



The effect of statins on periodontal treatment—a systematic review with meta-analyses and meta-regression

Francisco Wilker Mustafa Gomes Muniz¹ · Keity Taminski¹ · Juliano Cavagni¹ · Roger Keller Celeste² · Patrícia Weidlich¹ · Cassiano Kuchenbecker Rösing¹

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Abstract

Objective This study aimed to systematically review clinical trials about the effect of statins as adjunct to mechanical periodontal therapy, on probing pocket depth, clinical attachment level, and intrabony defects, in comparison to mechanical periodontal therapy alone or in association with placebo.

Material and methods Three databases were searched for controlled clinical trials that used any locally delivered or systemically statin as a sole adjunctive therapy to mechanical periodontal treatment. Weighted mean differences between baseline and 6 months after periodontal treatment for clinical attachment level (CAL), probing pocket depth (PPD), and intrabony defect (IBD) were calculated. A high heterogeneity was detected. Therefore, a meta-regression adjusted for type of statin and year of publication was performed.

Results Fifteen studies were included in the systematic review, and ten studies were included in the meta-analysis. In the meta-regression, the adjunct use of simvastatin, rosuvastatin, and atorvastatin additionally reduced PPD in comparison to mechanical periodontal therapy and a placebo gel (2.90 ± 0.35 , 3.90 ± 0.77 , 3.06 ± 0.71 mm, respectively; $p < 0.05$). Regarding the resolution of IBD, simvastatin and rosuvastatin significantly improved in comparison to control group (0.89 ± 0.35 and 1.93 ± 0.77 mm, respectively; $p < 0.05$). No statistically significant difference was found between the statins for both PPD and IBD ($p < 0.05$). Regarding CAL gain, simvastatin provided a statistically significant improvement as compared to the control group (2.02 ± 0.79 mm; $p = 0.043$).

Conclusions The use of statins, used as sole adjuncts to mechanical periodontal treatment, improved the periodontal parameters. In the quantitative analyses, simvastatin was the only drug that showed additional benefits in all evaluated parameters.

Clinical relevance Statins promote significantly clinical periodontal improvements when administered in association with non-surgical scaling and root planning (SRP), when compared to SRP alone or in association with a placebo.

Keywords Periodontal disease · Periodontitis · Hydroxymethylglutaryl CoA reductases

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✉ Francisco Wilker Mustafa Gomes Muniz
wilkermustafa@gmail.com

¹ Department of Periodontology, Faculty of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. Rua Ramiro Barcelos, 2492, Porto Alegre, RS 90035-003, Brazil

² Department of Preventive and Social Dentistry, Faculty of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. Rua Ramiro Barcelos, 2492, Porto Alegre, RS 90035-003, Brazil

Introduction

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 [1]. Statins are widely used because of their effectiveness on reducing the blood cholesterol levels, excellent tolerability, safety, and low cost [2]. The use of statins is an established therapy for hyperlipidemia and arteriosclerosis, and it is the primary and secondary prevention of coronary artery diseases, mainly due to lowering of low-density lipoprotein cholesterol (LDL-C) [3, 4].

So far, the control of biofilms, along with proper periodontal supportive therapy, is the gold-standard procedures to

prevent and treat periodontal diseases [5]. Several treatment modalities are reported in the literature, such as surgical periodontal therapy and scaling and root planing (SRP), both of them alone or with adjunct antimicrobial/several other pharmacological agents [6, 7]. When successful, all those therapies lead to reduction of probing pocket depth (PPD) and gain of clinical attachment. Furthermore, it is known that the healing process after conventional therapy is mainly due to repair, including establishment of a long junctional epithelium [8]. However, as some sites continue to experience periodontal breakdown, despite the conventional treatment [9], recent studies are exploring new strategies to manage periodontal diseases [10, 11].

Additional to its hypolipidemic effects, statins present the pleiotropic mechanisms, which have pharmacologic effects not directly related to the lipid lowering profile, such as antioxidant and antiinflammatory properties, angiogenesis, improvements in the endothelial function, and increased bone formation [12–15]. The literature also suggests that statins may attenuate periodontal inflammation by decreasing interleukin (IL)-1 β and increasing IL-10 levels in gingival crevicular fluid of patients with periodontitis [16]. Positive outcomes of simvastatin in patients with chronic periodontitis were demonstrated in observational studies [17–19]. Periodontitis patients treated with statins presented less periodontal pockets in comparison to those that did not use statin [17, 19]. Furthermore, a retrospective cohort study showed that chronic periodontitis patients under statin presented 48% decreased tooth loss rate in comparison to those that did not use the medication [18]. On the other hand, this finding is not consistent in the literature [20].

A previous systematic review about the effects of statins on the treatment of chronic periodontitis included cohort, cross-sectional, and clinical trial studies, but it did not perform a quantitative analysis of the selected clinical trials [11]. Therefore, this study aimed to systematically review clinical trials about the effect of statins in conjunction with mechanical periodontal therapy on probing pocket depth, clinical attachment level, and intrabony defects.

Material and methods

The focused question for this systematic review was “In patients with chronic/aggressive periodontitis, how effective are statins, when used as adjuncts to mechanical periodontal therapy, when compared to mechanical periodontal treatment alone or associated with placebo?” The PICO question comprised patients with chronic or aggressive periodontitis (P), mechanical periodontal treatment with statins (I), compared to mechanical treatment alone or placebo (C), and probing pocket depth, clinical attachment level, and intrabony defect alterations (O).

Search strategy

The search for this systematic review was performed in MEDLINE-Pubmed, Scopus, and EMBASE databases. Search strategy for Pubmed database was developed as follows:

- (1) periodontal disease[Title/Abstract] OR periodontal diseases[MeSH Terms] OR periodontal treatment[Title/Abstract] OR periodontal therapy[Title/Abstract] OR subgingival curettage[MeSH Terms] OR periodontal intervention[Title/Abstract] OR periodontium[MeSH Terms] OR periodontics[MeSH Terms] OR wound healing[MeSH Terms] OR periodontal repair[Title/Abstract] OR periodontal regeneration[Title/Abstract] OR chronic periodontitis [Title/Abstract]
- (2) dyslipidemias[MeSH Terms] OR hyperlipidemia[Title/Abstract] OR higher cholesterol[Title/Abstract] OR statin[Title/Abstract] OR hydroxymethylglutaryl-co reductase[MeSH Terms] OR anticholesteremic agents[MeSH Terms] OR cholesterol reductase[MeSH Terms] OR lovastatin[MeSH Terms] OR provastatin[Title/Abstract] OR atorvastatin[Title/Abstract] OR Rosuvastatin [Title/Abstract]
- (3) 1 and 2

The search strategy for Scopus and EMBASE databases is an adaptation of the above and the literature was searched up to July 2016.

Selection criteria and risk of bias assessment

Titles and abstracts resulting from the search as described were screened independently by two reviewers (FWMGM and KT). Any discrepancies with regard to the exclusion/inclusion of the studies of any study were solved by extensive discussion between the two reviewers. When any doubt was still remaining, another investigator (JC) was involved in these processes.

Full text reading and data extraction was performed when the titles or abstracts fulfilled the following criteria:

- Clinical trials with at least 1-month follow-up;
- Patients with diagnosis of chronic or aggressive periodontitis;
- Intervention group should use any statin, as any form of administration, as a solely adjunct to non-surgical mechanical periodontal treatment;
- The comparison group should comprise non-surgical mechanical periodontal therapy alone or associated with placebo;
- The outcome should include at least one clinical periodontal measurement, such as probing depth, clinical attachment level, and intrabony defect.

No language or publication date restrictions were applied. However, the studies were excluded, after full text reading, if they presented one of the following characteristics:

- Observational and experimental animal studies.
- Case reports, letters, and reviews.
- Included only patients younger than 18 years old.
- Those that did not perform any mechanical periodontal therapy.
- Studies that used statin and any other drug/biomaterial in the same study group.
- Studies that reported only a secondary analysis of a previously included study.

Studies without abstracts but whose titles suggested that they could be related to the objective of this systematic review were selected, so the full text could be screened for eligibility. All references of related reviews [11, 21] and of the studies included during the electronic search were screened for eligibility. Additionally, after the electronic first screening and selection, all the studies that have cited the included articles, in Scopus database, were also screened for eligibility.

The gray literature was also search through contact with the corresponding author of the included studies and in the following databases: trip database, NYAM gray literature report, Centre for Reviews and Dissemination, and Google scholar. Furthermore, the register of the Clinical Trial website was also screened for eligibility. The above mentioned databases were searched using an adaptation of the search strategy previously described.

The risk of bias of the non-randomized clinical trials was assessed by the ROBINS-I tool, developed by the Cochrane Group [22]. In this tool, different bias are assessed: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, selection of the reported result, and overall bias. The risk of bias of the randomized clinical trials was assessed according to the criteria defined by the Cochrane Collaboration [23]. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias were evaluated. When sufficient information description was provided, a positive mark was attributed to each item, indicating low risk of bias. In case of missing information, a negative mark was recorded to each of the seven items, indicating high risk of bias. When both low and high risk of bias could not be assessed, the item was classified as unclear. To both tools, each selected study was evaluated independently by two reviewers (FWMGM and JC). Any discrepancies in this regard were solved by extensive discussion between the two reviewers.

Data extraction

The data extraction was performed in a spreadsheet specifically developed for this study. The data extraction included the following variables: authors, date of publication, country of the patients, funding, number of individuals in each group, the statin used, mean or range age, the percentage of male/female, and the results of the periodontal outcomes assessed.

When some of the necessary data were missing in the original studies, a contact with the authors was made by e-mail. Through the same contact, the corresponding authors were asked if they knew any other trial that may fulfill the objectives of this systematic review. All the authors were contacted; however, none of them answered the contact. Studies with missing data were maintained in the systematic review, but not included in the quantitative analysis.

Data synthesis

Due to the larger number of statins locally delivered in periodontal pockets, the quantitative analysis was performed only for these studies, despite the type of statin used. In order to standardize data synthesis, mean alterations (\pm standard deviation) in probing pocket depth (PPD), intrabony defect assessed radiographically (IBD), and clinical attachment level (CAL), from 6 months to baseline, were included in the meta-analysis. This information was originally available in all included studies. When two different statins were evaluated in the same study, both statin groups were included in the analysis, but the sample size in the group without statin was divided in half.

Statistical analysis: meta-analyses and meta-regression

Meta-analyses were performed using the weighted mean difference (WMD) between baseline and 6 months after periodontal therapy. When difference between 6 months and baseline was not presented in the article, the study was not eligible for meta-analysis. Quantitative analyses were conducted for PPD, IBD, and CAL applying linear meta-analyses. The primary outcome for the meta-analysis was mean alteration in CAL and secondary outcomes were alterations in PPD and IBD. Heterogeneity was assessed by the Q test and quantified with the I^2 statistic. Publication bias was assessed using the Egger's and Begg's test. Additionally, the overall quality of evidence for each of the main outcomes included in the meta-analyses was rated using the GRADE approach [24].

When high heterogeneity was found ($I^2 > 40\%$), sources of effect modification of the pooled WMD were investigated using linear meta-regression [25]. Due to the number of studies (only one/two studies, respectively), we could not test effect modification by diabetes or smoking status. Therefore,

only the following study characteristics were included in the meta-regression: year of publication and type of statin.

The heterogeneity parameter (τ^2), which denotes the standard deviation of the true between-group variance, was calculated using the method of moment, and p values were estimated with Monte Carlo simulation from 1000 permutations. The analyses were adjusted for the year 2010, as the first study was published in this year. Meta-analyses and meta-regression were conducted using Stata 13.1 software [26, 27].

Results

Study selection

One-thousand three-hundred and sixty-three titles/abstracts were retrieved from the search, of which 15 were selected based on the criteria previously described (Fig. 1) [28–42]. One study reported a secondary analysis of an included clinical trial, and was excluded [43]. The additional searches resulted in 393 studies, but did not increase the number of selected studies. All the selected studies were written in English;

the demographic sample characteristics and the main results of these studies are shown in Table 1.

Characteristics of included studies

Among the included studies, 3 were non-randomized clinical trials [29, 30, 39], and 12 were randomized clinical trials [28, 31–38, 40–42]. All the studies included in the systematic review comprised chronic periodontitis patients. Statins used were atorvastatin, simvastatin, and rosuvastatin. Eleven studies used locally delivered statins with a 1.2% concentration [32–42]. From these, 5 used simvastatin [32–35, 37], 3 used atorvastatin [36, 40, 42], and 1 used rosuvastatin [38]. Furthermore, one study used rosuvastatin and atorvastatin [41] and another used simvastatin and atorvastatin in different patients [39]. All these studies used statins as adjunct to site-specific mechanical periodontal treatment and compared to a placebo gel plus site-specific mechanical periodontal treatment. One study used 2% atorvastatin in a dentifrice compared to a control dentifrice [31]. Atorvastatin was the only drug used systemically as adjunctive to whole-mouth scaling and root planing in three studies. In one study, it was compared to placebo pills [28], and in the two others, the comparison was solely with mechanical treatment [29, 30].

Fig. 1 Flow of the studies during the review

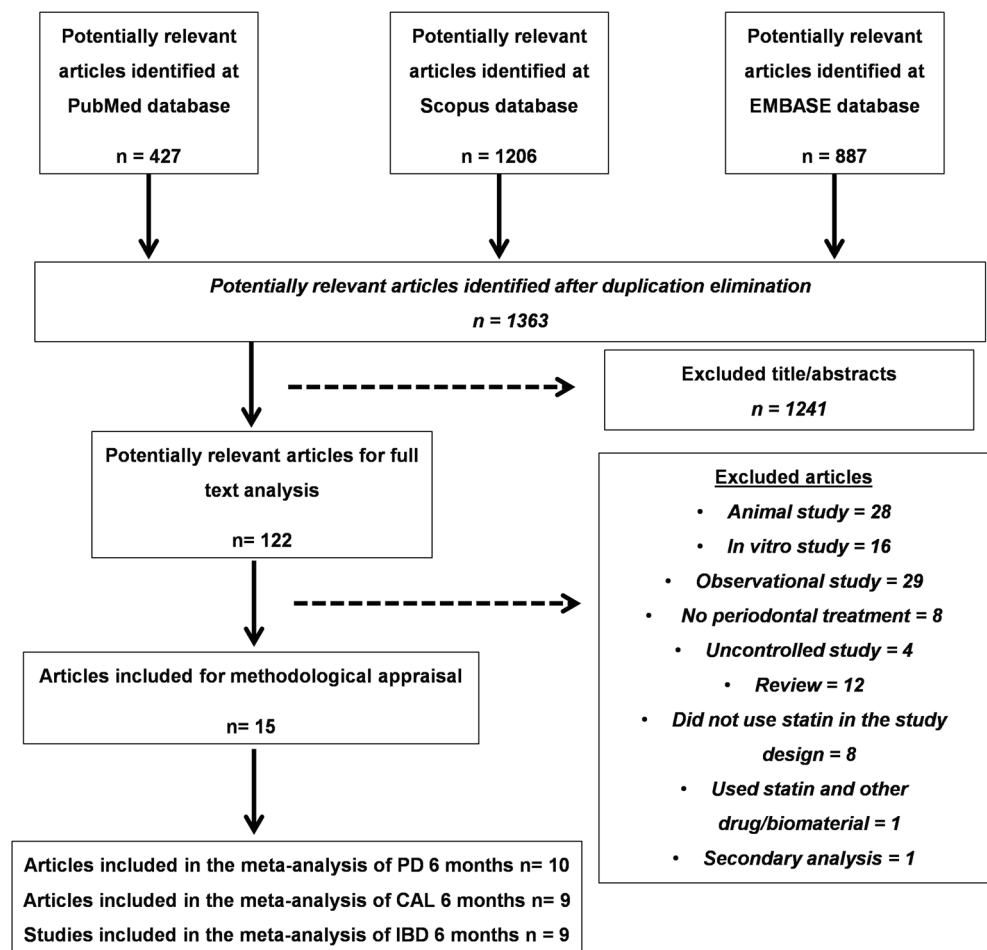


Table 1 Country, demographic characteristics, number of subjects per groups, statins used, and main results of the selected studies

Author, year; country; study design	Groups with and without statin	Sample size Age; male/female Sample characteristics Smoking exposure	Main results
Statin systemically delivered			
Fajardo, 2010; Mexico; RCT [28]	Group with statin: atorvastatin, 20 mg; group without statin: placebo	Group with statin: 19; group without statin: 19 Whole sample (range)—40 to 60 years; 6/32 Good general health No smokers	Both groups improved after therapy. Mean \pm SD decrease in PPD (in mm)—from baseline to 3 months Group with statin: 1.79 \pm 0.57 Group without statin: 1.47 \pm 0.36 <i>p</i> value: 0.03 Mean \pm SD CAL gain (in mm)—from baseline to 3 months Group with statin: 1.58 \pm 1.2 Group without statin: 1.26 \pm 1.0 <i>p</i> value: 0.46 Mean \pm SD decrease in BOP (%)—from baseline to 3 months Group with statin: 0.4 \pm 0.15 Group without statin: 0.5 \pm 0.25 <i>p</i> value: 0.18
Fentoglu, 2012; Turkey; nRCT [29]	Group with statin: atorvastatin 10/20 mg; group without statin: systemically health with no additional therapy	Hyperlipidemic patients with statin: 28; group without statin: 28 Group without statin: range—30 to 57; 14/14 Hyperlipidemic: range—31 to 54; 26/26 Hyperlipidemic/good general health No smokers	All groups improved after therapy, except for CAL. Median (min–max) PPD (in mm) 3 months after therapy Hyperlipidemic with statin: 2.30 (1.84–2.67) Group without statin: 2.38 (1.96–3.50) <i>p</i> value: not reported Median (min–max) BOP (%) 3 months after therapy Hyperlipidemic with statin: 15.60 (5.79–32.69) Group without statin: 45.00 (0.23–100) <i>p</i> value: not reported
Sangwan, 2016; India; nRCT [30]	Group with statin: atorvastatin 20 mg; group without statin: systemically health with no additional therapy	Hyperlipidemic patients with statin: 36; group without statin: 35 Hyperlipidemic with statin: 44.56 \pm 10.44; 24/12—group without statin: 43 \pm 10.73; 17/18 Hyperlipidemic/good general health No smokers	All groups improved after therapy Mean \pm SD PPD (in mm) 3 months after therapy Hyperlipidemic with statin: 2.46 \pm 0.68 Group without statin: 2.27 \pm 0.54 <i>p</i> value: 0.447 Mean \pm SD CAL (in mm) 3 months after therapy Hyperlipidemic with statin: 3.63 \pm 1.07 Group without statin: 3.14 \pm 0.71 <i>p</i> value: 0.616
Statin in a dentifrice			
Rosenberg, 2015; Chile; RCT [31]	Group with statin: 2% atorvastatin in dentifrice; group without statin: placebo dentifrice	Group with statin: 19; group without statin: 19 Whole sample (mean): 45.28; group with statin: 4/14—group without statin: 7/11 Good general health/patients with well-controlled diabetes No smokers/smokers	One month after therapy, statically significant differences in the group with statin, when compared to the group without statin, were showed to Mean decrease in PPD— <i>p</i> value: 0.02* Mean decrease in CAL— <i>p</i> value: 0.001* Decrease of percentage of sites with BOP— <i>p</i> value: <0.001*
Statin locally delivered			
Pradeep, 2010;	Group with statin: 1.2 mg simvastatin gel; group without statin: placebo gel	Group with statin: 30; group without statin: 30	Both groups improved after therapy.

Table 1 (continued)

Author, year; country; study design	Groups with and without statin	Sample size Age; male/female Sample characteristics Smoking exposure	Main results
India; RCT [32]		Whole sample (mean): 30.5 ± 4.1; 33/31 Good general health No smokers	<p>Mean ± SD decrease in PPD (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.26 ± 1.59 Group without statin: 1.20 ± 1.24 <i>p</i> value: 0.001</p> <p>Mean ± SD CAL gain (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.36 ± 1.92 Group without statin: 1.63 ± 1.99 <i>p</i> value: 0.001</p> <p>Mean ± SD decrease in IBD (%)—from baseline to 6 months</p> <p>Group with statin: 1.41 ± 0.74 Group without statin: 0.09 ± 0.58 <i>p</i> value: <0.05</p>
Pradeep, 2012; India; RCT [33]	Group with statin: 1.2 mg simvastatin gel; group without statin: placebo gel	Group with statin: 18; group without statin: 18 Whole sample (range)—30 to 50; sample screening: 38/34—before exclusions Good general health No smokers	<p>Both groups improved after therapy.</p> <p>Mean ± SD decrease in PPD (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.05 ± 1.31 Group without statin: 1.30 ± 1.01 <i>p</i> value: 0.001</p> <p>Mean ± SD gain in RVAL (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.63 ± 1.01 Group without statin: 2.46 ± 1.49 <i>p</i> value: 0.001</p> <p>Mean ± SD gain in RHAL (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.33 ± 1.42 Group without statin: 2.43 ± 1.66 <i>p</i> value: 0.001</p>
Rath, 2012; India; RCT [34]	Group with statin: 1.2% simvastatin gel; group without statin: placebo gel	Group with statin: 30; group without statin: 30 Whole sample (range)—25 to 45 years; group with statin: 18/12—group without statin: 15/15 Good general health No smokers	<p>Both groups improved after therapy.</p> <p>Mean ± SD decrease in PPD (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.00 ± 1.6 Group without statin: 2.1 ± 0.8 <i>p</i> value: <0.01</p> <p>Mean ± SD CAL gain (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.6 ± 1.5 Group without statin: 4.6 ± 1.5 <i>p</i> value: 1.00</p> <p>Mean ± SD decrease in IBD (%)—from baseline to 6 months</p> <p>Group with statin: 0.57 ± 1.0 Group without statin: 0.08 ± 0.1 <i>p</i> value: 0.02</p>
Pradeep, 2013a; India; RCT [35]	Group with statin: 1.2% simvastatin gel; group without statin: placebo gel	Group with statin: 17; group without statin: 18 Whole sample (range)—30 to 50; 20/18 Patients with diabetes No smokers	<p>Both groups improved after therapy.</p> <p>Mean ± SD decrease in PPD (in mm)—from baseline to 6 months</p> <p>Group with statin: 3.79 ± 1.15 Group without statin: 1.69 ± 0.76 <i>p</i> value: <0.01</p>

Table 1 (continued)

Author, year; country; study design	Groups with and without statin	Sample size Age; male/female Sample characteristics Smoking exposure	Main results
			<p>Mean ± SD CAL gain (in mm)—from baseline to 6 months</p> <p>Group with statin: 3.83 ± 0.97</p> <p>Group without statin: 1.38 ± 0.56</p> <p><i>p</i> value: <0.01</p> <p>Mean ± SD decrease in IBD (%)—from baseline to 6 months</p> <p>Group with statin: 1.38 ± 0.73</p> <p>Group without statin: 0.19 ± 0.37</p> <p><i>p</i> value: <0.01</p>
Pradeep, 2013b; India; RCT [36]	Group with statin: 1.2% atorvastatin gel; group without statin: placebo gel	Group with statin: 30; group without statin: 30 Whole sample (range)—30 to 50; sample screening: 35/32—before exclusions Good general health No smokers	<p>Both groups improved after therapy.</p> <p>Mean ± SD decrease in PPD (in mm)—from baseline to 6 months</p> <p>Group with statin: 3.40 ± 0.56</p> <p>Group without statin: 1.56 ± 0.53</p> <p><i>p</i> value: <0.001</p> <p>Mean ± SD CAL gain (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.20 ± 0.60</p> <p>Group without statin: 2.36 ± 0.51</p> <p><i>p</i> value: <0.001</p> <p>Mean ± SD decrease in IBD (%)—from baseline to 6 months</p> <p>Group with statin: 1.60 ± 0.24</p> <p>Group without statin: 0.13 ± 0.25</p> <p><i>p</i> value: <0.001</p>
Rao, 2013; India; RCT [37]	Group with statin: 1.2% simvastatin gel; group without statin: placebo gel	Group with statin: 17; group without statin: 18 Whole sample (range)—30 to 50; 35/0 Good general health Smokers	<p>Both groups improved after therapy.</p> <p>Mean ± SD decrease in PPD (in mm)—from baseline to 6 months</p> <p>Group with statin: 3.37 ± 1.27</p> <p>Group without statin: 1.90 ± 1.32</p> <p><i>p</i> value: < 0.01</p> <p>Mean ± SD CAL gain (in mm)—from baseline to 6 months</p> <p>Group with statin: 3.20 ± 1.32</p> <p>Group without statin: 1.67 ± 1.18</p> <p><i>p</i> value: < 0.01</p> <p>Mean ± SD decrease in IBD (%)—from baseline to 6 months</p> <p>Group with statin: 1.17 ± 0.45</p> <p>Group without statin: 0.13 ± 0.26</p> <p><i>p</i> value: < 0.01</p>
Pradeep, 2015; India; RCT [38]	Group with statin: 1.2% rosuvastatin gel; group without statin: placebo gel	Group with statin: 32; group without statin: 33 Whole sample (range)—22 to 55 years; 33/37 Good general health No smokers	<p>Both groups improved after therapy.</p> <p>Mean ± SD decrease in PPD (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.04 ± 0.34</p> <p>Group without statin: 1.31 ± 0.24</p> <p><i>p</i> value: < 0.01</p> <p>Mean ± SD CAL gain (in mm)—from baseline to 6 months</p> <p>Group with statin: 4.2 ± 0.17</p> <p>Group without statin: 1.4 ± 0.15</p> <p><i>p</i> value: < 0.01</p>

Table 1 (continued)

Author, year; country; study design	Groups with and without statin	Sample size Age; male/female Sample characteristics Smoking exposure	Main results	
			Mean \pm SD decrease in IBD (%)—from baseline to 6 months	Group with statin: 2.23 \pm 0.32 Group without statin: 0.46 \pm 0.02 <i>p</i> value: < 0.01
Surve, 2015; India; nRCT [39]	Group with statin: 1.2% atorvastatin and 1.2% simvastatin gel; group without statin: placebo gel	Atorvastatin group: 15; simvastatin group: 15 group without statin: 15 Whole sample (range)—35 to 55 years; not reported Good general health No smokers	All groups improved after therapy. Mean \pm SD PPD (in mm) 6 months after therapy	Atorvastatin group: 3.43 \pm 0.75 Simvastatin group: 3.33 \pm 0.62 Group without statin: 3.23 \pm 0.59 <i>p</i> value (all groups): > 0.05 Mean \pm SD RAL (in mm) 6 months after therapy
				Atorvastatin group: 9.19 \pm 1.35 Simvastatin group: 9.07 \pm 1.66 Group without statin: 9.61 \pm 1.12 <i>p</i> value (all groups): > 0.05
Kumari, 2016; India; RCT [40]	Group with statin: 1.2% atorvastatin gel; group without statin: placebo gel	Group with statin: 33; group without statin: 33 Whole sample (range)—30 to 50 years; not reported Good general health Smokers	Both groups improved after therapy. Mean \pm SD decrease in PPD (in mm)—from baseline to 6 months	Group with statin: 2.66 \pm 1.34 Group without statin: 1.00 \pm 0.93 <i>p</i> value: < 0.001
			Mean \pm SD CAL gain (in mm)—from baseline to 6 months	Group with statin: 3.61 \pm 1.41 Group without statin: 1.91 \pm 1.24 <i>p</i> value: < 0.001
			Mean \pm SD decrease in IBD (%)—from baseline to 6 months	Group with statin: 1.44 \pm 0.41 Group without statin: 0.14 \pm 0.09 <i>p</i> value: < 0.001
Pradeep, 2016; India; RCT [41]	Rosuvastatin group: 1.2% rosuvastatin gel; atorvastatin group: 1.2% atorvastatin gel; group without statin: placebo gel	Rosuvastatin group: 27; atorvastatin group: 27; group without statin: 27 Whole sample (range)—25 to 45 years; 45/45 Good general health No smokers	All groups improved after therapy. Mean \pm SD decrease in PPD (in mm)—from baseline to 6 months	Rosuvastatin group: 3.03 \pm 0.43 Atorvastatin group: 2.33 \pm 0.48 Group without statin: 1.47 \pm 0.50 <i>p</i> value (in comparison to group without statin): < 0.001
			Mean \pm SD CAL gain (in mm)—from baseline to 6 months	Rosuvastatin group: 2.88 \pm 0.42 Atorvastatin group: 2.33 \pm 0.48

Table 1 (continued)

Author, year; country; study design	Groups with and without statin	Sample size Age; male/female Sample characteristics Smoking exposure	Main results
			Group without statin: 1.37 ± 0.49 <i>p</i> value (in comparison to group without statin): < 0.001
			Mean ± SD decrease in IBD (%)—from baseline to 6 months Rosuvastatin group: 2.83 ± 0.53 Atorvastatin group: 2.29 ± 1.06 Group without statin: 0.07 ± 0.26 <i>p</i> value (in comparison to group without statin): < 0.001
Pradeep, 2016; India; RCT [42]	Group with statin: 1.2% atorvastatin gel; group without statin: placebo gel	Group with statin: 30; Group without statin: 30 Whole sample (range)—30 to 50 years; 53/51 Good general health No smokers	Both groups improved after therapy. Mean ± SD decrease in PPD (in mm)—from baseline to 6 months Group with statin: 2.46 ± 0.97 Group without statin: 1.06 ± 0.90 <i>p</i> value: < 0.001 Mean ± SD CAL gain (in mm)—from baseline to 6 months Group with statin: 3.7 ± 0.91 Group without statin: 1.16 ± 0.94 <i>p</i> value: < 0.001 Mean ± SD decrease in IBD (%)—from baseline to 6 months Group with statin: 1.90 ± 0.44 Group without statin: 0.09 ± 0.17 <i>p</i> value: < 0.001

RCT randomized clinical trial, nRCT non-randomized clinical trial, PPD probing pocket depth, CAL clinical attachment level, BOP bleeding on probing, IBD intrabony defect, RVAL relative vertical attachment level, RHAL relative horizontal attachment level, RAL relative attachment level

*Mean values were not reported

Two studies treated patients with both periodontitis and hyperlipidemia [29, 30]. Another study treated only patients with type 2 diabetes [35], and Rosenberg et al. (2015) [31] included patients without diabetes and well-controlled diabetics. The others studies included only systemically healthy patients with no use of systemic statin [28, 32–34, 36–42]. Furthermore, only two studies included smokers with periodontitis [31, 37]. Regarding to the side effects of statins, 13 studies reported no adverse effects in any patient [28, 31–42]. However, two studies did not report adverse events [29, 30].

Risk of bias assessment

Figure 2 presents the quality analysis of the RCT included in the present systematic review [28, 31–38, 40–42]. Only one

study fulfilled all criteria with low risk of bias [28]. The majority of the studies did not provide any explanation of how allocation concealment was performed [31–38, 40–42]. Despite of that, all RCT had low risk of bias for random sequence generation [28, 31–38, 40–42]. Additionally, all RCT had low risk of bias for incomplete outcome data. No study had unclear risk of bias. Overall, this analysis showed that there is a moderate heterogeneity in the risk of bias in the selected studies, ranging from zero negative marks (low risk of bias) to four negative marks (high risk of bias).

Table 2 shows the risk of bias of the non RCT included in the present systematic review. All studies presented an overall bias ranging from moderate [29, 30] to critical [39]. Risks of bias due to confounding were classified as moderate in all non-RCT. One study was classified in the other domains as

Fig. 2 Risk of bias of the included studies

	+	-	+	+	+	+	+	Key
Fajardo, 2010	+	+	+	+	+	+	+	+ Low risk of bias
Pradeep, 2010	+	-	+	+	+	+	-	- High risk of bias
Pradeep, 2012	+	-	+	+	+	+	+	? Unclear risk of bias
Rath, 2012	+	-	-	-	+	+	-	
Pradeep, 2013a	+	-	+	+	+	+	+	
Pradeep, 2013b	+	-	+	+	+	+	+	
Rao, 2013	+	-	+	+	+	+	+	
Pradeep, 2015	+	-	+	+	+	+	-	
Rosenberg, 2015	+	-	+	+	+	+	+	
Kumari, 2016	+	-	+	+	+	+	+	
Pradeep, 2016a	+	-	+	+	+	+	+	
Pradeep, 2016b	+	-	+	+	+	+	+	

RANDOM SEQUENCE GENERATION
 ALLOCATION CONCEALMENT
 BLINDING OF PARTICIPATIONS AND PERSONNEL
 BLINDING OF OUTCOME ASSESSMENT
 INCOMPLETE OUTCOME DATA
 SELECTIVE REPORTING
 OTHER BIAS

low risk of bias [30]; meanwhile, another study presented a moderate risk of bias only in measurement of outcomes [29]. The other non-RCT was evaluated as critical/serious in almost all domains [39].

Qualitative results—statins used systemically

Considering the three studies that used systemic administration of atorvastatin, only one demonstrated significant improvements in PPD and dental mobility, favoring the group that used statin [28]. The two remaining studies included hyperlipidemic patients with prescribed atorvastatin and compared with normolipidemic patients [29, 30]. In one study,

no statistically significant differences between both groups for all periodontal parameters were shown [30]. Comparisons between groups with and without atorvastatin as adjunct to mechanical periodontal treatment in relation to periodontal parameters are not reported in the other study [29].

Qualitative results—statins used in a dentifrice

One of the selected studies reported 1-month follow-up results of a 2% atorvastatin dentifrice compared with a placebo dentifrice [31]. Both groups showed improvements in periodontal parameters after non-surgical periodontal treatment. Furthermore, when compared to a placebo dentifrice,

Table 2 Risk of bias of the non-randomized clinical trial, assessed by ROBINS-I tool, included in the present systematic review

Author, Year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Fentoglu, 2012 [29]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Surve, 2015 [39]	Moderate	Critical	Serious	Serious	Serious	Critical	Low	Critical
Sangwan, 2016 [30]	Moderate	Low	Low	Low	Low	Low	Low	Moderate

atorvastatin dentifrice was able to additionally enhance CAL gain, reduce PPD, and bleeding on probing.

Qualitative results—statins used locally

Eleven studies used locally delivered statins adjunctive to periodontal therapy [32–42], of which nine were performed by the same research group [32, 33, 35–38, 40–42]. All studies, but one [39], showed statistically significant reduction in PPD, favoring the statin group. Similarly to PPD, only one study [39] showed no statistically significant improvements in the IBD favoring the statin group. Regarding the CAL gain, only two studies did not demonstrate statistically significant differences between groups with and without statin [34, 39]. All of these studies performed intraoral radiographic analyses.

Meta-analyses and meta-regression for alterations in probing pocket depth

From the 15 selected studies, ten were included in the quantitative analysis of PPD [32–38, 40–42]. For PPD at 6 months, this analysis showed a pooled WMD of 1.93 mm (95% CI 1.44; 2.41), favoring the statin group (Fig. S1). However, this analysis showed a high heterogeneity (93.9%, $p < 0.001$). No publication bias was shown in both tests for this analysis ($p = 0.213$ and $p = 0.146$ for Begg’s and Egg’s tests, respectively)

(Fig. S2). In the sensitivity analysis, no major changes were detected for the pooled WMD ranging from 1.81 mm (95% CI 1.44; 2.18) to 2.04 mm (95% CI 1.62; 2.47) (Fig. S3).

The cumulative meta-analysis showed that over the years, the effect size was decreasing significantly across the published studies ($p = 0.041$). For each year, a mean decrease of 0.21 mm on PPD was observed. On the other hand, the meta-regression showed that all statins, when associated to SRP, reduced significantly PPD in comparison to SRP plus placebo (Table 3). When controlling for the year of publication (at year 2010), rosuvastatin demonstrated numerically the higher coefficient of PPD reduction. However, no statistically significant differences were found between the statins.

Meta-analyses and meta-regression for alterations in intrabony defect

Nine studies were included in the quantitative analysis of alterations in IBD [32, 34–38, 40–42]. The resolution of IBD 6 months after periodontal therapy was also included in the meta-analysis. A pooled WMD of 1.54 mm (95% CI 1.24; 1.84) was shown, favoring the statin group. High heterogeneity was also found in this analysis (96.5%, $p < 0.001$) (Fig. S4). No publication bias was observed in both tests for this analysis ($p = 0.721$ and $p = 0.661$ for Begg’s and Egg’s tests, respectively) (Fig. S5). No major

Table 3 Meta-regression of clinical trials for three periodontal outcomes using different types of statin adjusted for year of publication (at year 2010)

References of the included studies	Type of statin	Coefficient ± SE (in mm when compared to control)	95% CI	Adjusted R^2	p values in comparison to			
					Without statin	Atorvastatin	Rosuvastatin	Simvastatin
Reduction on PPD at 6 months								
[32–38, 40–42]	Simvastatin	2.90 ± 0.35	2.06–3.74	25.76%	<0.001	0.768	0.128	–
	Atorvastatin	3.06 ± 0.71	1.38–4.74		0.004	–	0.056	0.768
		3.90 ± 0.77	2.09–5.72		0.001	0.056	–	0.128
	Rosuvastatin							
CAL gain at 6 months								
[32, 34–38, 40–42]	Simvastatin	2.02 ± 0.79	0.89–3.96	–43.59%	0.043	0.658	0.480	–
	Atorvastatin	2.56 ± 1.57	–1.29–6.42		0.155	–	0.624	0.658
		3.01 ± 1.71	–1.18–7.20		0.130	0.624	–	0.480
	Rosuvastatin							
Decrease on IBD at 6 months								
[32, 34–38, 40–42]	Simvastatin	0.89 ± 0.35	0.33–1.76	47.19%	0.044	0.404	0.136	–
	Atorvastatin	1.37 ± 0.71	–0.36–3.10		0.102	–	0.213	0.404
		1.93 ± 0.77	0.30–3.82		0.047	0.213	–	0.136
	Rosuvastatin							

SE standard error, PPD probing pocket depth, CAL clinical attachment level, IBD intrabony defect

changes were detected for the pooled WMD ranging from 1.40 mm (95% CI 1.16; 1.65) to 1.65 mm (95% CI 1.36; 1.94) in the sensitivity analysis (Fig. S6).

The year of publication presented a positive statistically significant effect, with each year increment promoting a decrease of 0.20 mm in the IBD ($p = 0.041$). In the meta-regression, when the year of publication (at year 2010) and the type of statin were considered, both rosuvastatin and simvastatin showed significantly more resolution of IBD in comparison to the group without statin ($p = 0.047$ and $p = 0.044$, respectively). However, no statistically significant differences between the three statin were found (Table 3).

Meta-analyses and meta-regression for alterations in clinical attachment level

Nine studies were included in the quantitative analysis of alterations in CAL [32, 34–38, 40–42]. Regarding CAL gain 6 months after the therapy, the pooled WMD found was 1.82 mm (95% CI 1.24; 2.41), also favoring the statin group (Fig. S7). However, a high heterogeneity (96.5%, $p < 0.001$) was observed. Publication bias was found with the Egger's test ($p = 0.024$) (Fig. S8) but not with the Begg's test ($p = 0.592$). The sensitivity analysis showed a ranged of pooled WMD of 1.70 mm (95% CI 1.22; 2.19) to 2.01 mm (95% CI 1.44; 2.58) (Fig. S9).

In the meta-regression, this periodontal outcome did not show statistically significant correlation with year of publication ($p = 0.951$). When statins were compared to the groups without statin, simvastatin was the only statin to promote significantly CAL gain, when adjusted for the year of publication ($p = 0.043$; Table 3). The comparison among statin groups failed to show statistically significant differences between them. Furthermore, the inclusion of type of statin and year of publication in the meta-regression included more confounders in the model, as the adjusted R^2 was -43.59% .

Quality of evidence at the review level

The GRADE quality of evidence of both primary and secondary outcomes performed in the meta-analyses is presented in Table 4. To all outcomes assessed, the quality of evidence was rated as low.

Discussion

This systematic review aimed to analyze the effect of statins, in any form of administration, as a solely adjuvant to the mechanical periodontal treatment. Generally, most of the included studies showed additional periodontal clinical benefits when statins were used in along with mechanical periodontal treatment. Meta-analyses were performed using locally

delivered statins as an adjunct to mechanical periodontal treatment and showed high heterogeneity. Meta-regression showed that simvastatin, atorvastatin, and rosuvastatin significantly reduced PPD in comparison to the group without statin. Simvastatin and rosuvastatin gel significantly decreased IBD when compared to a placebo gel. Regarding CAL gain, the meta-regression showed that only simvastatin was able to significantly improve this periodontal parameter in comparison to a placebo group.

Statins are important drugs used in the treatment of hypercholesterolemia that act through the inhibition of the HMG-CoA reductase. By inhibiting this enzyme, the mevalonate synthesis is reduced, and consequently, other isoprenoid pathways are affected [44]. Therefore, cholesterol is lowered and many cardiovascular diseases may be prevented [1, 44]. Additional to their lipid-lowering effect, statins present the pleiotropic effects, which are dependent of their direct activity in a target site or as consequence to their inhibition on the biosynthesis of cholesterol. These pleiotropic effects include antiinflammatory and antioxidant effects and increase bone formation [15, 45, 46]. In this respect, an interest raised in assessing the possible effects of statins in periodontal treatment outcomes.

The literature showed that statins are able to significantly reduce the expressions of IL-6, IL-8, IL-1 β , and tumor necrosis factor- α levels [14, 47]. These drugs also showed an in vitro activity against Gram-positive and Gram-negative bacteria [48]. A decrease on the release of matrix metalloproteinase-1 (MMP-1) and MMP-3 from macrophages and endothelial cells is also reported [14, 49]. Furthermore, simvastatin reduced the levels of inducible nitric oxide synthase (iNOS), receptor activator of nuclear factor κ B (RANK), RANK ligand (RANKL), and increased the level of osteoprotegerin (OPG) in periodontal tissues [50].

These important pleiotropic effects may be the main reason why statin showed additional improvements in PPD reduction, CAL gain, and IBD decrease in most of the included studies in this systematic review. The beneficial effects of statins on the periodontal tissues were also reported on others systematic reviews [11, 21]. However, to the best of the authors' knowledge, this is the first study to show a quantitative analysis of these studies. Additionally, this is the first systematic review to report the risk of bias of the included studies.

Regarding the studies that used systemically statin, only one study showed additional improvements in PPD in normolipidemic patients, favoring the group that used atorvastatin [28]. The atorvastatin antiinflammatory effect may be responsible for this additional improvement [51]. Two other studies used systemically atorvastatin in patients with hyperlipidemia [29, 30]. The literature shows a significant association between altered lipid profile and periodontal disease [52, 53]. Therefore, it may be hypothesized that the use of statins, in

Table 4 Summary of the quality assessment to all outcomes included in the meta-analyses

Quality assessment		No. of patients		Effect	Absolute (95% CI)	Quality	Importance					
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stains adjunct to mechanical therapy	Placebo or mechanical therapy alone	WMD	(95% CI)	LO- W	
10	Randomized trials	Serious ^a	Very serious ^a	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	306	267	1.93	higher (1.44 to 2.41)	LO- W	CRITICAL
9	Randomized trials	Serious ^a	Very serious ^a	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	273	249	1.54	mm higher (1.24 to 1.84)	LO- W	CRITICAL
9	Randomized trials	Serious ^a	Very serious	Not serious	Not serious	All plausible residual confounding would reduce the demonstrated effect.	273	249	1.82	mm higher (1.24 to 2.41)	LO- W	IMPORTANT

CI confidence interval, WMD weighted mean difference

^a In all studies, mechanical therapy (control arm) did not provide the results commonly demonstrated by this therapy modality. It can be inferred by the results that mechanical therapy performed in all studies was suboptimal, thus leading to a false impression that test treatment was superior to control

patients with altered lipid profile, may not promote additionally reduction of PPD when compared to normolipidemics without statins use.

After an oral administration, statins are quickly absorbed because of their higher liver specificity, making their bioavailability very low (approximately 5–30% of the administered dose) [44]. Therefore, it may be important to have a higher drug concentration in the target site. Locally delivered drug is an approach that presents the advantage of achieving high intrasuticular drug concentration directly in the target site with a reduced dosage, better patient compliance, and reduced side effects in comparison to its systemic administration [54, 55]. Due to the higher number of studies using locally delivered statins, a meta-analysis was performed only on those studies.

Three different meta-analyses were performed, and demonstrate that statins, when used as adjunct to mechanical treatment, promote additional improvements in clinical parameters. The pooled WMD (95% CI) for PPD, IBD, and CAL were, respectively, 1.93 mm (1.44; 2.41), 1.54 mm (1.24; 1.84), and 1.82 mm (1.24; 2.41) (Figs. S1, S4, and S7). Despite these interesting findings, a higher heterogeneity was detected in all the analyses. Therefore, due to the lack of consistency, the clinical relevance of these results should be interpreted with caution, as it may not be directly translated into the clinical practice. Similar results are also reported in a recent published systematic review [56]. This study showed a pooled WMD (95% CI) for PPD and CAL of, respectively, 1.51 mm (1.04; 1.97) and 1.84 mm (1.37; 2.31). High heterogeneity was also demonstrated in this systematic review. Moreover, this study showed that rosuvastatin and a longer follow-up period were associated with improved periodontal outcomes [56]. However, no meta-regression was detailed to address the heterogeneity, which is one of the main strength of the present systematic review.

Additionally, the GRADE evaluation showed that evidence provided for the studies included in the meta-analyses was ranked as low quality. Another point to be raised is statistical versus clinical significance. This fact needs to be individually interpreted. However, a statistically significant difference in such a pool of studies at least points out for a strong tendency of better results. The clinical extrapolation of them needs to consider other points of evidence-based approaches, such as the skills of the professional and the preferences and beliefs of the patients.

Overall, in the meta-regression, all the tested statins (simvastatin, atorvastatin, and rosuvastatin) showed additional benefits in reducing PPD. However, simvastatin was the only drug able to additionally improve CAL gain when compared to a placebo gel. The higher number of studies using this statin may explain this result.

The use of other drugs as an adjunct to mechanical periodontal treatment is also reported in the literature. Local and

systemic antibiotics are largely studied. Overall, despite of their statistically significant improvements in periodontal parameters, this additional benefit is small and may not represent a clinical benefit. For example, a systemic review with meta-analysis showed that the use of systemic amoxicillin/metronidazole, as adjunct to mechanical periodontal treatment, promote significantly CAL gain (WMD = 0.21; 95% CI = 0.02 to 0.4) and PPD reduction (WMD = 0.43; 95% CI = 0.24 to 0.63) [57]. Additionally, the subgingival application of antimicrobials, adjunctive to periodontal treatment, also showed a significantly improvement in PPD reduction and CAL gain, with a WMD of 0.407 and 0.310, respectively [58]. Comparing with these results of the present meta-analyses, the magnitude of CAL gain and PPD reduction was higher with the adjunct use of statins than with the adjunct use of antimicrobials.

All kinds of statin administration were included to give a broader view of this drug when associated with mechanical periodontal therapy. Of the 15 studies included in this systematic review, 11 used locally delivered statin. From these, 9 were performed by the same research group in India. All those studies were included in at least one of the performed meta-analyses/meta-regression. Additionally, these 11 studies performed periodontal treatment and the gel application in only one/two sites of each participant. These facts should be put in perspective when analyzing the quantitative data presented in this study, as a research center effect may be expected and one/two sites treatment may not represent the periodontal treatment as a whole.

The study of Surve et al. (2015) [39] was the only study included in this systematic review that did not show an additional benefit of locally delivered statin to any periodontal parameter evaluated. This study was not included in the quantitative analysis, as the data extraction could not be performed in a standardized manner. Despite its methodology similarities to the included ones, this study did not present a sample size calculation, and used only 15 sites on each group. Additionally, it should be highlighted that this study presented a critical/serious risk of bias in several domains of the ROBINS-I tool (Table 2). Those observations may explain the discrepancies between the studies.

The most common side effects related to statin are muscle toxicity with myopathy and rhabdomyolysis, which occur in patients using higher statin doses or drugs that interact with the hepatic metabolism [59]. Almost of all the included studies in the systematic review showed no adverse events related to use of statin either locally delivered or systemically. This is in agreement with the literature that states that statins are well tolerated and the adverse events are rare [60].

The results herein presented are challenging in terms of interpretation. However, the possible benefits of the adjunct use of statins in periodontal therapy should be considered, with further clinical studies exploring this hypothesis,

especially due to some of the limitations of the included studies, with a high degree of heterogeneity and the possible strong research center effect.

Conclusion

It was concluded that statins, used as sole adjuncts to mechanical periodontal treatment, additionally improved at least one of the following periodontal parameters: probing pocket depth, clinical attachment level, and intrabony defect. The use of locally delivered statins in periodontal pockets is largely studied. Within the limits of this review, in the meta-regression analyses, simvastatin was the only drug that showed additional benefits in probing depth, clinical attachment level, and intrabony defect, when compared to the groups without statin.

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Compliance with ethical standards

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

Ethical approval Ethical approval does not apply to systematic reviews.

Informed consent Informed consent does not apply to systematic reviews.

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