal probing depth reduction

The mean differences showed the same trend for estimated significance effect sizes at 3 and 6 months. Thus, a significant PPD reduction favoring SRP + statins could be seen at 3 months (MD = 0.95; 95% CI 0.78–1.12) (Fig. 4a), showing high heterogeneity (*Q* test *p* value < 0.000; I^2 = 94.1%) and following the same high heterogeneity trend at 6 months (MD = 1.69; 95% CI 1.37–2.04) (*Q* test *p* value < 0.000; I^2 = 98.4%), in favor of SRP + statins (Fig. 4c). Both subgroup analyses failed to detect significant differences; all subgroups showed high heterogeneity with I^2 values over 90%.

Modified sulcus bleeding index

The mean differences at 3 months indicated statistical significance in mSBI reduction in favor of SRP + statins (MD 0.41; 95% CI 0.28–0.54) (Fig. 5a) and showed high heterogeneity (*Q* test *p* value < 0.000; I^2 = 98.1%). The intervention effect followed the same trend at 6 months for SRP + statins, but showed a slightly greater effect (MD

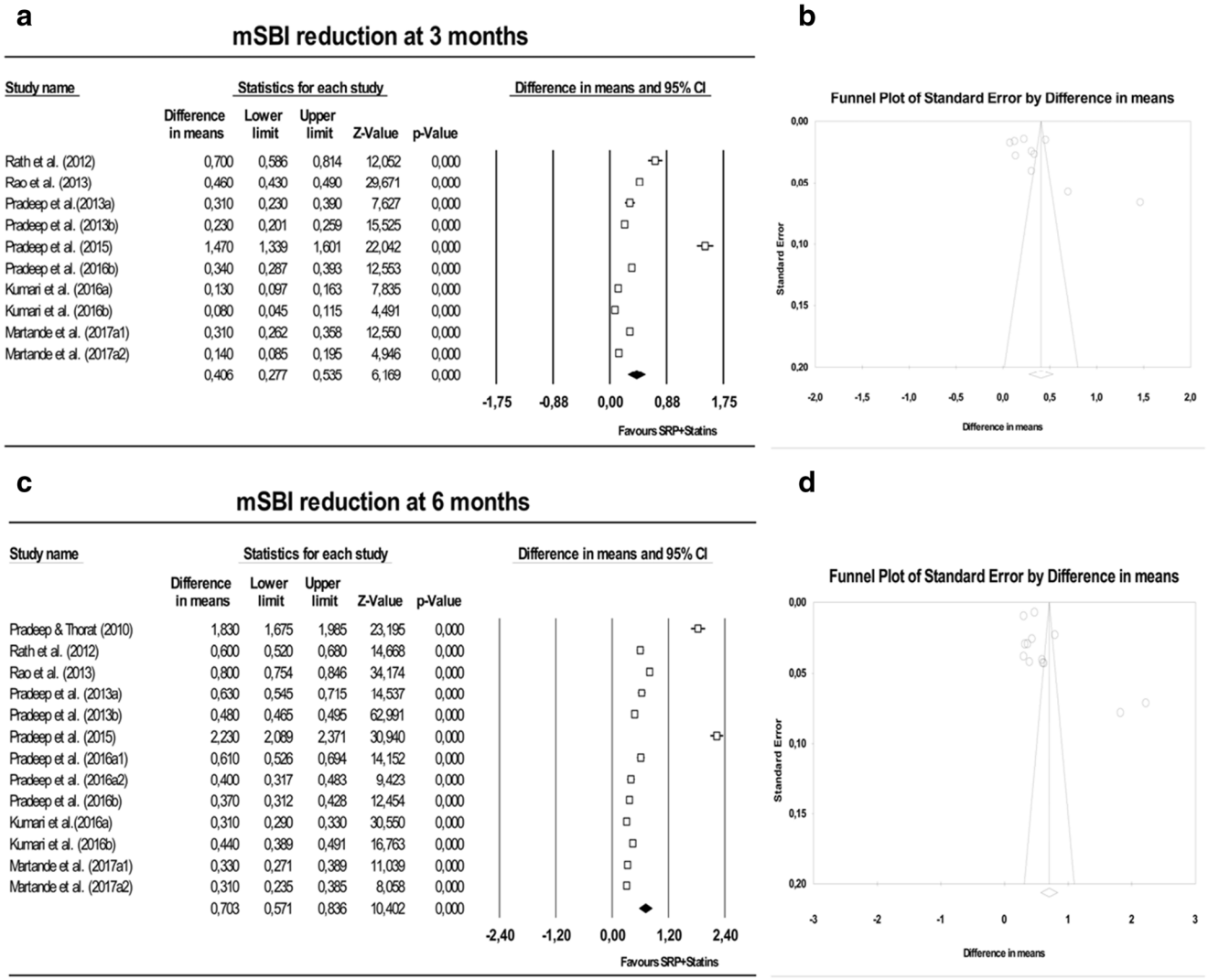

Fig. 5 Forest plot of random effects meta-analyses evaluating mSBI reduction, and the funnel plot for publication bias at 3 months (**a**, **b**) and 6 months (**c**, **d**), between SRP + Statins versus SRP + placebo; Z-Value = Z test; CI = confidence interval

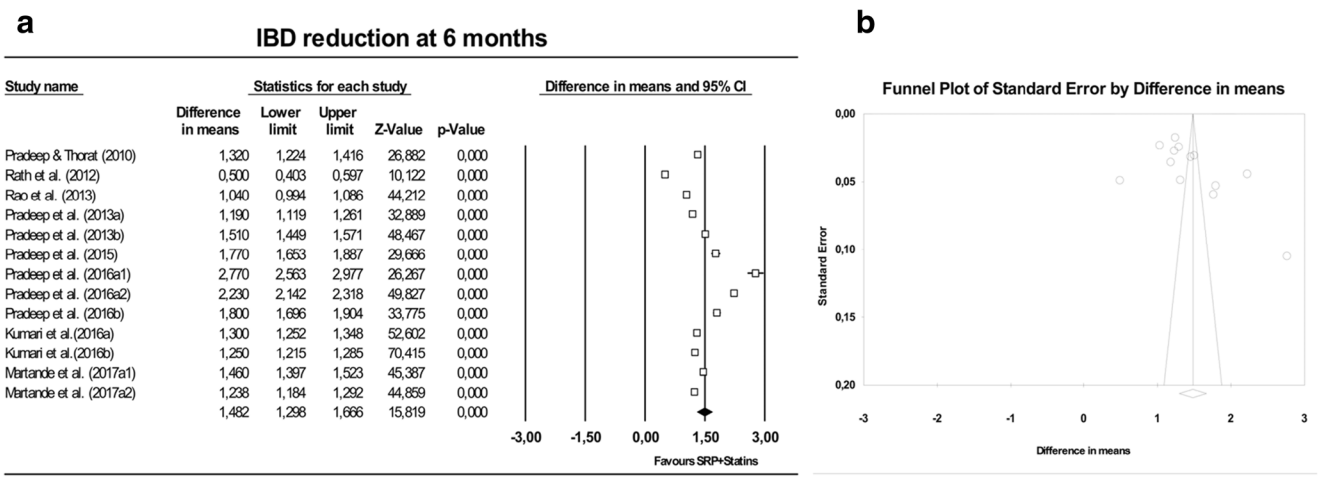

Fig. 6 Forest plot of random effects meta-analyses evaluating IBD reduction, and the funnel plot for publication bias at 6 months (**a**, **b**), between SRP + statins versus SRP + placebo; *Z* value, *Z* test; CI, confidence interval

Table 2 GRADE summary of findings table for the main outcome of the systematic review

Quality assessment							No. of patients		Effect		Quality	Recommendation
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SRP + statins	SRP + placebo	Relative (95% CI)	Absolute (95% CI)		
Clinical attachment gain (follow-up: mean 6 months; assessed with: mm; scale from 1.458 to 2.228)												
13	Randomized trials	Serious [75,76,77,a,b]	Serious [78,c]	Not serious [d,e,f]	Not serious [79,g]	Publication bias strongly suspected;strong association;all plausible residual confounding would suggest spurious effect, while no effect was observed [h]	440	424	–	MD 1.84 mm higher (1.46 to 2.23 higher)	⊕⊕⊕○ moderate	Weak

CI confidence interval, *MD* mean difference, *CAL* clinical attachment level, *SRP* scaling and root planing

[a] Recent evidence suggests that bias associated with lack of blinding and lack of concealment may be greater in trials with subjective outcomes (65, 66)

[b] Randomized controlled trials of surgical interventions are frequently more difficult to blind than RCTs of medications, which typically achieve blinding with placebos. Downgrade by 1 level, because of the presence of unclear and high risk of bias across studies (67)

[c] High heterogeneity; however, effects agree in direction and confidence regarding the decision being unaffected; no apparent reason to downgrade. A quantitative interaction is evident (Yusuf 1991) (48), because the effect size varies but not the direction in favor of SRP + statins

[d] Directly relevant; no apparent reason to downgrade. The magnitude of the effect did not differ substantially when risk populations were excluded in the sensitivity analysis (Fig. 7)

[e] No apparent reason to downgrade. There is a continuum of similarity of the intervention, in both groups. Because, the scaling and root planing receive as an adjuvant, a statin-based gel or a placebo gel with the same aqueous vehicle and similar consistency

[f] The present study considers CAL gain as the main outcome. However, it is a surrogate outcome, but regarding periodontal health, the tooth maintenance may have an impact on patient oral health and well-being concerning appropriate dietary intake and social interaction. There is no apparent reason to downgrade

[g] Despite the relatively small sample sizes across studies that may overestimate the effects, the confidence interval does not include the null effect, showing benefits in favor of SRP + Statins. Therefore, we calculated the "optimal information size" (OIS) (68) for a minimal effect size $\partial = (0.22)$ standard deviations, representing a small effect, with an alpha error (0.05) and statistical power $\beta = (0.2)$, requiring a total sample size of 652 individuals (321 per group), which is a smaller number in comparison to the 864 patients actually included. We considered not rating down for imprecision

[h] The likelihood of publication bias still exists despite the not observed asymmetry within funnel plots; it is important to consider that 9 out of 13 studies were industry sponsored, suggesting a potential presence of publication bias. Moreover, it is evident that early reports have shown more optimistic results than those recently published, even though the effect size remains significant. Continuously diminishing effects strongly suggest time-lapse bias

Table 3 Significance of the four levels of evidence according to the GRADE approach (adapted from Balshem et al. 2011) [60]

Quality level	Current definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

0.70; 95% CI 0.57–0.84) and heterogeneity that remained high (Q test p value < 0.000; I^2 = 99.2%) (Fig. 5c). According to the statin type analysis at both time intervals, the Q test detected a more significant effect for RSV, as compared with ATV and SMV. All subgroups showed high heterogeneity, at I^2 values over 90%.

Intrabony defect depth reduction

The random effects meta-analyses were assessed only at 6 months. They showed an IBD reduction in favor of SRP + statins (MD 1.48; 95% CI 1.30–1.67) (Fig. 6a) and showed high heterogeneity (Q test p value < 0.000; I^2 = 99.0%) (Fig. 6). The Q test detected a slightly greater effect size for RSV, according to the statin type. The heterogeneity remained at I^2 values over 95%.

Publication bias

The funnel plots visually showed slight asymmetry. However, the Egger's regression intercept p value showed no significant p values over 0.05, thus suggesting a low probability of publication bias. The p values obtained for CAL at 3 and 6 months were 0.464 and 0.288, respectively (Fig. 3b, d). The PPD values at 3 and 6 months were 0.180 and 0.638, respectively (Fig. 4b, d). The mSBI values at 3 and 6 months were 0.128 and 0.086, respectively (Fig. 5b, d). Finally, the IBD value at 6 months was 0.097 (Fig. 6b). The classic fail-safe number suggests high tolerance, indicating a low risk of publication bias for the average effect size estimations among studies included in the meta-analysis (data not shown).

Clinical relevance scale for interpreting mean differences in clinical attachment level (Adapted from Smiley et al. 2015)	
CLINICAL ATTACHMENT LEVEL RANGE (MILLIMETERS)	JUDGED CLINICAL RELEVANCE
0-0.2	Zero effect
> 0.2-0.4	Small effect
> 0.4-0.6	Moderate effect
> 0.6	Substantial effect

Fig. 7 Expected results in terms of mean differences for CAL after SRP, with or without adjuncts

Sensitivity analyses

The sensitivity test failed to detect a study that may introduce bias for estimation (data not shown).

Grading the evidence

The grading process allows us to give a reasonable explanation for several aspects depicted in Table 2. Moreover, our judgment process was thoroughly explained in the online data. We determined that the quality of evidence for the main CAL gain outcome was "moderate" (Table 3), with a substantial effect size (Fig. 7), and that the recommendation derived was "weak" in favor of SRP + statins. The terminology of being "weak" refers to variability; it is related to the quality of evidence and to a lower confidence rate for the balance between desirable intervention and undesirable consequences (Fig. 8).

Discussion

This systematic review and meta-analysis made a thorough assessment of the effect of local application of statins as adjuvants in non-surgical periodontal treatments up to March 2017. The data focused on at least three types of statins with different chemical properties regarding molecular affinity [43, 44], including hydrophilic/rosuvastatin and lipophilic/simvastatin-atorvastatin types. The risk of bias across the studies was high and unclear. The two most inadequately reported aspects were allocation concealment and personnel blinding. It is also noteworthy to mention that one study [29] was obtained through (gray/unpublished) data searches.

The meta-analysis showed that the SRP + statins group provided a significant improvement in the parameters assessed; the authors observed that greater changes occur at 6 months. The effect size for CAL gain was considered large at 3 and 6 months for the test group. This statistically significant and clinically relevant

Balancing level of certainty and net benefit rating to arrive at clinical recommendation strength

LEVEL OF CERTAINTY	NET BENEFIT RATING		
	Benefit Outweigh Potential Harms	Benefits Balanced With Potential Harms	No Benefits or Potential Harms Outweigh Benefits
High	Strong	In favor	Againts
Moderate	In favor	Weak	Againts
Low	Expert opinion for or expert opinion againts		

Strong: Evidence strongly supports providing this intervention. There is a high level of certainty of benefits, and benefits outweigh the potential harms.
In favor: Evidence favors providing this intervention. Either there is a high certainty of benefits, but the benefits are balanced with the potential harms, or there is a moderate level of certainty of benefits, and the benefits outweigh the potential harms.
Weak: Evidence suggest implementing this intervention after alternatives have been considered. There is a moderate level of certainty of benefits, and either the benefits are balanced with potential harms or there is uncertainty about the magnitude of the benefit.
Against: Evidence suggest no implementing this intervention or discontinuing ineffective procedures. There is moderate or high certainty that there are no benefits or the potential harms outweigh the benefits.
Expert opinion: For/Against**,** Expert opinion suggest this intervention can be/ not be implemented, but there is a low level of certainty of benefits / there is no benefits, and there is uncertainty in the benefit-to-harm-balance / potential harms outweigh benefits.

Fig. 8 Level of certainty to arrive at a clinical recommendation according to the GRADE approach [61]; (adapted from Smiley et al. 2015) [62]

(MD = 1.84 mm) result was interpreted as substantial, based on the scale described in (Fig. 7). Furthermore, significant differences were noticed for PPD, mSBI, and IBD changes. The subgroup analyses failed to detect significant differences. However, we should point out the greater and slightly greater effects for rosuvastatin, in mSBI and IBD, compared with atorvastatin and simvastatin. However, this result is not conclusive, since the observation was based on two reports; therefore, new studies must be performed to confirm this apparently better effect.

Regarding publication bias, funnel plots demonstrated slight asymmetry; the authors cannot explain the source of heterogeneity despite the subgroup and sensitivity analyses. However, we did observe that the primary potential source is related to the publication year, because trials with positive results are published sooner than other more conservative trials, suggesting a possible time-lapse bias [63]. Additionally, the great majority of reports providing data from the Asia region suggest a kind of location bias or "developed-country bias," which tends to show more significant results, as suggested by empirical evidence [64]. On the other hand, sensitivity analyses failed to detect a study that may introduce bias for estimation. A quantitative interaction was observed with effect size changes across the studies [65].

The effect of SRP + statins in risk populations provides interesting results, compared with other local adjuvants in well-controlled diabetics or in smokers [66–68]. Locally applied antibiotics as adjuncts to non-surgical periodontal treatment in smokers with PPD ≥ 5 mm result in significant reductions in PPD and CAL (0.81/0.91 mm, respectively) at 6 months [66]. Strikingly, the SRP + statins results seem to be slightly higher, even considering the less plausible value attributable from the lower boundaries of the 95% confidence intervals at 6 months, for both parameters (Figs. 3 and 4). Moreover, only one report involves post-menopausal women [29] and observes lesser effect size values, showing 0.70 mm for CAL gain at 6 months. This finding corroborates that of a previous study reporting greater CAL loss in patients with this condition [69]. Our results corroborate those of another systematic review [70] focused on evaluating the effect of statins on periodontal intrabony defects. Nevertheless, some methodological differences in design and execution allowed us to include more articles.

Finally, the side effects from taking statins include myopathy, myalgia, rhabdomyolysis, and elevated liver function that

could possibly lead to liver damage [71]. However, these adverse events are rare when given at standard doses [72], and the potential events may be prevented using local delivery systems.

This review has several strengths and some limitations, such as the comprehensive literature search, the effort to use the methodology tools for the qualitative and quantitative synthesis of data, and the subgroup and sensitivity analyses to test the robustness of results. The assessment of confidence of results determined the main outcome by the GRADE approach. Furthermore, we included mostly small randomized trials and observed methodological flaws that may influence the meta-analysis results across studies.

Conclusion

Within the limitations of this study, the collective evidence may support the use of locally applied statins as adjuncts to SRP in CP treatment, based on being easy, low-cost alternatives, with lesser adverse effects on bacterial resistance. Even though the confidence in the estimates for CAL gain is moderate, the strengths and recommendations emerging from this review are "weak" in regard to the application of statins, owing to study limitations, inconsistencies, and unreported, unknown potential adverse effects. These results should be interpreted with caution. An informed decision should be taken considering the patient's values and preferences, and the intervention to be performed by the clinician.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval No ethical approval was required for this study, since no human participants or animals were used in this study.

Informed consent Formal consent is not required for a systematic review and meta-analysis.

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