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Review Article

The Effect of Statins on Orthodontic Tooth Movements: A Meta-analysis of Animal Studies

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Abstract

Background: Statins are effective therapeutic agents for the treatment of cardiovascular diseases. Their favorable effects on various aspects of oral health including promising effects on bone metabolism and pleiotropic impacts such as anti-inflammatory properties made these drugs a current area of interest in the field of orthodontics. Therefore, the aim of this study was to evaluate the effects of statins on orthodontic tooth movement (OTM) in animals undergoing orthodontic treatments.

Methods: Several databases were comprehensively searched for studies measuring the effects of statins on the OTM up to January 2020, including MEDLINE, ISI Web of Science, EMBASE, Scopus, and Cochrane. Animal studies evaluating the effects of statins on tooth movements in animals undergoing orthodontic treatments were selected based on the PICO model .Study selection, data extraction, risk of bias, and study quality assessment were independently performed by two reviewers. Finally, the data were analyzed using random-effects meta-analysis and the mean difference (MD) was used for comparing the outcome measures.

Results: Three randomized trials were finally included in this meta-analysis. According to the Systematic Review Centre for Laboratory animal Experimentation Tool, all the included studies had at least one domain at a high risk of bias. The amount of the OTM was insignificantly lower in the statin group (MD = 0.134 mm, %95 confidence interval = -0.020-0.288, $P > 0.05$).

Conclusions: Due to the low quality and methodological inconsistencies among the included studies, conclusive confirmation regarding the effect of statins on the OTM remains debatable.

Trail Registration: The protocol of this study was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) with the ID # CRD42020164155.

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Background

Nowadays, the prevalence of obesity-related diseases such as hyperlipidemia has increased, especially in adults and causes atherosclerosis and other coronary diseases. Lipid-lowering medications such as the statin family of drugs are mostly used by these patients. Clinical trials have shown that statins are well-tolerated in adult and younger populations (1-3).

The statin family of drugs is a safe therapeutic agent for the treatment of arteriosclerotic cardiovascular disease. They act as potential inhibitors of 3-hydroxy-3-methylglutaryl reductase A (HMG-CoA), which is a rate-limiting enzyme in the mevalonate pathway of cholesterol biosynthesis, thus preventing the synthesis of cholesterol in the liver and reducing the levels of blood cholesterol and triglycerides (4). In addition to their cholesterol-lowering effects, it is reported that statins have several promising effects on human health, including pleiotropic effects, improvement of endothelial function, and anti-inflammatory, antioxidant, and immunomodulatory effects (5-13). It has been clarified that statins affect bone metabolism in different ways. They stimulate the osteoblastic differentiation of bone marrow stem cells through the increased gene expression of bone morphogenic protein-2 and angiogenesis. Statins may also stimulate bone formation by preventing osteoblastic apoptosis (14-18). Furthermore, statins inhibit bone resorption through suppressing osteoclastogenesis (19,20). Thus, they could influence orthodontic tooth movements (OTM) and orthodontic relapse in adult patients by their stimulatory effects on bone formation and pleiotropic effects such as anti-inflammatory and immunomodulatory ones (21). Factors affecting the remodeling process will influence OTM (22). Pharmacological factors could potentially affect tooth movements either for reducing (when anchorage strengthening is desirable) or increasing the movement (23-26). Various experimental trials evaluated the effects

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of pharmacologic factors on the periodontal responses of the OTM. Various animal studies have proved the stimulatory effects of statins on bone formation during its use by different carriers (9,15,27-35). Statins are one of the most commonly prescribed therapeutic agents for the prevention of cardiovascular diseases, thus their plausible effect of arresting tooth movements in adult patients could justify their relevance in orthodontic practice. Considering these facts, the present study aimed to systematically review the efficacy of statin delivery in orthodontic movements.

Materials and Methods
Protocol
This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines (36). The protocol of this study was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) with the ID # CRD42020164155.

Focus Question
The present systematic review and meta-analysis sought to assess the null hypothesis that "there would be no difference in the amount of the OTM by the administration of statins". The focused question according to the PICO format (i.e., Population, Intervention, Control group, and Outcome) was "*whether there is a significant decrease in the OTM of statin receivers compared to the control group in animal models*". Population (P) indicated animals who underwent orthodontic treatments; Interventions (I) represented orthodontic treatments with statin administration. Finally, control intervention (C)

included orthodontic treatments without adjunct statin administration and outcome measured (O) denoted the amount of the OTM.

Search Strategy
An electronic search was performed until 1st January 2020 to acquire potentially eligible studies with no time or language restrictions in several electronic bibliographic databases such as PubMed, EMBASE, Web of Science, Scopus, and Cochrane. The search strategies of each database are presented in Table 1. The reference part of the retrieved full-text articles (cross-referencing) was also searched for further papers. Non-English translatable papers were included in this study.

Eligibility Criteria
The following selection criteria were applied for this systematic review:
1. *Inclusion Criteria*: Randomized experimental trials and parallel and split-mouth groups were considered in this study. Articles providing data regarding the effects of statins on the OTM were considered eligible in the first analysis.
2. *Exclusion Criteria*: (*a*) in vitro histological studies, (*b*) review articles, case reports, and letters to editors.

Study Selection
The titles and abstracts of the searched studies were independently screened by two authors. Studies were excluded if they were either irrelevant to the current study and duplicates and/or failed to address the focused question. The controversies were resolved through discussion. Publications were included for full-text

Table 1. Databases, Applied Search Strategy and Numbers of Retrieved Studies

Database of Published Trials	Applied Search Strategy	Hits
MEDLINE searched via PubMed on 1 January 2020 via www.ncbi.nlm.nih.gov/sites	((orthodontic[All Fields] OR ("tooth movement techniques"[MeSH Terms] OR ("tooth"[All Fields] AND "movement"[All Fields] AND "techniques"[All Fields]) OR "tooth movement techniques"[All Fields] OR ("tooth"[All Fields] AND "movement"[All Fields]) OR "tooth movement"[All Fields])) AND ((("simvastatin"[MeSH Terms] OR "fluvastatin"[MeSH Terms]) OR ("hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR "hydroxymethylglutaryl-coa reductase inhibitors"[MeSH Terms] OR ("hydroxymethylglutaryl-coa"[All Fields] AND "reductase"[All Fields] AND "inhibitors"[All Fields]) OR "hydroxymethylglutaryl-coa reductase inhibitors"[All Fields] OR "statin"[All Fields])) OR Atorvastatin[All Fields])	10
ISI Web of Science, and Core Collection were searched via the web of knowledge on 1 January 2020 via apps. webofknowledge.com	ALL FIELDS: (*simvastatin*) OR ALL FIELDS: (*Atorvastatin*) OR ALL FIELDS: (*fluvastatin*) OR ALL FIELDS: (*statin*)) AND (ALL FIELDS: (*tooth movement*) OR ALL FIELDS: (*orthodontic*))	12
EMBASE searched via Embase on 1 January 2020 via www.embase.com	(((orthodontic) OR tooth movement)) AND ((((simvastatin) OR fluvastatin) OR hydroximethylgluthuaryl coenzyme a reductase inhibitor) OR atorvastatin)	120
Scopus searched via Scopus on 1 January 2020 via https://www.scopus.com	TITLE-ABS-KEY ((*simvastatin*) OR (*Atorvastatin*) OR (*fluvastatin*) OR (*statin*)) AND ((*tooth* AND *movement*) OR (*orthodontic*)) (*dent*)	99
Cochrane Central Register of Controlled Trials searched via the Cochrane Library searched on 1 January 2020 via www. thecochranelibrary.com	((*simvastatin*) OR (*Atorvastatin*) OR (*fluvastatin*) OR (*statin*)) AND ((*tooth movement*) OR (*orthodontic*))	3
Total		244

evaluations if they met the inclusion criteria in the first analysis or if insufficient information was provided in the title and abstract so that to make a decision on. A third review author was consulted where the resolution was impossible. The review authors were not blinded to the author(s), institution, or the site of the publication of all studies.

All eligible studies then underwent validity assessments and data extraction. Data were independently extracted by at least two review authors. Any disagreement was discussed and a third review author consulted where necessary. In papers that included inadequate or limited information about the OTM in the statin receivers, the corresponding authors were contacted via an e-mail for making clarification and a request for the missing data, and a reminder e-mail was sent twice after. Finally, several data were extracted from the eligible studies using extraction forms by one of the reviewers, including study design, sample size, animal spices, type and dosage of statin, method of statin administration, active tooth movement period, time of final analysis, the outcome measurement method, and the measured outcome (the amount of the OTM).

Risk of Bias in Individual Studies

The assessment of the risk of bias and the study quality of the included trials were undertaken as part of the data extraction process by at least two review authors independently and in duplicate. The risk of bias assessment was conducted using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) Tool (37). It is a two-part tool addressing ten specific domains (i.e., random sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and/or investigators, random outcome assessment, blinding of assessors, incomplete outcome data, selective outcome reporting, and 'other biases'). Each domain includes one specific entry in a 'Risk of bias' table. Within each entry, the first part of the tool involves reporting the events occurring in the study. The second part of the tool includes assigning a judgment relating to the risk of bias for that entry. Consequently, it was judged in terms of having a low, unclear, or high risk of bias. "Yes" and "No" judgments indicate a low and high risk of bias, respectively. The judgment will be "unclear" if insufficient details have been reported to assess the risk of bias properly. Any differences regarding the reviewers' judgments were resolved by a third review author.

Quality of Evidence

The quality of evidence was evaluated using the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) tool (38). It addresses ten specific domains including peer-reviewed publication, control of temperature, random allocation to treatment or control,

blinded induction of ischemia, blinded assessment of outcomes, and use of anesthetic without significant intrinsic neuroprotective activity. Other domains were animal model (i.e., aged, diabetic, or hypertensive), sample size calculation, compliance with animal welfare regulations, and statement of the potential conflict of interests. Each domain included one specific entry in a study quality table and assigned a "Yes" or "No" judgment for that entry. Then, each study was given a quality score out of a possible total of 10 points.

Summary Measures and Synthesis of Results

The amount of the OTM was used as the outcome measure of this meta-analysis. The mean difference (MD) with 95% confidence intervals was calculated for the continuous data (the OTM amount in millimeter). Statistical analyses were conducted using Comprehensive Meta-analysis, version 2.2. A P value less than 0.05 was considered statistically significant. The random-effect method for analysis was used to compare the outcome measure due to high heterogeneity.

The subgroup analysis for different amounts of the OTM in different methods of statin administration, different types, and dosage of statins was not performed due to the lack of sufficient similar studies.

Results

Study Selection

In total, 244 studies were found after a comprehensive search of five online databases. After removing duplicates, the titles and abstracts of the remaining 240 studies were independently screened by two authors. Two hundred and thirty-four studies were excluded based on the eligibility criteria and the PICO model in this step. Moreover, one study was a review article and thus was excluded from the investigation. The full texts of the remaining 5 studies were assessed by the same two authors.

Consequently, five studies including a total number of 108 animals were included in the qualitative assessment (39-43), and three trials were considered in the quantitative analysis (40,41,43) (Figure 1).

Study Characteristics

All the five included studies were randomized experimental trials (39-43), of which two cases had a split-mouth design (39,40). The other three trials used a parallel-arm design (41-43).

Study characteristics varied in most of the included studies. Variations in animal models, animal age, type and dosage of the administered statins, the method, frequency and duration of statin administration, duration and force of orthodontic treatments, and methods of outcome assessments resulted in heterogeneity among the studies.

Different subjects such as rats, dogs, and rabbits were evaluated in studies. Among the included animal studies, three trials were performed on rat models (40,41,43), one
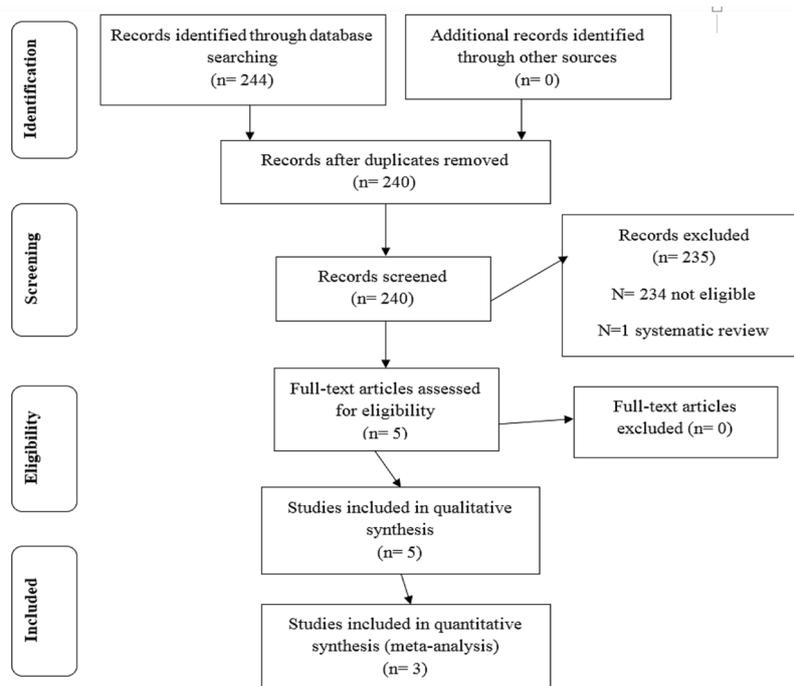
Figure 1. PRISMA Study Flow Diagram. *Note.* PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

study was conducted on rabbits 39, and one study used dogs as animal models (42). The number of applied rats in trials ranged from 24 to 36. Rats aged 6 and 8-10 weeks were used in 2 studies (40,41). The mean age of the rats was not reported in one study (43). The age of rabbits was 16 weeks in one study and that of the applied dogs in another study was 10-12 months (39,42) (Table 2).

Regarding the type of the Stains, three trials administered Simvastatin (SMV) (39,41,42) and the other two used atorvastatin (ATV) (40,43).

The studies used various modes of statin administration, including submucosal and intraligamentous injection (39), systemic (gavage) (40,43), intraperitoneal injection (41), and local injections (42).

The dosage of the applied SMV in animal model studies was 0.5 mg/0.48 mL, 0.6 mg/mL, and 0.5 mg/kg/mL

(39,41,42). Two studies performed their experiments by oral administration of ATV (15 mg/kg) and 5 mg/kg ATV in carboxymethyl cellulose (CMC) (40,43). Two studies administered the statin drug locally near the teeth under investigation (39,42). Overall, the exposure duration of the subjects to statin drugs in animal studies ranged between 14 and 37 days.

The control groups in all studies underwent orthodontic treatments and were administered to non-statins such as phosphate-buffered saline, CMC, and normal saline (40-42) (Table 3).

Method of Orthodontic Force Application
The method of orthodontic force application was similar in three trials and they used Nickel-Titanium closed coil springs stretched between maxillary first molar and

Table 2. General Characteristics of the Included Studies

Author	Study Design	Study Subjects/Total Number	Mean Age	Study Groups (Number of Animals) Case/Control	Primary Methods of Evaluation
AlSwafeeri et al (39)	Experimental (split-mouth design)	10 male New Zealand Rabbits	16 week	10/10	Impressions, casts, the 3-dimensional scanner and interproximal linear distance measurement tool (View box software), and H&E staining.
Dolci et al (40)	Experimental (split-mouth design)	24 Male Wistar Rats	6 week	12/12	A 100 mm calibrated ruler, impressions, stone casts, and photographs; TRAP and H&E staining.
Esnaashari Esfahani et al (41)	Experimental	32 Male Wistar Rats	8-10 weeks	16/16	Histology and interproximal measurement tools
Mirhashemi et al (43)	Experimental	36 Male Sprague-Dawley Rats	NM	12/12	Histology and interproximal distance measurement tools
Feizbakhsh et al (42)	Experimental	6 Male dogs	10-12 month	2/2	A digital caliper

Note. H&E, *Hematoxylin and eosin*; TRAP, tartrate-resistant acid phosphatase; NM, Not mentioned

Table 3. Characteristics of Statin Administration in the Included Studies

Author	Case Group	Control Group	Mode of Statin Administration	Frequency of Administration	Duration of Administration
AlSwafeeri et al (39)	Simvastatin 0/5 mg/480 µL solution (Pluronic F127 as carrier)	Pluronic control vehicle solution	Two local routes: 1) 300 µL submucosal close to mesial surface of mandibular first premolar 2) 180 µL intraligamentous at mesial periodontal space of mandibular first premolar	Weekly	On 0, 7, and 14 days
Dolci et al (40)	ATV15 mg/ kg	0/1 mL phosphate buffered saline solution	Gavage	Daily	14 days
Esnaashari et al (41)	Simvastatin 2.5 mg/ kg (0.06 mg/mL solution)	Normal saline	Intraperitoneal injection	Daily	17 days
Mirhashemi et al[43]	ATV 5 mg/ kg in CMC	No medication	Gavage	Daily	21 days
Feizbakhsh et al[42]	Simvastatin 0/5 mg/kg/ mL solution	Phosphate buffered saline solution	Local injection	twice	First administration: After one week of the orthodontic intervention. Second administration: After 37 days of the orthodontic intervention

Note. CMC, Carboxymethyl cellulose.

Table 4. Characteristics of Orthodontic Force in the Included Studies

Author	Orthodontic Appliance	Force	Site of OTM	Results	P Value
AlSwafeeri et al (39)	13 mm Nickle-Titanium closed coil spring	100 cN	Between the mandibular first premolars and incisors bilaterally	SMV administration could minimize bone resorption associated with the OTM and the number of osteoclasts.	<0.05
Dolci et al (40)	Super elastic Nickle-Titanium closed coil spring	50 cN	Between the maxillary right first molar and incisors (OTM); Maxillary left first molar and incisors (without OTM/control)	ATV can significantly promote osteoclast inhibition and reduce OTM in the first week. ATV did not affect bone turnover and endochondral ossification.	<0.05
Esnaashari Esfahani et al (41)	Nickle-Titanium closed coil spring	50 cN	Maxillary central incisor and maxillary first molar	The experimental group showed a significant decrease in tooth movements, a decrease in root resorption and the number of root resorption lacunae, and the mineral appositional rate.	<0.05
Mirhashemi et al (43)	6 mm Nickle-Titanium closed coil spring	60 cN	Maxillary left first molars and central incisors	The OTM reduction following the administration of ATV was statistically significant although no significant difference was observed in the histologic variables among the three groups.	<0.05
Feizbakhsh et al (42)	Nickle-Titanium closed coil spring	200 cN	Maxillary and mandibular canines (anchorage unit) and second premolars (movement unit)	Although tooth movement was less in the experimental group, it was not statistically significant compared to the control group.	>0.05

Note. OTM, Orthodontic tooth movement; SMV, simvastatin; ATV, Atorvastatin.

maxillary incisor (40,41,43). In one trial, animals received an orthodontic appliance consisting of nickel-titanium closed coil spring between the mandibular first premolar and mandibular incisor (39). One study used the maxillary and mandibular canines (anchorage unit) and second premolars (movement unit) to place the ligation wires (42). The applied forces ranged between 50 cN and 200 cN (Table 4).

Duration of Orthodontic Tooth Movements, Time, and Method of Outcome Assessments

These parameters also varied between the included trials in this review. The duration of the OTM ranged between 7

and 21 days. The time and method of outcome assessments also varied between the trials. The amount of the OTM was reported in micrometer in one study (40), thus this amount was reported in millimeter in our analysis (Table 5).

Risk of Bias Within Studies

A summary of the risk of bias in the included studies is presented in Figure 2. Although this study included five animal trials and 108 animals randomized to the Stains group, each of these trials had at least one domain at a high risk of bias.

Four of the studies did not report the method of sequence generation (selection bias) (40-43). All studies reported
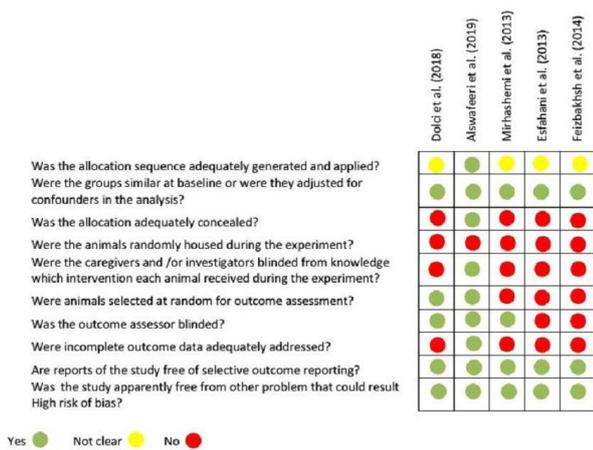
Figure 2. Risk of Bias Summary: Authors' Judgments About Each Risk of the Bias Item for Each Study.

similar groups at baseline (selection bias) (39-43). In terms of assessing allocation concealment, only one trial clearly indicated an adequate means of allocation concealment (39). Conversely, no study described random housing (performance bias) (39-43). Only three studies announced about the blinding of caregivers, outcome assessors, or investigators (performance and detection bias) (39,40,43). Two studies reported random outcome assessment (detection bias) (39,40). Only one study adequately addressed incomplete outcome (attrition bias) (39). Finally, none of the trials had selective reporting bias.

The quality assessment of the included studies is presented in Table 6.

Results of Individual Studies and Result Synthesis

The five included studies are inconsistent in terms of their methods and the frequency of statin administration, and the type and dosage of statins. In addition, different animal models were used and different final assessment times existed between the studies. However, four studies were consistent in their methodologies regarding the measurement and comparison of the amount of the OTM between the intervention (statin receivers) and control groups (39-41,43). The heterogeneity decreased from 90.65 to 66.37 when one of these four studies was excluded from meta-analysis (39) (Figure 3), and a meta-analysis of three studies was performed for differences in the amount of OTM (40,42,43).

Data were available comparing the outcomes at the end of the OTM. A random-effect model was performed due to differences in terms of methodologies (intervention) and the obvious heterogeneity of the data. The intervention group had a statistically insignificant lower amount of tooth movements compared to the control group ($P = 0.087$, MD = 0.134 (-0.020 – 0.288), degree of freedom (df) = 2, I^2= 66.37, Figure 4). This results from analyzing 92 participants in three studies.

Discussion

The aim of this study was to systematically review and

Table 5. Characteristics of Tooth Displacement in the Included Studies

Author	Duration of Tooth Movement	Teeth Measured for Displacement	Magnitude of OTM in the Final Time Point Mean ± SD (mm)		Tooth Movement Evaluation	P Value
			Control Groups	Experimental (Statin) Group		
AlSwafeeri et al (39)	21	The linear distance between the first plane drawn on the distal contact area of the distal surface of the mandibular first premolar and a second plane drawn on the mesial contact area of the mesial surface of the mandibular second premolar	1.77±0.15	1.04±0.38	Impressions recorded on days 7, 14, and 21	<0.05
Dolci et al (40)	21	Between the distal surface of the first molar and the mesial surface of the second molar at 3 points on each cast were measured on 7, 14, and 21 days	0.48±0.06	0.44±0.06	Impressions recorded on days 7, 14, and 21	<0.05
Esnaashari Esfahani, et al (41)	17	Maxillary central incisor and maxillary first molar	0.89±0.56	0.59±0.33	Distance between the incisor and maxillary molar was recorded using a digital caliper	<0.05
Mirhashemi et al (43)	21	Measurements were performed twice (for binding purposes) between the maxillary left first molar and the second molar	0.58±0.22	0.37±0.16	Interproximal distance between the left upper first and second molars was measured twice by filler gauge before removing the appliance	<0.05
Feizbakhsh et al (42)	7	Between canine and second premolar after one week of appliance placement and at the end of the second month	Rate of teeth displacement per month: Maxilla: 1.35±0.07 Mandible: 1.15±0.04	Rate of teeth displacement per month Maxilla: 1.21±0.2 Mandible: 1.03±0.15	Digital caliper measurement on day 1 after 1 week of the orthodontic intervention and on day 60 when animals were sacrificed	> 0.05

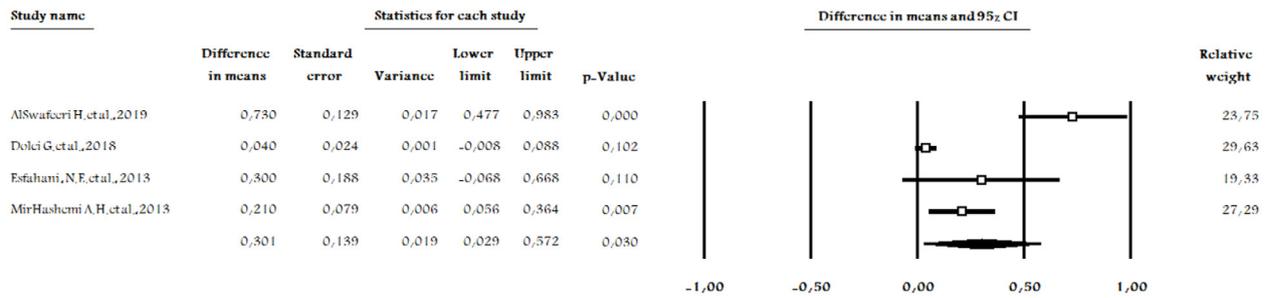*Note.* OTM, Orthodontic tooth movement; SD: Standard deviation.

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	p-Value		Relative weight
AlSwafeeri H,et al.,2019	0,730	0,129	0,017	0,477	0,983	0,000		23,75
Dolci G,et al.,2018	0,040	0,024	0,001	-0,008	0,088	0,102		29,63
Esfahani,N,E,et al.,2013	0,300	0,188	0,035	-0,068	0,668	0,110		19,33
MirHashemi A,H,et al.,2013	0,210	0,079	0,006	0,056	0,364	0,007		27,29
	0,301	0,139	0,019	0,029	0,572	0,030		

Figure 3. Forest Plot of Four Studies, Comparing the Effects of Statins vs. Control on Orthodontic .

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	p-Value		Relative weight
Dolci G,et al.,2018	0,040	0,024	0,001	-0,008	0,088	0,102		51,55
Esfahani,N,E,et al.,2013	0,300	0,188	0,035	-0,068	0,668	0,110		13,26
MirHashemi A,H,et al.,2013	0,210	0,079	0,006	0,056	0,364	0,007		35,20
	0,134	0,079	0,006	-0,020	0,288	0,087		
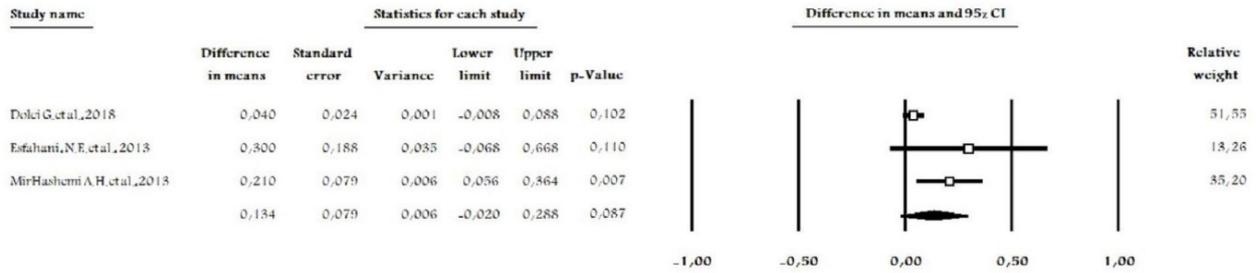
Figure 4. Forest Plot of Three Studies, Comparing the Effects of Statins vs. Control on Orthodontic Tooth Movements.

Table 6. Quality Assessment of the Included Studies (CAMARADES Checklist)

	Dolci et al	Alswafeeri et al	Mirhashemi et al	Esnaashari Esfahani et al	Feizbakhsh et al
Publication in peer-reviewed journals	Y	Y	Y	Y	Y
Statement of control of temperature	Y	N	Y	N	N
Randomization of treatment or control	Y	Y	Y	Y	Y
Allocation concealment	N	Y	N	N	N
Blinded assessment of the outcome	Y	Y	Y	N	N
Avoidance of anesthetics with marked intrinsic properties	N	N	N	N	N
Use of animals with hypertension or diabetes	N	N	N	N	N
Sample size calculations	Y	Y	N	N	N
Statement of compliance with regulatory requirements	Y	Y	Y	N	N
Statement regarding the possible conflict of interest	N	N	N	N	N
Total (on 10)	6	6	5	2	2

Note. CAMARADES: Collaborative approach to meta-analysis and review of animal data from experimental studies.

evaluate whether statins decrease the OTM in animals undergoing orthodontic treatments. The literature search was comprehensive and included several databases and a hand search in the reference lists of relevant articles.

Initial evidence from four of the included studies with a high risk of bias suggested a reduction in the OTM by statin administration (39-41,43). This effect could be explained by the role of Statins in stimulating alveolar bone formation (35,44-46). The delivery of statins during OTM inhibits bone resorption through the inhibition of osteoclast cells and increases in osteoblast differentiation (19,47,48). Moreover, statins exhibit anti-inflammatory properties by inhibiting the production of certain pro-inflammatory cytokines such as IL-6 and IL-8 which are responsible for the biological reaction of periodontal

tissues during OTM (49,50).

Only one study reported that OTM did not decrease following statins administration (42). This finding may be due to the frequency of statin administration, which was only twice. The number of evaluated samples in this study was also less than that of other studies. This lower sample size may result in insignificant findings.

The overall effect of statin (i.e., the type of drugs as HMGA-CoA inhibitors) on OTM magnitude was also quantitatively analyzed in this study. It should be noted that only three trials were evaluated in this meta-analysis due to heterogeneity among the included studies and their limited number, and sub-group analysis could not be undertaken in this study. The main finding of this meta-analysis is that, on average, statins do not reduce the magnitude of the

OTM. This finding may be due to the limited number of included studies which results in insignificant findings.

Although the results of this study showed no difference between statin and control groups, statins reduced bone resorptive lacunas, number of osteoclasts, and generation of inflammatory interleukins such as IL-6 and IL-8 in most of our included studies and the ones related to periodontology (51,52).

Nowadays, adult patients receiving comprehensive orthodontic treatment compromise a significant number of orthodontic patients. The previously discussed properties of statins could affect OTM in adult patients who are under the treatment with statins due to their cardiovascular diseases.

In recent years, several studies have evaluated the effect of the local and systemic administration of pharmacological agents on the control of OTM (anchorage or relapse) (23-26). Thus, the local administration of the statin type of drugs could have promising effects on anchorage in orthodontic treatments if they could be evaluated in further animal and human studies.

However, reliable conclusions about statins effect on the magnitude of the OTM could not be drawn with the insufficient evidence based on the current literature, and it is important to take caution when extrapolating animal studies to humans.

Limitation of the Study
Although this study was performed carefully following PRISMA guidelines, several limitations remain which deserve further discussion. First, the shortage of high-quality trials is evident. Although a comprehensive literature search was performed, only three studies could be included in this analysis. Future well-designed animal and human studies are needed to obtain a more reliable conclusion. When future animal studies are planned, greater consideration should be given to study design (i.e., sequence generation, allocation concealment, random housing, blinding, and the like) in order to reduce bias. Second, methodological heterogeneity is another limitation. Different types and dosages of statins were administered in each study. ATV and SMV, which were administered in most trials, are both lipophilic ones but have different chemical structures (53) and dosages (ranging between 2.5 mg/kg and 5 mg/kg of SMV, as well as 5 mg/kg and 15 mg/kg of ATV). The comparison of the effect of these two types of statins on OTM could not be performed due to the limited number of studies. Therefore, well-designed trials are needed to compare different types of statins and determine the most appropriate types and dosages of these drugs.

Additionally, different animal models were used in the included animal studies. Bone turnover and structure vary in different species of animals and from humans. Particularly, the bone and the root structure of rabbits are different from those of humans (54-56). In our meta-analysis,

the three included trials were performed on rats. To the best of our knowledge, no human study has so far evaluated the effect of statins on OTM. Only one human study was found regarding the effect of statins on orthodontic relapse (57). Accordingly, further evaluations of Stains should consider their potential side-effects on the turnover of other bones. Only one of the trials in this review reported both the benefits (regarding the amount of tooth movement) and the possible adverse effects (on long bone turn-over) associated with the administration of statins (40).

Conclusions
In general, the results of this meta-analysis showed that the reduction in the amount of OTM after the administration of statins was not statistically significant. Based on the information provided from the animal studies eligible for inclusion in this study, a cautionary perspective should be provided due to the low quality of evidence in this meta-analysis.

Conclusive confirmation regarding the effect of these drugs on OTM in humans is lacking since no human studies were conducted and investigations on animals cannot currently provide plausible explanations for the effects of these drugs.

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