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The effect of local and systemic statin use as an adjunct to non-surgical and surgical periodontal therapy. A systematic review and meta-analysis.

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Short running title: Statins and periodontal treatment

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Abstract

Objectives

To evaluate the effect of local and/or systemic statin use as an adjunct to non-surgical and/or surgical periodontal therapy.

Data

Literature search according to PRISMA guidelines with the following eligibility criteria: (a) English or German language; (b) interventional studies; (c) statins as monotherapy or as an adjunct to non-surgical and/or surgical treatment of periodontitis; (d) clinical and/or radiographic treatment effect size of statin intake reported.

Sources

Medline (PubMed), Embase (Ovid), CENTRAL (Ovid).

Study selection

Thirteen clinical studies regarding local application and 2 with systemic administration of statins as an adjunct to non-surgical treatment (SRP) and 4 studies regarding intrasurgical statin application with a maximum follow-up of 9 months could be included; simvastatin, atorvastatin, and rosuvastatin were used. Local but not systemic statin application as an adjunct to SRP yielded significantly larger probing pocket depth (PD), radiographic defect depth (RDD), and bleeding index reduction, and larger clinical attachment level gain, and less residual PD and RDD ($p \leq 0.016$); rosuvastatin appeared as the most

efficacious. Three of 4 studies reported a significant positive effect of intrasurgical statin application. No adverse events were reported after statin use. The vast majority of the included studies were from the same research group.

Conclusions

Significant additional clinical and radiographic improvements are obtained after local, but not systemic, statin use as an adjunct to SRP in deep pockets associated with intrabony defects and seemingly with furcation defects; intrasurgical statin application seems similarly beneficial. Confirmation of these results, and especially of the effect size, from other research groups is warranted.

Keywords: Atorvastatin; clinical trials; periodontal treatment; rosuvastatin; simvastatin; statins; systematic review.

Background

The use of local and/or systemic adjunct measures [e.g., chlorhexidine, hyaluronan, probiotics, antibiotics (AB), etc.] to mechanical treatment has been a common therapeutic approach aiming for better infection control, reduced tissue destruction by the immune response, and/or enhanced reparative processes. Due to concerns regarding the increasing bacterial resistance, systemic AB do not meet widespread acceptance [1]; thus, non-AB alternatives may be a more reasonable approach.

Statins is an example of a non-AB agent evaluated as an adjunct to periodontal therapy. Statins (i.e., 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are primarily indicated as lipid-lowering agents and for prevention of cardiovascular diseases [2–5]. Nevertheless, statins possess various additional properties relevant to the pathogenesis of periodontal diseases; e.g., statins are anti-inflammatory [6–11], promote bone formation [12–16], inhibit tissue degrading enzymes [i.e., matrix metalloproteinases (MMPs)] [6,17,18], and have anti-microbial properties [19,20]. Indeed, in a recent systematic review and meta-analysis of preclinical in vivo trials, a positive effect of statin intake was observed [21]; in particular, in standard experimentally induced periodontitis models in rodents, statin intake – local application or systemic administration – significantly prevented alveolar bone loss compared to the controls. In this context, there is already a considerable number of clinical trials on this topic, but appropriate systematic evaluation of the available evidence does not exist.

The aim of the present systematic review was to address the following focused question according to the Population, Intervention, Comparison, Outcomes, Study Design (PICOS) criteria [22]: “In periodontally diseased subjects, does local and/or systemic statin intake as monotherapy or as an adjunct to periodontal treatment, compared to no treatment or periodontal treatment alone, result in better histological and/or clinical periodontal parameters in randomized and/or controlled clinical trials?”

Materials and Methods

Protocol and eligibility criteria

The present systematic review was reported according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA; Appendix S1) [23,24]. The following inclusion criteria were applied during literature search on 3 sources (Medline – PubMed; Embase – Ovid; CENTRAL – Ovid; last search 31/12/2016 – no date restriction used): (a) English or German language; (b) interventional studies [i.e., controlled or randomized controlled trials (RCT)]; (c) statins as monotherapy or as an adjunct to non-surgical and/or surgical treatment of periodontitis; (d) at least 10 patients per group; (e) follow-up $\geq$ 3 months; (f) treatment effect size of statin intake evaluated [i.e., probing pocket depth (PD), clinical attachment level (CAL), bleeding index, and/or bone level];

and (h) full-text available. The following exclusion criteria were applied: (a) studies not meeting all inclusion criteria; and (b) systemic statin intake since > 1 month before study entry. Two authors (KB, AP) independently checked title, abstract, and finally full-text on the pre-defined eligibility criteria, and also assessed the risk of bias (RoB) of the included studies applying the Cochrane Collaboration's Tool for assessing RoB. One author (KB) repeated the literature search and RoB assessment. In case of ambiguity, consensus through discussion was achieved together with a third author (AS).

For information on literature search methodology and information sources, data collection and synthesis, RoB, and statistical analysis please see Appendix S2.

Synthesis of results

Two primary outcome parameters (i.e., residual PD, CAL gain) and several secondary outcome parameters [i.e., PD reduction, modified sulcus bleeding index (mSBI) reduction, residual radiographic defect depth (RDD), RDD reduction] were defined and values at 3-, 6-, and 9 months post-treatment were included – if available – for meta-analyses, separately for non-surgical and surgical trials.

Quantitative synthesis was performed using the DerSimonian and Laird random effects methods, in view of the variation in population and settings, and pooled estimates were calculated separately per follow-up period. Monte Carlo permutation test was used for meta-regression with the primary and secondary outcome measures as the response variables and statin type, smoking status, and follow-up period as explanatory variables. Finally, standard funnel plots including an Egger's test were used to examine publication bias if 10 or more comparisons were available. All statistical analyses were performed using STATA (StataCorp LLC, USA).

Results

Study selection

The flowchart of the literature search is presented in Figure 1. Out of 383 identified studies, 26 articles were selected for full-text review; 7 trials [25–31] were excluded for various reasons (Appendix S3). No studies were excluded due to language restriction (i.e. not English or German). Finally, 15 studies on non-surgical [32–46] and 4 studies on surgical [47–50] periodontal treatment were included. Additionally, 4 unpublished studies were identified on ClinicalTrials.gov (NCT02372656, NCT02516111, NCT02386033, NCT02612792; all with „status: completed“), but no detail data from those studies could be obtained.

Study characteristics

An overview of study populations, type of intervention, description of defect and site characteristics, and type and mode of statin application is given in Table 1. Results on RoB and publication bias assessment, and on funding of the studies are presented in Appendix S4.

Study populations (Table 1)

The studies on non-surgical periodontal treatment included between 38 and 99 patients and those on surgical periodontal treatment included between 15 and 110 patients, diagnosed with chronic periodontitis. Seventeen studies included only non-smokers and 2 studies [35,44] only smokers. All studies included systemically healthy patients, except for 3 studies including well-controlled diabetic patients [36,40], and hyperlipidemic patients [33].

Type of intervention (Table 1)

All studies on non-surgical periodontal treatment applied the statins as an adjunct to non-surgical treatment (SRP). Two studies [32,33] tested systemic administration of statins, while the other 13 studies applied a statin formulation locally and subgingivally. Except for 2 studies [33,46], all studies used a placebo in the control group. The follow-up period ranged between 6 and 9 months; loss to follow-up was reported in all studies, which was ranging per group from 0 to 8 patients (i.e., 0 to 21.1%). All studies on surgical periodontal treatment tested combination treatments with or without additional intra-operative statin application. Martande et al. [48] and Pradeep et al. [50] compared open flap debridement (OFD) with OFD with platelet-rich fibrin (PRF) with or without statin application, Kinra et al. [47] compared demineralized freeze-dried bone allograft with or without statin application, and Pradeep et al. [49] compared OFD with OFD with PRF and hydroxyapatite with or without statin application. One study [49] applied a placebo solution in the control group. The follow-up period was 6 to 9 months and loss to follow-up ranged per group from 0 to 2 patients (i.e., 0 to 6.3%).

Description of defect and site characteristics (Table 1)

Among the studies on non-surgical periodontal treatment 10 studies treated specifically intrabony defects with at least 3 mm vertical bone loss, 2 studies [34,38] furcation defects, and 3 studies [32,33,46] did not concentrate on a specific periodontal defect type. All studies clearly specified patient inclusion criteria by PD, CAL, and/or vertical bone loss. Three of the studies on surgical periodontal treatment [47,48,50] treated intrabony defects and the fourth [49] furcation defects. Except for one study [47], clear inclusion criteria have been presented.

Type and mode of statin application (Table 1)

Among the studies on non-surgical periodontal treatment 3 different statin types were tested: simvastatin (SMV); atorvastatin (ATV); rosuvastatin (RSV). Five studies tested SMV [37,38,40,44,45], 6

studies ATV (including both studies with systemic administration) [32,33,35,36,39,43], one study RSV [41], one study each compared SMV with ATV [46], and 2 studies compared ATV with RSV application [34,42], respectively. Among the studies on local application, 11 studies used a methylcellulose gel for statin application, one study used a sodium alginate suspension [46], and one study did not specify the gel composition [43]; all prepared a 1.2% statin solution. In most studies the statin formulation was applied a single time after SRP; in 2 studies [34,42] the statin-loaded gel was applied once more after 6 months. Both studies prescribing systemic statin administration [32,33] used a dose of 10 to 20 mg ATV per day and evaluated the effect 90 days after statin intake. One study [33] did not report on the presence or absence of adverse events, otherwise none were observed.

Three studies on surgical periodontal treatment applied once intra-operatively either ATV [48] or RSV [49,50] in a statin-loaded methylcellulose gel (i.e., 1.2%), and the fourth study [47] mixed the allograft with an aqueous SMV solution (10^{-8} M SMV). No adverse events were observed.

Reported outcome variables and treatment effect size (Table 2 and 3)

All studies evaluating local application or systemic administration of statins as an adjunct to SRP reported on the relevant clinical and/or radiographic outcome parameters (i.e., PD, CAL, mSBI, RDD). Four studies [32,33,45,46] determined inflammatory and bone-specific parameters in gingival crevicular fluid, periodontal tissue, and/or blood samples. All studies evaluating statin application during surgical periodontal treatment reported on PD, CAL, and RDD, but only one study [50] on site specific mSBI.

Except for one study ([46]; unclear risk of bias) all studies (9 studies low risk, 3 studies unclear risk of bias) assessing local statin application as an adjunct to SRP presented a significant added benefit for the test group compared to the control group regarding the clinical parameters (i.e., PD, CAL, and/or mSBI). Among the studies specifically treating intrabony defects (i.e., excluding 2 studies on furcation defects [34,38] and one study not specifically treating intrabony defects [46]) the radiographic measurements showed in all studies (8 studies low risk and 2 studies unclear risk of bias), at least in one of the test groups, a significant improvement after statin application. Both studies on non-surgical treatment of furcation defects [34,38] (low and unclear risk of bias) presented significant improvements regarding clinical and radiographic measurements. Noteworthy, in the 2 studies with systemic statin administration [32,33] (low risk of bias and no RCT), no significant differences have been detected between test and control group.

Application of statin during surgical periodontal treatment resulted in 3 [47,49,50] (high risk, unclear risk, and low risk of bias) out of 4 studies (4th study: unclear risk of bias) in a significant

improvement regarding clinical parameters, and in all studies regarding the radiographic measurements.

Synthesis of results

Eleven studies have been pooled together for the meta-analysis (8 studies low risk and 3 studies unclear risk of bias). The results of the studies on furcation defects were not pooled, as one treated residual defects (i.e., after previous SRP) [38] and the other study [34] untreated defects. Further, due to a different study population (i.e., healthy vs. hyperlipidemic patients) the 2 studies on systemic statin application were not pooled together. Two studies [48,50] (both unclear risk of bias) out of the 4 studies on surgical treatment have been comparable in terms of study design (i.e., intrabony defect, combination of statin with PRF, observation period 9 months) and were pooled in a meta-analysis.

Statin as an adjunct to non-surgical periodontal treatment (Figure 2, Appendix S5)

Statin application as an adjunct to SRP resulted in significantly improved clinical and radiographic parameters compared to SRP alone ($p \leq 0.019$) after 3-, 6-, and 9 months. Residual PD and CAL gain in the statin treated groups at the longest follow-up ranged between 2.3 – 5.0 mm and 1.1. – 4.7 mm, respectively, compared with 3.2 – 6.5 mm and 0.7 – 2.3 mm, respectively in the control sites. The corresponding RDD values were 1.8 – 6.6 mm and 2.7 – 7.2 mm in the statin and control groups, respectively. However, heterogeneity was for most comparisons significant (i.e., 13 out of 16 comparisons).

Statin as an adjunct to surgical periodontal treatment (Figure 3)

Statin application as an adjunct to PRF in surgical treatment of intrabony defects resulted in significantly improved clinical parameters compared to solely PRF application, after 9 months; residual PD and CAL gain in the statin treated groups at the longest follow-up ranged between 3.0 – 4.0 mm and 3.7 – 3.9 mm, respectively, compared with 3.8 – 4.5 mm and 3.3 – 3.4 mm, respectively in the control sites. Further, the test group was significantly better in terms of residual RDD but not RDD reduction; in particular, RDD ranged from 2.5 to 2.5 mm and 2.7 to 2.8mm in the statin and control groups, respectively. Heterogeneity was significant for the parameters PD reduction ($I^2 = 70.5\%$; $p = 0.065$), residual RDD ($I^2 = 89.8\%$; $p = 0.002$), and RDD reduction ($I^2 = 68.0\%$; $p = 0.077$).

Evaluation of possible explanatory variables

The results of the meta-regression on the studies evaluating statin as an adjunct to SRP showed that, while smoking status had no effect on any of the outcome parameters ($p \geq 0.163$), a longer follow-up period (i.e., 9 months) and statin type (i.e., RSV) have been associated with an improved outcome for

all parameters ($p \leq 0.049$). More in detail, RSV was superior to SMV for all outcome parameters ($p \leq 0.001$) and superior to ATV in all outcome parameters ($p \leq 0.021$) except for residual RDD ($p = 0.838$).

Discussion

The rationale to use statins as an adjunct to periodontal treatment has been based on their anti-inflammatory- [6–11], bone promoting- [12–16], and anti-MMP- [6,17,18] properties. Recently, it was demonstrated that statins also have some anti-microbial properties [19,20]. Indeed, in several preclinical in vivo trials in rodents, employing standard experimentally-induced periodontitis models, local application or systemic administration of statin resulted in significantly less alveolar bone loss compared to controls (for a systematic review, including meta-analyses, see: [21]).

In this context, application of locally applied products as an adjunct to mechanical periodontal treatment aims for better infection control, less tissue destruction, and/or improved wound healing; this, in the clinic, translates to larger improvements in terms of PD reduction and CAL gain, and radiographic bone defect resolution. For example, local application of hyaluronan as an adjunct to SRP was shown to have an added benefit in PD reduction in the range of 0.2 to 0.9 mm, but even more limited – if any – added benefit in terms of CAL gain [51]. Collectively, non-AB agents as adjuncts to SRP are reported to give 0.2 to 0.9 mm and 0.1 to 0.9 mm additional PD reduction and CAL gain, respectively (chlorhexidin/full-mouth disinfection [52,53]; povidone-iodine [54]; low-dose doxycycline [55]; probiotics [56]; several agents [57]). The added benefit of statin application in terms of PD reduction, CAL gain, and RDD reduction ranged herein between about 1.0 to 3.0 mm for deep pockets (i.e., > 6.5 mm). Thus, the magnitude of added clinical benefits after local statin application as an adjunct to SRP, observed in the present systematic review, appears remarkably larger than that of other non-AB adjuncts to SRP reported previously. Further, it must be mentioned that average values for PD reduction and CAL gain of around 1 to 2 mm and 0.5 to 1 mm, respectively, have previously been reported for deep pockets after SRP alone [58]; thus, the clinical results achieved in the control groups in the included studies were – more or less – similar to what is usually obtained after SRP alone, and, hence, the observed added benefits cannot be attributed to a worse response in the control groups. In context, the magnitude of clinical improvements is within the range reported after regenerative periodontal surgery in intrabony defects [59]. Nevertheless, there is no human histological evaluation of the outcome of healing after statin application so far, and a systematic evaluation of the currently available evidence from preclinical in vivo studies [21], showed that healing after intra-surgical local application of statins in acute/chronified periodontal defects was never characterized by complete regeneration of the tooth supporting apparatus; specifically, new cementum formation was not observed.

Similarly to what observed with local application of statins in conservative periodontal therapy, intra-surgical application of statins in combination with a bone substitute and/or PRF resulted, in general, in significantly better clinical and radiographic outcomes when compared to the use of a bone substitute and/or PRF alone. The beneficial effect of statins after application in a bone defect may be attributed to the up-regulation of osteoprotegerin, bone morphogenetic protein-2, and vascular endothelial growth factor, as demonstrated in preclinical in vivo studies [60–64]. The magnitude of improvements in the “control” groups of these studies compares well with the outcomes reported elsewhere after application of such type of technologies [65–67]; thus, the added benefits observed in the test groups could be attributed to the statins. Nevertheless, the lack of a group where only statins were used, precludes any clear conclusions regarding intra-surgical statin use.

Preclinical studies, using experimentally induced periodontitis models in rodents, have demonstrated that statin intake (local application or systemic administration) induced a strong anti-inflammatory response in the periodontal tissues, e.g. by reducing the expression of pro-inflammatory cytokines and tissue degrading enzymes and/or processes and by increasing the expression of anti-inflammatory cytokines.[61–64,68,69]. In the only 2 studies included in the present review, that assessed the effect of local application of statins as an adjunct to SRP on the level of inflammatory cytokines in the periodontal tissues and/or in gingival crevicular fluid [45,46], no significant difference between test and control groups was observed. Nevertheless, no significant clinical benefit from statin use was observed in one of the studies [45,46], while in the other study the added clinical benefit from statin use did not include CAL gain [45,46]. In general, local statin application as an adjunct to SRP resulted in significantly decreased bleeding indices after treatment, a finding consistent with the significant clinical improvements observed in the studies.

In contrast to the apparent beneficial effect from local statin application, systemic statin administration as an adjunct to SRP does not seem to provide any significant additional improvements. In both included studies involving systemic statin administration [32,33], no significant advantage for the ATV groups was observed, neither on clinical periodontal parameters nor on inflammatory and bone metabolism markers. As mentioned above, in a systematic review of preclinical in vivo studies, systemic statin administration – irrespective of statin type – was found to exhibit a significant positive effect on the periodontal tissues, in terms of limiting disease progression and/or enhancing wound healing [21]. A reason for the lack of effect in the clinical studies herein might be the administered ATV dose (i.e., 10 to 20 mg/d); in one study excluded from the present review, because of no control group without statin application [31], administration of 10 mg ATV did not show any significant effect, while a significant reduction of the periodontal inflammation was observed after administration of 80 mg of ATV. On the other hand, 80 mg is considered the highest daily dose for ATV; taking into account that patients taking statins systemically report frequently muscle symptoms (i.e., 10 to 25%) and are

exposed to an increased risk for myopathy and also a slightly higher risk for developing diabetes mellitus [70], while no adverse effects have so far been reported after local application of statins in combination with SRP, it seems reasonable not to consider systemic administration of statins in combination with periodontal therapy.

Metaregression herein showed that statin type had a significant impact on the outcome of treatment. In particular, RSV yielded significantly better outcomes compared to SMV and ATV; however, these results are based on only 2 studies testing RSV. Although the action of the various statin types is based on a common mechanism, there are differences in their chemical structure and potency [71,72]. Specifically, the fully synthetic RSV, which is considered as the most potent to reduce low-density lipoprotein cholesterol, is hydrophilic and has the longest elimination half-life (i.e., 19 hours), while SMV and ATV are lipophilic and have a more rapid half-time. Thus, the longer half-life time of RSV appears as a probable explanation of better clinical outcomes with this statin type. In this context, when interpreting the results, one has to consider the fact that in most of the studies included in this review, statins have been mixed in a gel with specific formulation prior to application; different types of carriers for local drug delivery possess potentially significant differences in terms of pharmacokinetic and may indeed have great impact on the treatment outcome. Further, considering the anti-microbial effect of statins in vitro [19,20], a comparison of the pre- and post-treatment periodontal microbiota would be interesting; surprisingly, this has not been evaluated/reported up to now. In perspective, despite the fact that the studies included in this review, in general, appeared with low risk of bias and publication bias was unlikely, the vast majority of studies included in the present systematic review are from the same research group, whose conflict of interest remains unclear; as already mentioned, the additional benefit of statins as an adjunct to SRP was not consistently confirmed in the only 2 studies from other research groups, included herein [45,46].

In summary, the present systematic review showed:

- Local application of statins as an adjunct to SRP during non-surgical periodontal treatment of deep pockets associated with intrabony defects, results in significant additional clinical and radiographic improvements compared to SRP alone.
- This benefit from statins is also seen in smokers and well-regulated diabetics, and it seems also to be valid in furcation defects.
- Mostly a single concentration (1.2%) has been tested and mostly as a single application after SRP.
- There are differences among the various statin types, in terms of efficacy, and RSV appears as the most efficacious for local application.
- Systemic statin intake does not enhance the outcome of SRP.

- Local application of statins as an adjunct to surgical periodontal treatment in combination with grafts and/or PRF results in significant improvements in clinical and radiographic periodontal parameters compared to grafting or PRF alone.

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Table legends

Figure legends **Figure 1.** Flowchart of the inclusion process of studies for the systematic review.

Residual PD

Figure 2a and b. Forest plot on the effect size of treatment after SRP compared to SRP + statin on (a) residual probing pocket depth and (b) clinical attachment level gain; simvastatin (blue), atorvastatin (orange), and rosuvastatin (green).

Figure 3. Forest plot on the effect size of treatment after open flap debridement + platelet rich fibrin compared to open flap debridement + platelet rich fibrin + statin; atorvastatin (orange), and rosuvastatin (green).

Appendix legends

Appendix S1. Prisma 2009 checklist.

Appendix S2. Information sources and literature search, data collection and synthesis, risk of bias assessment, and statistical analysis.

Appendix S3. Reasons for exclusion of 7 full-texts.

Appendix S4. Risk of bias of studies on non-surgical and surgical periodontal treatment according to the Cochrane Collaboration's Tool (Higgins & Green 2011).

Appendix S5a to d. Forest plot on the effect size of treatment after SRP compared to SRP + statin on (a) probing pocket depth reduction, (b) modified sulcus bleeding index reduction, (c) residual radiographic defect depth, and (d) radiographic defect depth reduction.

Table 1. Characteristics of human trials evaluating statins as adjunct to non-surgical and surgical periodontal treatment in periodontitis patients.

Study (year)	Study design	No. of patients, disease (m/f, age) smoking status Additional info	Inclusion criteria	Loss to follow-up (n) Follow-up period (m)	Intervention (test vs. control)	No. of application sites (S) / patients (P)	Application mode/site	Application frequency Dosis	Application period (days)	Test product Placebo product
Non-surgical treatment - Local application										
Pradeep & Thorat (2010)	RCT (placebo), PG	60, CP (33/31, mean 31) NS -	intrabony defects, moderate (PD 5-6mm or CAL 4-6mm) to deep pockets (PD≥7mm or CAL 6-9mm) & vertical BL≥3mm	0 6	SRP + SMV vs. SRP + placebo	1 S / P	subgingival	1 0.1ml of SMV gel (1.2mg/0.1ml)	1	SMV (1.2mg) in methylcellulose gel NR
Pradeep et al. (2012)	RCT (placebo), PG	72, CP (38/34, range 30-50) NS -	furcation defects (buccal, class II, mandibular 1 st & 2 nd molars), PD≥5mm & horizontal PD≥3mm after SRP	6 6	SRP + SMV vs. SRP + placebo	1 S / P	subgingival – into the furcation defect	1 0.1ml of SMV gel (1.2mg/0.1ml)	1	SMV (1.2mg) in methylcellulose gel NR
Rath et al. (2012)	RCT (placebo), PG	60, CP (33/27, range 25-45) NS -	intrabony defects, PD>5mm & vertical BL≥3mm	0 6	SRP + SMV vs. SRP + placebo	1 S / P	subgingival	1 0.1ml of SMV gel (1.2mg/0.1ml)	1	SMV (1.2%) in methylcellulose gel NR
Pradeep et al. (2013a)	RCT (placebo), PG	38, CP (20/18, range 30-50) NS well-controlled DMT2	intrabony defects, PD≥5mm or CAL≥4mm & vertical BL≥3mm, ≥20 teeth	3 9	SRP + SMV vs. SRP + placebo	in total 36/34 S in test/control P	subgingival	1 10µl of SMV gel (1.2mg/0.1ml)	1	SMV (1.2%) in methylcellulose gel NR
Pradeep et al. (2013b)	RCT (placebo), PG	67, CP (35/32, range 30-50) NS -	intrabony defects, PD≥5mm or CAL≥4mm & vertical BL≥3mm	7 9	SRP + ATV vs. SRP + placebo	1 S / P	subgingival	1 10µl of ATV gel (1.2mg/0.1ml)	1	ATV (1.2%) in methylcellulose gel NR
Rao et al. (2013)	RCT (placebo), PG	40, CP (40/0, range 30-50) S -	intrabony defects, PD≥5mm or CAL≥4mm & vertical BL≥3mm	5 9	SRP + SMV vs. SRP + placebo	in total 43/43 S in test/control P	subgingival	1 10µl of SMV gel (1.2mg/0.1ml)	1	SMV (1.2%) in methylcellulose gel NR
Pradeep et al. (2015)	RCT (placebo), PG	70, CP (33/37, range 25-55) NS -	intrabony defects, moderate pockets (PD 5-6mm or CAL 4-6mm) & vertical BL≥3mm, ≥20 teeth	5 6	SRP + RSV vs. SRP + placebo	1 S / P	subgingival	1 0.1ml of RSV gel (1.2mg/0.1ml)	1	RSV (1.2%) in methylcellulose gel NR
Surve et al. (2015)	(R)CT, PG	45, CP (NR, range 35-55) NS -	PD≥5mm & radiographic evidence of BL _v ≥14 teeth	0 6	SRP + SMV vs. SRP + ATV vs. SRP	1 S / P	subgingival	1 NR	1	SMV (1.2%) / ATV (1.2%) in sodium alginate suspension with calcium chloride solution -

Kumari et al. (2016a)	RCT (placebo), PG	71, CP (NR, range 30-50) S -	intrabony defects, PD $\geq$ 5mm or CAL $\geq$ 4mm & vertical BL $\geq$ 3mm	5 9	SRP + ATV vs. SRP + placebo	1 S / P	subgingival	1 10 μ l of ATV gel (1.2mg/0.1ml)	1	ATV (1.2%) in methylcellulose gel NR
Kumari et al. (2016b)	RCT (placebo), PG	75, CP (38/37, range 40-50) NS well-controlled DMT2	intrabony defects, PD $\geq$ 5mm or CAL $\geq$ 4mm & vertical BL $\geq$ 3mm, $\geq$ 20 teeth	15 9	SRP + ATV vs. SRP + placebo	1 S / P	subgingival	1 10 μ l of ATV gel (1.2mg/0.1ml)	1	ATV (1.2%) in methylcellulose gel NR
Pradeep et al. (2016b)*	RCT (placebo), PG	99, CP (53/51, range 30-50) NS -	intrabony defects, PD $\geq$ 5mm or CAL $\geq$ 4-6mm & vertical BL $\geq$ 3mm, $\geq$ 20 teeth	9 9	SRP + ATV vs. SRP + placebo	1 S / P	subgingival	1 10 μ l of ATV gel (1.2mg/0.1ml)	1	ATV gel (1.2%) NR
Pradeep et al. (2016c)	RCT (placebo), PG	90, CP (45/45, range 25-45) NS -	intrabony defects, PD $\geq$ 5mm or CAL $\geq$ 3mm & vertical BL $\geq$ 3mm	9 9	SRP + ATV vs. SRP + RSV vs. SRP + placebo	1 S / P	subgingival	2 0.1ml of ATV gel (1.2mg/0.1ml) 0.1ml of RSV gel (1.2mg/0.1ml)	180 (at BL & after 6 months)	ATV (1.2%) in methylcellulose gel RSV (1.2%) in methylcellulose gel NR
Garg & Pradeep (2017)	RCT (placebo), PG	90, NR (NR, range 30-50) NS -	mandibular furcation defects class II, PD $\geq$ 5mm & horizontal PD $\geq$ 3mm	0 9	SRP + ATV vs. SRP + RSV vs. SRP + placebo	1 S / P	subgingival	2 0.1ml of ATV gel (1.2mg/0.1ml) 0.1ml of RSV gel (1.2mg/0.1ml)	180 (at BL & after 6 months)	ATV (1.2%) in methylcellulose gel RSV (1.2%) in methylcellulose gel methylcellulose gel
Non-surgical treatment - Systemic administration										
Fajardo et al. (2010)	RCT (placebo), PG	38, CP (6/32, range 40-60) NS -	PD $\geq$ 3 mm in at least 3 teeth, gingival index of 2 or 3, plaque index of 2 or 3, gingival recession, $\geq$ 15 teeth	0 3	SRP + ATV vs. SRP + placebo	-	Oral	90 20mg/d	90	ATV Trivitamin preparation (thiamin 100mg, pyridoxine 50mg, cyanocobalamin 250mg)
Fentoglu et al. (2012)	CT, PG	80, CP (40/40, range 30-57) NS hyperlipidemic patients	$\geq$ 4 teeth with PD $\geq$ 5mm & CAL $\geq$ 2mm, $\geq$ 18 teeth	0 3	I (systemically healthy): SRP II (hyperlipidemic): SRP + diet III (hyperlipidemic): SRP + ATV	-	Oral	90 10 or 20mg/d	90	ATV -
Surgical treatment - Local application										
Kinra et al (2010)	RCT, SM	15, NR (8/7, NR) NS -	intrabony defects, 2-3-walls	0 6	I: DFDBA II: DFDBA + SMV	2 S / P (1 S / group)	intra-operative	1 10 $^{-8}$ M SMV solution	1	10 $^{-8}$ M SMV dissolved in water -
Martande et al. (2016)	RCT, PG	96, CP (48/48, mean 38) NS -	intrabony defects, 3-walls & depth $\geq$ 3mm	6 9	I: OFD II: OFD + PRF III: OFD + PRF + ATV	1 S / P	intra-operative	1 10 μ l of 1.2% ATV	1	ATV (1.2%) in methylcellulose gel -
Pradeep et al. (2016a)	RCT (placebo), PG	110, CP (60/50, range 25-55) NS -	furcation defects (buccal, class II, mandibular 1 st & 2 nd molars), PD $\geq$ 5mm & horizontal PD $\geq$ 3mm after SRP	5 9	I: OFD + placebo II: OFD + PRF + HA III: OFD + PRF + HA + RSV	1 S / P	intra-operative	1 0.1ml of RSV gel (1.2mg/0.1ml)	1	RSV (1.2mg) in methylcellulose gel NR
Pradeep et al. (2016d)	RCT, PG	90, CP (NR, range 25-45) NS -	intrabony defects (mandibular molar), 2-3 walls & PD $\geq$ 5mm, CAL $\geq$ 3mm,	0 9	I: OFD II: OFD + PRF III: OFD + PRF + RSV	1 S / P	intra-operative	1 RSV gel coated on the PRF membrane	1	RSV (1.2%) in methylcellulose gel -

vertical
BL $\geq$ 3mm

** Only control groups and test groups on statin application are listed.*

ATV – atorvastatin, BL – bone loss, CAL - clinical attachment level, CP - chronic periodontitis, DFDBA – demineralized freeze-dried bone allograft, DMT2 – diabetes mellitus type 2, HA – hydroxyapatite, NR - not reported, NS - non-smokers, OFD – open-flap debridement, PD - probing pocket depth, PG – parallel group design, PRF – platelet-rich fibrin, RCT - randomized controlled clinical trial, (R)CT - according to authors randomized, but randomisation process not defined or of high risk of bias, RSV – rosuvastatin, SM – split-mouth design, SMV – simvastatin, S – smokers, SRP - scaling & root planing.

Table 2. Clinical outcomes of human trials evaluating statins as adjunct to non-surgical and surgical periodontal treatment in periodontitis patients.

Study (year)	Group	Baseline			Follow-up period (m)	Outcome				Comparison based on
		mSBI	PD (mm)	RDD (mm)		mSBI	PD (mm)	CAL gain (mm)	RDD (mm)	
Non-surgical treatment - Local application										
Pradeep & Thorat (2010) ^{1*}	Test	3.1±0.7	7.4±1.6	4.4±1.1	6	0.8±0.7	3.2±1.6	4.4±1.9	2.9±1.1	B
	Control	2.9±0.8	6.9±1.6	4.4±1.2		2.4±1.2	5.7±2.1	1.6±2.0	4.3±1.3	
Pradeep et al. (2012) ^{1^A}	Test	2.8±0.3	7.3±1.5	4.6±1.1	6	0.8±0.2	3.3±0.8	v: 4.6±1.0 h: 4.3±1.2	3.4±1.0	B (PD, CAL, RDD)
	Control	2.5±0.4	6.8±1.3	4.3±1.0		1.6±0.4	5.5±1.3	v: 2.5±1.5 h: 2.4±1.3	4.3±0.9	
Rath et al. (2012) ^{1*}	Test	2.7±0.4	6.3±1.7	7.2±1.2	6	0.2±0.4	2.3±0.6	4.7±1.4	6.6±1.3	B
	Control	2.6±0.5	6.6±1.5	7.3±1.1		0.7±0.7	4.5±1.7	2.3±1.1	7.2±1.0	
Pradeep et al. (2013a) ^{1*}	Test	3.0±0.3	8.3±1.0	4.9±0.5	9	1.3±0.2	4.3±1.0	4.0±1.2	3.3±0.6	A B (PD, CAL, RDD)
	Control	2.8±0.4	7.9±1.1	4.9±0.6		2.1±0.3	6.3±0.9	1.1±0.8	4.7±0.6	
Pradeep et al. (2013b) ^{1*}	Test	2.8±0.2	7.8±1.3	4.8±0.5	9	1.1±0.2	4.1±1.0	4.5±0.6	3.1±0.4	A B (PD, CAL, RDD)
	Control	2.7±0.2	7.7±1.1	4.8±0.5		1.6±0.2	6.3±1.1	2.3±0.5	4.7±0.5	
Rao et al. (2013) ^{1*}	Test	2.1±0.4	7.9±0.9	4.8±0.9	9	1.2±0.2	4.0±0.9	3.6±1.1	3.2±0.9	A B (PD, CAL, RDD)
	Control	2.0±0.4	7.9±1.1	4.9±0.5		1.9±0.3	6.4±1.0	1.5±1.4	4.7±0.5	
Pradeep et al. (2015) ^{1*}	Test	4.1±0.5	7.1±0.7	4.6±0.6	6	0.4±0.2	3.0±0.4	4.2±0.2	2.4±0.3	B
	Control	3.9±0.6	7.1±0.7	4.6±0.7		2.4±0.3	5.7±0.9	1.4±0.2	4.1±0.7	
Surve et al. (2015) ^{1*}	Test (SMV)	3.3±0.6	5.8±0.8	2.5±0.9	6	1.1±0.6	3.3±0.6	1.1±1.6	1.8±0.8	A
	Test (ATV)	3.5±0.6	5.7±0.7	3.0±0.8		1.2±0.6	3.4±0.8	0.9±1.3	2.4±0.7	
	Control	3.3±0.7	5.5±0.7	2.8±0.9		1.1±0.8	3.2±0.6	0.7±1.3	2.7±0.8	
	Test	2.7±0.3	7.0±1.4	4.7±0.5		1.2±0.3	3.8±0.8	4.1±1.6	3.2±0.4	
Kumari et al. (2016a) ^{1*}	Control	2.7±0.3	7.0±1.4	4.7±0.5	9	1.6±0.2	6.1±1.1	1.9±1.3	4.6±0.5	A B (PD, CAL, RDD)
	Test	2.8±0.2	8.2±1.1	4.8±0.5		1.3±0.4	4.4±1.0	3.8±1.4	3.3±0.5	
Kumari et al. (2016b) ^{1*}	Control	2.7±0.2	8.0±1.2	4.8±0.5	9	1.7±0.4	6.5±1.3	1.4±1.5	4.7±0.5	A, B
	Test	2.0±0.6	6.6±1.4	5.5±0.8		0.4±0.5	3.0±0.7	4.3±1.1	3.5±0.7	
Pradeep et al. (2016b) ^{1*}	Control	1.9±0.6	6.8±1.2	5.2±0.4	9	0.8±0.7	5.3±0.6	1.5±1.1	5.0±0.4	A B (PD, CAL, RDD)
	Test (ATV)	2.9±0.4	7.3±0.7	6.0±0.2		1.0±0.4	5.0±1.0	2.3±0.5	3.7±0.1	
Pradeep et al. (2016c) ^{1*}	Test (RSV)	2.9±0.3	7.4±0.6	6.0±0.4	6	0.8±0.3	4.3±0.8	2.9±0.4	3.1±0.7	A, B (for ATV + RSV)
	Control	2.8±0.4	7.3±0.6	5.9±0.3		1.4±0.6	5.9±0.6	1.4±0.5	5.9±0.5	
	Test (ATV)	2.3±0.6	7.2±1.3	4.1±0.3		0.8±0.3	4.8±0.9	v: 3.0±1.2 h: 2.7±1.2	3.0±0.1	
Garg & Pradeep (2017) ¹	Test (RSV)	2.3±0.6	7.4±1.1	4.2±0.2	6	0.7±0.2	4.1±0.9	v: 3.6±1.2 h: 3.2±1.2	2.9±0.2	A B (PD, CAL, RDD)
	Control	2.3±0.6	7.6±1.1	4.1±0.4		1.2±0.3	6.0±1.1	v: 1.8±1.0 h: 1.9±1.2	3.9±0.3	
	Non-surgical treatment - Systemic administration									
Fajardo et al. (2010) ^{1*}	Test	46±19 [#]	3.5±0.6	-	3	5±6 [#]	1.7±0.2	-	-	A, B
	Control	58±29 [#]	3.4±0.4	-		8±11 [#]	1.9±0.5	-	-	
Fentoglu et al. (2012) ³	Test (III)	91.5 (0.6-100) [#]	2.9 (1.8-3.9)	-	3	15.6 (5.8-32.7) [#]	2.3 (1.8-2.7)	0.4	-	C
	Control (II)	52.2 (3.4-100) [#]	3.1 (1.2-7.1)	-		16.2 (6.3-54.0) [#]	2.3 (1.8-3.8)	0.1	-	
	Control (I)	50.0 (8.4-100) [#]	2.7 (1.1-4.1)	-		45.0 (0.2-100) [#]	2.4 (2.0-3.5)	0.1	-	
Surgical treatment – Local application										
Kinra et al. (2010) ⁴	Test (II)	-	6.7±0.3	7.1±0.2	6	-	1.6±0.2	4.6±0.4	1.5±0.2	B
	Control (I)	-	6.3±0.3	7.1±0.2		-	2.8±0.2	3.2±0.3	3.1±0.2	
Martande et al. (2016) ^{1*}	Test (III)	-	8.1±1.1	5.0±0.3	9	-	4.0±1.0	3.7±1.4	2.5±0.2	B\$
	Control (II)	-	8.2±1.2	5.1±0.3		-	4.5±0.8	3.4±1.1	2.7±0.1	
	Control (I)	-	7.9±1.1	5.0±0.3		-	5.1±0.8	2.5±1.3	4.7±0.3	
Pradeep et al. (2016a) ^{1^A}	Test (III)	-	7.7±1.1	5.9±0.2	9	-	3.0±0.2	v: 4.2±0.7	2.3±0.2	B\$

								h: 4.1±0.5		
	Control (II)	-	7.7±1.1	5.9±0.1		-	4.0±0.2	v: 3.3±0.5 h: 3.0±0.5	2.7±0.1	
	Control (I)	-	7.3±0.8	6.0±0.2		-	5.2±0.9	v: 1.8±0.8 h: 1.6±0.5	5.4±0.3	
Pradeep et al. (2016d) ^{1*}	Test (III)	2.9±0.3	7.9±0.3	5.9±0.9	9	0.4±0.1	3.0±0.2	3.9±0.8	2.2±0.4	B\$
	Control (II)	2.9±0.3	7.8±0.4	6.0±0.9		0.4±0.1	3.8±0.4	3.3±0.7	2.8±0.4	
	Control (I)	2.8±0.4	7.9±0.3	5.9±0.5		0.5±0.1	4.8±0.4	2.5±0.8	4.4±0.6	

Bold values indicate significantly different values between test and control group ($p<0.05$) as follows: A, comparisons between groups regarded the post-treatment outcome variable values; B, comparisons between groups regarded the differences between baseline and post-treatment values; C no inter-group comparison.

* CAL values measured only on buccal and lingual surface; ° Studies included in the meta-analysis among studies on non-surgical or surgical treatment; ^ Studies on furcation defects [RDD corresponds to furcation defect height and CAL to vertical (v) / horizontal (h) CAL measurements]; # BoP; \$ Comparison to control group II.

1 mean±SD; 2 median (interquartil range); 3 median (min-max); 4 mean±SEM.

ATV – atorvastatin, BoP – bleeding on probing, CAL – clinical attachment level, PD – probing pocket depth, RDD – radiographic defect depth, RSV – rosuvastatin, SMV – simvastatin.

Table 3. Effect of statins as an adjunct to periodontal treatment on inflammatory and bone-specific parameters.

Study (year)	Intervention	GCF ¹ / periodontal tissue ² / blood ³ sample		
Non-surgical treatment - Local application				
Rath et al. (2012)		IL-6 ² *		
	SRP + SMV	baseline: 100% IL-6 positive; after 3months: 13% IL-6 positive		
	SRP + placebo	NR		
Surve et al. (2015)		IL-1 α ¹ (pg; after 1 month)*		
	SRP + SMV	330.2 $\pm$ 308.1		
	SRP + ATV	383.2 $\pm$ 281.2		
	SRP	282.7 $\pm$ 260.2		
Non-surgical treatment - Systemic administration				
Fajardo et al. (2010)		bone-specific alkaline phosphatase ³ (U/l)*	cross-linked N-telopeptides of type I collagen ³ (nM)*	
	SRP + ATV	13.3 $\pm$ 5.1	14.3 $\pm$ 6.0	
	SRP + placebo	13.7 $\pm$ 6.9	13.7 $\pm$ 8.4	
Fentoglu et al. (2012)		TNF- α ^{1/3} (pg/ml) ^o	IL-1 β ^{1/3} (pg/ml) ^o	IL-6 ^{1/3} (pg/ml) ^o
	SRP (SHP)	0.6 (0.5-0.6) / 13.6 (3.8-893.1)	2.8 (1.5-22.4) / 2.9 (0.6-40.4)	1.0 (0.7-1.5) / 6.1 (3.5-37.2)
	SRP + diet (HP)	0.7 (0.3-1.1) / 16.2 (3.1-179.6)	3.0 (0.6-33.4) / 6.2 (1.0-19.3)	1.0 (0.8-1.7) / 5.2 (4.0-7.8)
	SRP + ATV (HP)	0.2 (0.1-1.0) / 20.7 (4.9-75.9)	2.4 (1.3-48.5) / 1.7 (0.7-14.3)	0.1 (0.1-0.3) / 6.1 (3.3-10.9)

* mean $\pm$ standard deviation, ^o median (min-max).

ATV – atorvastatin, GCF – gingival crevicular fluid, HP – hyperlipidemic patients, IL – interleukin, NR - not reported, SMV – simvastatin, SHP – systemically healthy patients, SRP - scaling & root planning, TNF – tumor necrosis factor.

Table 1. Characteristics of human trials evaluating statins as adjunct to non-surgical and surgical periodontal treatment in periodontitis patients.

Study (year)	Study design	No. of patients, disease (m/f, age) smoking status Additional info	Inclusion criteria	Loss to follow-up (n) Follow-up period (m)	Intervention (test vs. control)	No. of application sites (S) / patients (P)	Application mode/site	Application frequency Dosis	Application period (days)	Test product Placebo product
Non-surgical treatment - Local application										
Pradeep & Thorat (2010)	RCT (placebo), PG	60, CP (33/31, mean 31) NS -	intrabony defects, moderate (PD 5-6mm or CAL 4-6mm) to deep pockets (PD≥7mm or CAL 6-9mm) & vertical BL≥3mm	0 6	SRP + SMV vs. SRP + placebo	1 S / P	subgingival	1 0.1ml of SMV gel (1.2mg/0.1ml)	1	SMV (1.2mg) in methylcellulose gel NR
Pradeep et al. (2012)	RCT (placebo), PG	72, CP (38/34, range 30-50) NS -	furcation defects (buccal, class II, mandibular 1 st & 2 nd molars), PD≥5mm & horizontal PD≥3mm after SRP	6 6	SRP + SMV vs. SRP + placebo	1 S / P	subgingival – into the furcation defect	1 0.1ml of SMV gel (1.2mg/0.1ml)	1	SMV (1.2mg) in methylcellulose gel NR
Rath et al. (2012)	RCT (placebo), PG	60, CP (33/27, range 25-45) NS -	intrabony defects, PD≥5mm & vertical BL≥3mm	0 6	SRP + SMV vs. SRP + placebo	1 S / P	subgingival	1 0.1ml of SMV gel (1.2mg/0.1ml)	1	SMV (1.2%) in methylcellulose gel NR
Pradeep et al. (2013a)	RCT (placebo), PG	38, CP (20/18, range 30-50) NS well-controlled DMT2	intrabony defects, PD≥5mm or CAL≥4mm & vertical BL≥3mm, ≥20 teeth	3 9	SRP + SMV vs. SRP + placebo	in total 36/34 S in test/control P	subgingival	1 10µl of SMV gel (1.2mg/0.1ml)	1	SMV (1.2%) in methylcellulose gel NR
Pradeep et al. (2013b)	RCT (placebo), PG	67, CP (35/32, range 30-50) NS -	intrabony defects, PD≥5mm or CAL≥4mm & vertical BL≥3mm	7 9	SRP + ATV vs. SRP + placebo	1 S / P	subgingival	1 10µl of ATV gel (1.2mg/0.1ml)	1	ATV (1.2%) in methylcellulose gel NR
Rao et al. (2013)	RCT (placebo), PG	40, CP (40/0, range 30-50) S -	intrabony defects, PD≥5mm or CAL≥4mm & vertical BL≥3mm	5 9	SRP + SMV vs. SRP + placebo	in total 43/43 S in test/control P	subgingival	1 10µl of SMV gel (1.2mg/0.1ml)	1	SMV (1.2%) in methylcellulose gel NR
Pradeep et al. (2015)	RCT (placebo), PG	70, CP (33/37, range 25-55) NS -	intrabony defects, moderate pockets (PD 5-6mm or CAL 4-6mm) & vertical BL≥3mm, ≥20 teeth	5 6	SRP + RSV vs. SRP + placebo	1 S / P	subgingival	1 0.1ml of RSV gel (1.2mg/0.1ml)	1	RSV (1.2%) in methylcellulose gel NR
Surve et al. (2015)	(R)CT, PG	45, CP (NR, range 35-55) NS -	PD≥5mm & radiographic evidence of BL, ≥14 teeth	0 6	SRP + SMV vs. SRP + ATV vs. SRP	1 S / P	subgingival	1 NR	1	SMV (1.2%) / ATV (1.2%) in sodium alginate suspension with calcium chloride solution -
Kumari et al. (2016a)	RCT (placebo), PG	71, CP (NR, range 30-50) S -	intrabony defects, PD≥5mm or CAL≥4mm & vertical BL≥3mm	5 9	SRP + ATV vs. SRP + placebo	1 S / P	subgingival	1 10µl of ATV gel (1.2mg/0.1ml)	1	ATV (1.2%) in methylcellulose gel NR

Kumari et al. (2016b)	RCT (placebo), PG	75, CP (38/37, range 40-50) NS well-controlled DMT2	intrabony defects, PD $\geq$ 5mm or CAL $\geq$ 4mm & vertical BL $\geq$ 3mm, $\geq$ 20 teeth	15 9	SRP + ATV vs. SRP + placebo	1 S / P	subgingival	1 10 μ l of ATV gel (1.2mg/0.1ml)	1	ATV (1.2%) in methylcellulose gel NR
Pradeep et al. (2016b)*	RCT (placebo), PG	99, CP (53/51, range 30-50) NS -	intrabony defects, PD $\geq$ 5mm or CAL $\geq$ 4-6mm & vertical BL $\geq$ 3mm, $\geq$ 20 teeth	9 9	SRP + ATV vs. SRP + placebo	1 S / P	subgingival	1 10 μ l of ATV gel (1.2mg/0.1ml)	1	ATV gel (1.2%) NR
Pradeep et al. (2016c)	RCT (placebo), PG	90, CP (45/45, range 25-45) NS -	intrabony defects, PD $\geq$ 5mm or CAL $\geq$ 3mm & vertical BL $\geq$ 3mm	9 9	SRP + ATV vs. SRP + RSV vs. SRP + placebo	1 S / P	subgingival	2 0.1ml of ATV gel (1.2mg/0.1ml) 0.1ml of RSV gel (1.2mg/0.1ml)	180 (at BL & after 6 months)	ATV (1.2%) in methylcellulose gel RSV (1.2%) in methylcellulose gel NR
Garg & Pradeep (2017)	RCT (placebo), PG	90, NR (NR, range 30-50) NS -	mandibular furcation defects class II, PD $\geq$ 5mm & horizontal PD $\geq$ 3mm	0 9	SRP + ATV vs. SRP + RSV vs. SRP + placebo	1 S / P	subgingival	2 0.1ml of ATV gel (1.2mg/0.1ml) 0.1ml of RSV gel (1.2mg/0.1ml)	180 (at BL & after 6 months)	ATV (1.2%) in methylcellulose gel RSV (1.2%) in methylcellulose gel methylcellulose gel
Non-surgical treatment - Systemic administration										
Fajardo et al. (2010)	RCT (placebo), PG	38, CP (6/32, range 40-60) NS -	PD $\geq$ 3 mm in at least 3 teeth, gingival index of 2 or 3, plaque index of 2 or 3, gingival recession, $\geq$ 15 teeth	0 3	SRP + ATV vs. SRP + placebo	-	Oral	90 20mg/d	90	ATV Trivitamin preparation (thiamin 100mg, pyridoxine 50mg, cyanocobalamin 250mg)
Fentoglu et al. (2012)	CT, PG	80, CP (40/40, range 30-57) NS hyperlipidemic patients	$\geq$ 4 teeth with PD $\geq$ 5mm & CAL $\geq$ 2mm, $\geq$ 18 teeth	0 3	I (systemically healthy): SRP II (hyperlipidemic): SRP + diet III (hyperlipidemic): SRP + ATV	-	Oral	90 10 or 20mg/d	90	ATV -
Surgical treatment - Local application										
Kinra et al (2010)	RCT, SM	15, NR (8/7, NR) NS -	intrabony defects, 2-3-walls	0 6	I: DFDBA II: DFDBA + SMV	2 S / P (1 S / group)	intra-operative	1 10 $^{-8}$ M SMV solution	1	10 $^{-8}$ M SMV dissolved in water -
Martande et al. (2016)	RCT, PG	96, CP (48/48, mean 38) NS -	intrabony defects, 3-walls & depth $\geq$ 3mm	6 9	I: OFD II: OFD + PRF III: OFD + PRF + ATV	1 S / P	intra-operative	1 10 μ l of 1.2% ATV	1	ATV (1.2%) in methylcellulose gel -
Pradeep et al. (2016a)	RCT (placebo), PG	110, CP (60/50, range 25-55) NS -	furcation defects (buccal, class II, mandibular 1 st & 2 nd molars), PD $\geq$ 5mm & horizontal PD $\geq$ 3mm after SRP	5 9	I: OFD + placebo II: OFD + PRF + HA III: OFD + PRF + HA + RSV	1 S / P	intra-operative	1 0.1ml of RSV gel (1.2mg/0.1ml)	1	RSV (1.2mg) in methylcellulose gel NR
Pradeep et al. (2016d)	RCT, PG	90, CP (NR, range 25-45) NS -	intrabony defects (mandibular molar), 2-3 walls & PD $\geq$ 5mm, CAL $\geq$ 3mm, vertical BL $\geq$ 3mm	0 9	I: OFD II: OFD + PRF III: OFD + PRF + RSV	1 S / P	intra-operative	1 RSV gel coated on the PRF membrane	1	RSV (1.2%) in methylcellulose gel -

* Only control groups and test groups on statin application are listed.

ATV – atorvastatin, BL – bone loss, CAL - clinical attachment level, CP - chronic periodontitis, DFDBA – demineralized freeze-dried bone allograft, DMT2 – diabetes mellitus type 2, HA – hydroxyapatite, NR - not reported, NS - non-smokers, OFD – open-flap debridement, PD - probing pocket depth, PG – parallel group design,

PRF – platelet-rich fibrin, RCT - randomized controlled clinical trial, (R)CT - according to authors randomized, but randomisation process not defined or of high risk of bias, RSV – rosuvastatin, SM – split-mouth design, SMV – simvastatin, S – smokers, SRP - scaling & root planing.

Table 2. Clinical outcomes of human trials evaluating statins as adjunct to non-surgical and surgical periodontal treatment in periodontitis patients.

Study (year)	Group	Baseline			Follow-up period (m)	Outcome				Comparison based on
		mSBI	PD (mm)	RDD (mm)		mSBI	PD (mm)	CAL gain (mm)	RDD (mm)	
Non-surgical treatment - Local application										
Pradeep & Thorat (2010) ^{1o}	Test	3.1±0.7	7.4±1.6	4.4±1.1	6	0.8±0.7	3.2±1.6	4.4±1.9	2.9±1.1	B
	Control	2.9±0.8	6.9±1.6	4.4±1.2		2.4±1.2	5.7±2.1	1.6±2.0	4.3±1.3	
Pradeep et al. (2012) ^{1^A}	Test	2.8±0.3	7.3±1.5	4.6±1.1	6	0.8±0.2	3.3±0.8	v: 4.6±1.0 h: 4.3±1.2	3.4±1.0	B (PD, CAL, RDD)
	Control	2.5±0.4	6.8±1.3	4.3±1.0		1.6±0.4	5.5±1.3	v: 2.5±1.5 h: 2.4±1.3	4.3±0.9	
Rath et al. (2012) ^{1o}	Test	2.7±0.4	6.3±1.7	7.2±1.2	6	0.2±0.4	2.3±0.6	4.7±1.4	6.6±1.3	B
	Control	2.6±0.5	6.6±1.5	7.3±1.1		0.7±0.7	4.5±1.7	2.3±1.1	7.2±1.0	
Pradeep et al. (2013a) ^{1o}	Test	3.0±0.3	8.3±1.0	4.9±0.5	9	1.3±0.2	4.3±1.0	4.0±1.2	3.3±0.6	A B (PD, CAL, RDD)
	Control	2.8±0.4	7.9±1.1	4.9±0.6		2.1±0.3	6.3±0.9	1.1±0.8	4.7±0.6	
Pradeep et al. (2013b) ^{1o}	Test	2.8±0.2	7.8±1.3	4.8±0.5	9	1.1±0.2	4.1±1.0	4.5±0.6	3.1±0.4	A B (PD, CAL, RDD)
	Control	2.7±0.2	7.7±1.1	4.8±0.5		1.6±0.2	6.3±1.1	2.3±0.5	4.7±0.5	
Rao et al. (2013) ^{1o}	Test	2.1±0.4	7.9±0.9	4.8±0.9	9	1.2±0.2	4.0±0.9	3.6±1.1	3.2±0.9	A B (PD, CAL, RDD)
	Control	2.0±0.4	7.9±1.1	4.9±0.5		1.9±0.3	6.4±1.0	1.5±1.4	4.7±0.5	
Pradeep et al. (2015) ^{1o}	Test	4.1±0.5	7.1±0.7	4.6±0.6	6	0.4±0.2	3.0±0.4	4.2±0.2	2.4±0.3	B
	Control	3.9±0.6	7.1±0.7	4.6±0.7		2.4±0.3	5.7±0.9	1.4±0.2	4.1±0.7	
Surve et al. (2015) ^{1o}	Test (SMV)	3.3±0.6	5.8±0.8	2.5±0.9	6	1.1±0.6	3.3±0.6	1.1±1.6	1.8±0.8	A
	Test (ATV)	3.5±0.6	5.7±0.7	3.0±0.8		1.2±0.6	3.4±0.8	0.9±1.3	2.4±0.7	
	Control	3.3±0.7	5.5±0.7	2.8±0.9		1.1±0.8	3.2±0.6	0.7±1.3	2.7±0.8	
Kumari et al. (2016a) ^{1^A}	Test	2.7±0.3	7.0±1.4	4.7±0.5	9	1.2±0.3	3.8±0.8	4.1±1.6	3.2±0.4	A B (PD, CAL, RDD)
	Control	2.7±0.3	7.0±1.4	4.7±0.5		1.6±0.2	6.1±1.1	1.9±1.3	4.6±0.5	
Kumari et al. (2016b) ^{1o}	Test	2.8±0.2	8.2±1.1	4.8±0.5	9	1.3±0.4	4.4±1.0	3.8±1.4	3.3±0.5	A, B
	Control	2.7±0.2	8.0±1.2	4.8±0.5		1.7±0.4	6.5±1.3	1.4±1.5	4.7±0.5	
Pradeep et al. (2016b) ^{1o}	Test	2.0±0.6	6.6±1.4	5.5±0.8	9	0.4±0.5	3.0±0.7	4.3±1.1	3.5±0.7	A B (PD, CAL, RDD)
	Control	1.9±0.6	6.8±1.2	5.2±0.4		0.8±0.7	5.3±0.6	1.5±1.1	5.0±0.4	
Pradeep et al. (2016c) ^{1o}	Test (ATV)	2.9±0.4	7.3±0.7	6.0±0.2	6	1.0±0.4	5.0±1.0	2.3±0.5	3.7±0.1	A, B (for ATV + RSV)
	Test (RSV)	2.9±0.3	7.4±0.6	6.0±0.4		0.8±0.3	4.3±0.8	2.9±0.4	3.1±0.7	
	Control	2.8±0.4	7.3±0.6	5.9±0.3		1.4±0.6	5.9±0.6	1.4±0.5	5.9±0.5	
Garg & Pradeep (2017) ¹	Test (ATV)	2.3±0.6	7.2±1.3	4.1±0.3	6	0.8±0.3	4.8±0.9	v: 3.0±1.2 h: 2.7±1.2	3.0±0.1	A B (PD, CAL, RDD)
	Test (RSV)	2.3±0.6	7.4±1.1	4.2±0.2		0.7±0.2	4.1±0.9	v: 3.6±1.2 h: 3.2±1.2	2.9±0.2	
	Control	2.3±0.6	7.6±1.1	4.1±0.4		1.2±0.3	6.0±1.1	v: 1.8±1.0 h: 1.9±1.2	3.9±0.3	
Non-surgical treatment - Systemic administration										
Fajardo et al. (2010) ^{1*}	Test	46±19 [#]	3.5±0.6	-	3	5±6 [#]	1.7±0.2	-	-	A, B
	Control	58±29 [#]	3.4±0.4	-		8±11 [#]	1.9±0.5	-	-	
Fentoglu et al. (2012) ³	Test (III)	91.5 (0.6-100) [#]	2.9 (1.8-3.9)	-	3	15.6 (5.8-32.7) [#]	2.3 (1.8-2.7)	0.4	-	C
	Control (II)	52.2 (3.4-100) [#]	3.1 (1.2-7.1)	-		16.2 (6.3-54.0) [#]	2.3 (1.8-3.8)	0.1	-	
	Control (I)	50.0 (8.4-100) [#]	2.7 (1.1-4.1)	-		45.0 (0.2-100) [#]	2.4 (2.0-3.5)	0.1	-	
Surgical treatment – Local application										
Kinra et al. (2010) ⁴	Test (II)	-	6.7±0.3	7.1±0.2	6	-	1.6±0.2	4.6±0.4	1.5±0.2	B
	Control (I)	-	6.3±0.3	7.1±0.2		-	2.8±0.2	3.2±0.3	3.1±0.2	
Martande et al. (2016) ^{1o}	Test (III)	-	8.1±1.1	5.0±0.3	9	-	4.0±1.0	3.7±1.4	2.5±0.2	B\$
	Control (II)	-	8.2±1.2	5.1±0.3		-	4.5±0.8	3.4±1.1	2.7±0.1	
	Control (I)	-	7.9±1.1	5.0±0.3		-	5.1±0.8	2.5±1.3	4.7±0.3	
Pradeep et al. (2016a) ^{1^A}	Test (III)	-	7.7±1.1	5.9±0.2	9	-	3.0±0.2	v: 4.2±0.7 h: 4.1±0.5	2.3±0.2	B\$
	Control (II)	-	7.7±1.1	5.9±0.1		-	4.0±0.2	v: 3.3±0.5 h: 3.0±0.5	2.7±0.1	

	Control (I)	-	7.3±0.8	6.0±0.2		-	5.2±0.9	v: 1.8±0.8 h: 1.6±0.5	5.4±0.3	
Pradeep et al. (2016d) ^{1*}	Test (III)	2.9±0.3	7.9±0.3	5.9±0.9	9	0.4±0.1	3.0±0.2	3.9±0.8	2.2±0.4	B\$
	Control (II)	2.9±0.3	7.8±0.4	6.0±0.9		0.4±0.1	3.8±0.4	3.3±0.7	2.8±0.4	
	Control (I)	2.8±0.4	7.9±0.3	5.9±0.5		0.5±0.1	4.8±0.4	2.5±0.8	4.4±0.6	

Bold values indicate significantly different values between test and control group ($p<0.05$) as follows: A, comparisons between groups regarded the post-treatment outcome variable values; B, comparisons between groups regarded the differences between baseline and post-treatment values; C no inter-group comparison.

* CAL values measured only on buccal and lingual surface; ° Studies included in the meta-analysis among studies on non-surgical or surgical treatment; ^ Studies on furcation defects [RDD corresponds to furcation defect height and CAL to vertical (v) / horizontal (h) CAL measurements]; # BoP; \$ Comparison to control group II.

1 mean±SD; 2 median (interquartile range); 3 median (min-max); 4 mean±SEM.

ATV – atorvastatin, BoP - bleeding on probing, CAL - clinical attachment level, PD - probing pocket depth, RDD – radiographic defect depth, RSV – rosuvastatin, SMV – simvastatin.

Table 3. Effect of statins as an adjunct to periodontal treatment on inflammatory and bone-specific parameters.

Study (year)	Intervention	GCF ¹ / periodontal tissue ² / blood ³ sample		
Non-surgical treatment - Local application				
Rath et al. (2012)		IL-6 ² *		
	SRP + SMV	baseline: 100% IL-6 positive; after 3months: 13% IL-6 positive		
	SRP + placebo	NR		
Surve et al. (2015)		IL-1 α ¹ (pg; after 1 month)*		
	SRP + SMV	330.2±308.1		
	SRP + ATV	383.2±281.2		
	SRP	282.7±260.2		
Non-surgical treatment - Systemic administration				
Fajardo et al. (2010)		bone-specific alkaline phosphatase ³ (U/l)*	cross-linked N-telopeptides of type I collagen ³ (nM)*	
	SRP + ATV	13.3±5.1	14.3±6.0	
	SRP + placebo	13.7±6.9	13.7±8.4	
Fentoglu et al. (2012)		TNF- α ^{1/3} (pg/ml) ^o	IL-1 β ^{1/3} (pg/ml) ^o	IL-6 ^{1/3} (pg/ml) ^o
	SRP (SHP)	0.6 (0.5-0.6) / 13.6 (3.8-893.1)	2.8 (1.5-22.4) / 2.9 (0.6-40.4)	1.0 (0.7-1.5) / 6.1 (3.5-37.2)
	SRP + diet (HP)	0.7 (0.3-1.1) / 16.2 (3.1-179.6)	3.0 (0.6-33.4) / 6.2 (1.0-19.3)	1.0 (0.8-1.7) / 5.2 (4.0-7.8)
	SRP + ATV (HP)	0.2 (0.1-1.0) / 20.7 (4.9-75.9)	2.4 (1.3-48.5) / 1.7 (0.7-14.3)	0.1 (0.1-0.3) / 6.1 (3.3-10.9)

* mean $\pm$ standard deviation, ^o median (min-max).

ATV – atorvastatin, GCF – gingival crevicular fluid, HP – hyperlipidemic patients, IL – interleukin, NR - not reported, SMV – simvastatin, SHP – systemically healthy patients, SRP - scaling & root planning, TNF – tumor necrosis factor.