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The effect of Statins on relapse after orthodontic treatment: a systematic review

Running title: Statins and relapse after orthodontic treatment

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Abstract

***Introduction**:*

Statins are effective therapeutic agents for the treatment of cardiovascular diseases. Their favorable effects on various aspects of the oral health including positive effects on bone metabolism and their pleiotropic effects such as anti-inflammatory properties made this group of drugs as a current area of interest in the field of orthodontic relapse. Our review systematically investigates and evaluates the quality of the available evidence regarding the effects of Statins on relapse after orthodontic treatment.

***Materials and Methods**:*

A comprehensive search of MEDLINE, ISI web of science, EMBASE, Scopus, and Cochrane databases for studies measuring the effects of Statins on the amount of relapse after orthodontic treatment up until February 2020 was performed. To assess risk of bias and study quality while in our review SYRCLE and COMARADES tools were used. The protocol of this review was registered via (crd.york.ac.uk/Prospero) with the ID CRD42020170389.

***Results**:*

Seven animal trials were finally included in this review. According to the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) Tool, all of the included studies had at least one domain in high risk of bias. Four studies reported decrease in the orthodontic relapse after statins administration, but 3 studies showed no statistically significant changes.

***Conclusions**:*

Based upon the animal studies and methodological inconsistencies among the included studies, conclusive confirmation regarding the effect of Statins on relapse after orthodontic treatment remains debatable.

Keywords: Statin; Orthodontic relapse; Orthodontic treatment, Systematic review.

Introduction

Currently, 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 Statin family of drugs are generally used by these patients. Clinical trials have revealed that statins are well tolerated in adult and younger populations.[1-3]

The Statin family of drugs is a safe and valuable therapeutic agent for the treatment of arteriosclerotic cardiovascular disease. They are potential inhibitors of 3-hydroxy-3-methyl glutaryl reductase A(HMG-CoA),a rate limiting enzyme involved in mevalonate pathway of cholesterol biosynthesis, so they prevent the synthesis of cholesterol in the liver and decrease the levels of low-densitylipoprotein cholesterol (LDL-C),blood cholesterol and triglycerides.[4] Additionally to their cholesterol lowering properties, it is showed that Statins have several promising effects on human health including pleiotropic effects, improvement of endothelial function, anti-inflammatory effects antioxidant and immune modulatory effects.[5-12] It has been clarified that Statins have anabolic effects on bone metabolism in different ways. They induce osteoblastic differentiation of bone marrow stem cells by increasing the gene expression of bone morphogenic protein-2 (BMP-2) and angiogenesis. Statins may also increase bone formation through inhibiting osteoblast apoptosis.[13-17] Since bone is continuously remodeling, Statins inhibit osteoclastic bone activity during high bone turnover, resulting in the inhibition of bone resorption.[18,19] This effect involve modulation of the receptor activator of nuclear kappa B(RANK),receptor activator of nuclear kappa B ligand (RANKL), and osteoprotegerin (OPG), eventually suppressing osteoclastogenesis.[20,21] Thus, their action in stimulating bone formation and having other pleiotropic effects, such as anti-inflammatory and immunomodulatory could justify their importance in orthodontic tooth movement (OTM) and orthodontic relapse.[22] Since there is a great tendency to relapse after orthodontic tooth movement and in view of the problems of different type of retainers, recent studies have suggested that pharmacologic therapy which inhibits osteoclastic resorption, might be beneficial to control orthodontic relapse.[23-30] Osteoclastic resorption and osteoblastic formation of surrounding alveolar bone are critical elements for relapse, so stimulation of alveolar bone creation or inhibition of bone resorption after orthodontic tooth movement should inhibit the relapse. Considering the bone modulation properties of Statins, their plausible effect of arresting orthodontic relapse could be a concern in orthodontic treatments. Considering these facts, the aim of the present study was to systematically review the efficacy of statin delivery in orthodontic relapse.

Method and Materials

Protocol

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement Guidelines.[31] The protocol of this study was registered on PROSPERO (https://www.crd.york.ac.uk/PROSPERO/) with the ID# CRD42020170389.

Focus question

The aim of the present systematic review was to assess the null hypothesis" that there would be no difference in the amount of orthodontic relapse by administration of statins". The focused question according to the PICO format (i.e. Population, Intervention, Control group and Outcome) was: Is there a significantly decrease in orthodontic relapse of Statin receivers compared to control group in animal models. Population (P): animals who underwent orthodontic treatment; Interventions (I): orthodontic treatment with statin administration; Control intervention (C): Orthodontic treatment without adjunct statin administration; and Outcome measured (O): the amount of orthodontic relapse.

Search strategy

An electronic search was performed until 20stFebruary 2020 to acquire potentially eligible studies, with no time or language restrictions, in the following electronic bibliographic databases: PubMed, EMBASE, Web of Science, Scopus and Cochrane. Search strategies of each database are presented on Table 1. The reference part of the retrieved full text articles (cross-referencing) was also searched for further papers.

Table 1. Databases, applied search strategy and numbers of retrieved studies.

Database of published trials	Search strategy used	Hits
MEDLINE searched via PubMed, viawww.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])) OR ("recurrence"[MeSH Terms] OR "recurrence"[All Fields] OR "relapse"[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 atrovastatin[All Fields])	920
ISI web of science Core Collection was searched via web of knowledge,via apps.webofknowledge.com	(ALL FIELDS: (simvastatin) OR ALL FIELDS: (atrovastatin) OR ALL FIELDS: (fluvastatin) OR ALL FIELDS: (statin)) AND (ALL FIELDS: (relapse) OR ALL FIELDS: (orthodontic) OR ALL FIELDS: (tooth movement))	141
EMBASE searched via Embase, via www.embase.com	((((orthodontic) OR ((tooth movement) OR relapse)) AND ((((simvastatin) OR fluvastatin) OR hydroximethylglutharyl coenzyme a reductase inhibitor) OR atorvastatin)	230
Scopus searched, via https://www.scopus.com	TITLE-ABS-KEY((simvastatin) OR (atrovastatin) OR (fluvastatin) OR (statin)) AND ((tooth AND movement) OR (orthodontic) OR (relapse)) (dent)	19
Cochrane Central Register of Controlled Trials searched via the Cochrane Library Searched via www thecochranelibrary.com	((simvastatin) OR (atrovastatin) OR (fluvastatin) OR (statin)) AND ((tooth movement) OR (orthodontic) OR (relapse))	94
Total		1404

Eligibility criteria

The following selection criteria were applied for this systematic review:

1. Inclusion Criteria: experimental trials, both parallel group and split mouth were considered. Articles providing data considering the effects of statins on orthodontic relapse were considered eligible in the first analysis.
2. Exclusion Criteria: in vitro histological studies, (b) review articles, case reports.

Study Selection

Two authors (Z. A. and F. Sh.) screened the titles and abstracts of the searched studies independently. Studies were excluded if they were not either relevant to the current study, duplicates and/or when the

focused question was not addressed. Full text evaluation of publications was considered if they met the inclusion criteria in the first analysis or if sufficient information was not provided in the title and abstract to enable a decision to be made. The disagreements were resolved through discussion. Where resolution was not possible, a third review author was consulted (Sh.T.). The review authors were not blinded to author(s), institution or site of publication of all studies.

All eligible studies then underwent validity assessment and data extraction. At least two review authors (Z. A. and F. Sh.) extracted data independently. Any disagreement was discussed and a third review author consulted where necessary. In the papers that included inadequate or limited information about orthodontic relapse in the statin receivers, the corresponding authors were contacted via e-mail for clarification and requesting the missing data, and a reminder e-mail was sent twice after. Finally, the following data were extracted from the eligible studies using extraction forms: study design, sample size, animal spices, animals' age; type, dosage and frequency of Statins' administration, control group, method of Statin administration, method and magnitude of force application, active tooth movement period, duration of relapse period, time of final analysis, the outcome measurement method, the outcome measured (the amount of orthodontic relapse) and main result.

Risk of bias in individual studies

The assessment of risk of bias and study quality of the included trials were undertaken as part of the data extraction process by at least two review authors (Z. A., Sh. T.) independently and in duplicate. Systematic Review Centre for Laboratory animal Experimentation (SYRCLE) Tool was used to assess the Risk of bias.[32] It is a two-part tool, addressing the ten specific domains (namely 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 bias'). Each domain includes one specific entry in a 'Risk of bias' table. Within each entry, the first part of the tool involves explaining what was reported to have happened in the study. The second part of the tool involves 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. A “yes” judgment indicates a low risk of bias; a “no” judgment indicates high risk of bias; the judgment will be "unclear” if insufficient details have been reported to assess the risk of bias properly. Any controversies regarding the reviewers’ judgments were resolved by a third review author (F.Sh).

Quality of evidence

Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) tool was used to evaluate the quality of evidence.[33] It addresses ten specific domains (Peer reviewed publication, Control of temperature, Random allocation to treatment or control, Blinded induction of ischemia, Blinded assessment of outcome, Use of anesthetic without significant intrinsic neuroprotective activity, Animal model (aged, diabetic, or hypertensive), Sample size calculation, Compliance with animal welfare regulations, and Statement of potential conflict of interests). Each domain includes one specific entry in a study quality table and involves assigning a "yes" or "no" judgment for that entry. Then each study was given a quality score out of a possible total of 10 points.

Results

Study selection

In total, 1404 studies were found after a comprehensive search of the online five databases. After removing duplicates, the titles and abstracts of the remaining 1250 studies were screened by two authors independently. Six studies were included based on the eligibility criteria and the PICO model in this step. Moreover, manual search of reference lists of previously selected studies was carefully performed to gather additional scientific reports. One study was included in this step. Consequently, 7 studies from 2008 to 2019 evaluated their full text and qualified for the review analysis (Figure 1).[20,23, 34-38]

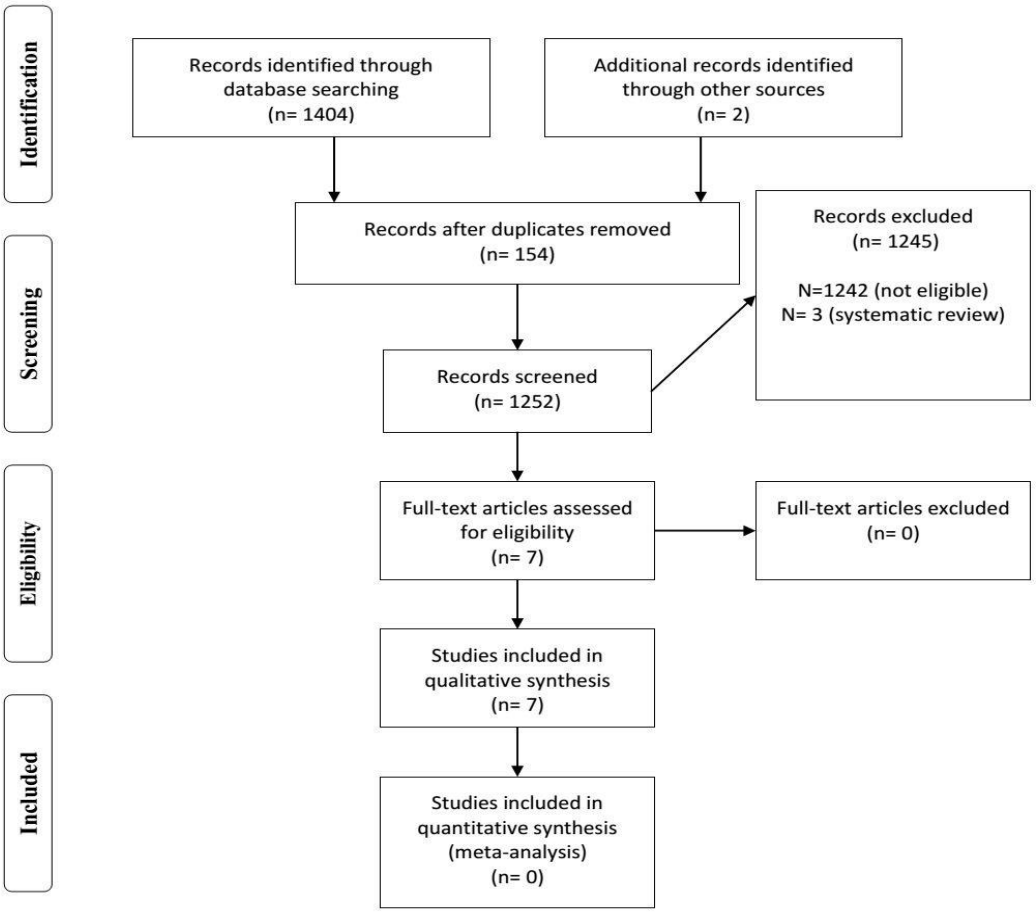

Figure 1. PRISMA study flow diagram.

Study characteristics

All of the 7 included studies were randomized experimental trials,[20,23,34-38] of which two studies had split-mouth design.[23,34] The other five trials used parallel-arm design.

Study characteristics were different in the most of included studies. Variations in animal models, animals' age, type and dosage of Statins administered; the method, frequency and duration of Statin administration; duration and force of orthodontic treatment, methods of outcome assessment resulted in heterogeneity among studies.

All of the subjects evaluated in most of the studies were rats. Only one study was conducted in rabbits.[34] The number of rats used in trials ranged from 25 to 48. In 6 studies rats aged 6 and 16 weeks were used. In 1 study, the mean age of rats was 6 weeks 4 month. The age of rabbits was 16 weeks in one study (Table 2).

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 H. et al., 2018(34)	experimental (split mouth design)	10 male New Zealand Rabitts	16 week	10/10	Impressions, casts, 3-dimensional scanner and interproximal linear distance

					measurement tool (View box software), and H&E staining.
Dolci G. et al., 2017(26)	experimental (split mouth design)	36 Male Wistar Rats	6 week	18/18	100 mm calibrated ruler, impressions, stone casts and photographs; TRAP and H&E staining.
Han G. et al., 2010(20)	experimental	32 Male Wistar Rats	7-8 weeks	16/16	Histology, immunohistochemistry, interproximal measurement on stone models
Vieira G. M. T et al., 2015(37)	experimental (split mouth design)	25 Male Wistar Rats	16 week	15/10	Micro CT scanner
Vieira G. M. T et al., 2019(38)	Experimental (split mouth design)	40 Male Wistar Rats	4 month	15/10	Micro CT scanner
Chen Y.P. et al., 2008(36)	experimental	32 Male Wistar Rats	8 week	8/8	Impressions, casts, Scan the model into the computer and use the image Software Photoshop7. 0
Cao et al.,2010(35)	experimental	48 male SD rats	8 week	12/12	Impressions, casts, Electronic cursor Caliper (accurate to 0.01 mm)

Regarding the type of Stains, four trials administered Simvastatin.[20,34,37,38] Different dosages of Simvastatin were evaluated and compared in one of included studies.[36] One study evaluated the effect of Atorvastatin[23] and both Simvastatin and Atorvastatin were administered in another trial.[35]

Included studies used various modes of Statin administrations such as submocusal,[34] interperitoneal injection,[20] systemic (oral gavage),[23,37,38] and local injections.[35]

The dosage of SMV used in the animal model studies was 0.5 mg/ 0.48 ml, 2.5, 5, 10 mgkg/ day and one study used 0.1 ml of Simvastatin/atorvastatin.[35] One of the studies compared the effect of three different dosages of Simvastatin with control group.[36] Two studies performed their experiments by administration of Atorvastatin; one of them used oral administration (15 mg/ kg)[23] and the other administered 0.1 ml Atorvastatin by local injection.[35]

Among the included studies, the maximum time period for measurement of tooth relapse was 4 weeks after Statin administration.[20,36]

The control groups in all studies underwent orthodontic treatment and also were administered to non-Statins such as phosphate buffered saline, carboxymethyl cellulose and normal saline. Some of the included studies did not use any drug or carrier in control group. (Table 3)

Table 3. Characteristics of statin administration in included studies

Author	Case group	control group	Mode of Statin administration	Frequency of administration	Duration of administration
AlSwafeeri H. et al., 2018(34)	Simvastatin 0/5 mg/480 microliter solution (Plunoric F127 as carrier)	Plunoric control vehicle solution	Two local routes: 1) 300ml sub mucosal close to mesial surface of	weekly	On 0, 7 and 14 days

			mandibular first PM 2) 180ml IL at mesial periodontal space of mandibular first PM		
Dolci G. et al., 2017(26)	Atorvastatin15 mg/kg	0/1 ml phosphate buffered saline solution	gavage	daily	14 days
Han G. et al., 2010(20)	Simvastatin 2.5 mg/kg	Normal saline	Intraperitoneal injection	daily	4 weeks from last day of OTM
Vieira G. M. T et al., 2015(37)	Simvastatin 5mg/kg	0.5% carboxy methyl cellulose as vehicle)	gavage	daily	20days (19th to 38th day), the day after the end of tooth movement
Vieira G. M. T et al., 2019(38)	simvastatin 5mg/kg	(0.5% carboxy methyl cellulose as vehicle)	gavage	daily	20days (19th to 38th day), the day after the end of tooth movement
Chen Y.P. et al., 2008(36)	simvastatin ,low dose group 2.5mg / kg, medium dose group 5.0 mg / kg, high dose group 10.0 mg / kg	Normal saline	subperitoneal injection	daily	Starting 1 day before removal, once a day for 4 weeks
Cao et al.,2010(35)	0.1 ml of Simvastatin/ atorvastatin	Normal saline	Local injection	daily	Remove the booster device, and start injecting drugs on the same day for 14 days

Method of orthodontic force application

In four trials, the method of orthodontic force application was similar; they used Nickel- Titanium closed coil springs stretched between maxillary first molar and maxillary incisor.[20,23,35,36] One trial, animals received orthodontic appliance consisted Nickel- Titanium closed coil spring between mandibular first

premolar and mandibular incisor.[34] Two studies used Steel closed coil springs stretched between maxillary first molar and maxillary incisor.[37,38] The applied forces ranged between 50 cN and 100 cN. (Table 4)

Table 4. Characteristics of orthodontic force in included studies

Author	Orthodontic appliance	Force	Site of OTM	Teeth measured for displacement	Main Results
AlSwafeeri H. et al., 2018(34)	13 mm Nickle-Titanium closed coil spring	100 cN	Between the mandibular first premolars and incisors bilaterally	between first plane drawn on distal contact area of 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	local simvastatin administration could not minimize the post orthodontic relapse magnitude to a significant level
Dolci G. et al., 2017(26)	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)	Between 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	Atorvastatin induced OPG overexpression reduces relapse after orthodontic tooth movement, in a phenomenon correlated with decreased osteoclast counts
Han G. et al., 2010(20)	Nickle-Titanium closed coil spring	50 cN	bilaterally between maxillary first molar and incisors	between distal grooves of maxillary first and second molars was measured	Relapse distances and relapse percentages were decreased, OPG expression increased, and RANKL decreased in the simvastatin group compared with the controls
Vieira G. M. T et al., 2015(37)	Closed steel spiral springs	75 cN	Between maxillary right and left first molar to right and left lateral incisor	Between most convex point of the distal surface of root of first molar and the most convex point of mesial surface of the root of second molar on day 18.	Relapse was lower in the simvastatin group than in the control group, however without a statistically significant difference.
Vieira G. M. T et al., 2019(38)	Closed steel spiral springs	75 cN	Between maxillary right and left first molar to right and left lateral incisor	Between most convex point of the distal surface of root of first molar and the most convex point of mesial surface of the root of second molar on day 18.	Relapse was lower in the simvastatin group than in the control group, however without a statistically significant difference.

Author	Orthodontic appliance	Force	Site of OTM	Teeth measured for displacement	Main Results
Chen Y.P. et al., 2008(36)	Coil spring	50 g	between the maxillary incisor and the first molar	between the first and second molars	Simvastatin can effectively inhibit the degree of tooth recurrence after experimental tooth movement, and the effect is most obvious at low doses
Cao et al.,2010(35)	NI-TI spiral spring	40 g	between the maxillary incisor and the right first molar	between the middle lingual sulcus point and the mesial lingual sulcus point of the third molar	Local injection of statins can effectively inhibit the recurrence of orthodontic teeth, and the effect of atorvastatin increases with the time of injection Better than simvastatin.

Duration of orthodontic tooth movement and relapse, time and method of outcome assessment

The duration range of orthodontic tooth movement was between 18 and 21 days. After active tooth movement, the orthodontic appliances were removed and the experimental teeth were allowed to relapse. During the relapse phase, statins were administered to experimental groups. In all included studies, statins were administered from the last day of OTM or the day after the end of OTM. Up to 3, 7, 14, 20, 21 and 28 days of statin administration, the amount of relapse was measured in included studies.[20,23,34-38]

Time and method of outcome assessment also varied between trials. (Table 5) Some of the studies assessed the relapse distance (in mm) and the others evaluated the relapse percentage.

Table 5. Characteristics of tooth displacement in the studies included

Author	Duration of tooth movement (day)	Duration of relapse phase (day)	Type of statin	Experimental (statin) group Mean+SD	Control group Mean+SD	relapse evaluation method
AlSwafeeri et al.[34]	21	21	Sim[1]	**Magnitude of movement (mm):** 1.55 ± 0.36	**Magnitude of movement (mm):** 1.53 ± 0.34	Impressions recorded on days 21 and 42.
				Magnitude of relapse (mm): 1.01 ± 0.54	**Magnitude of relapse (mm):** 1.15 ± 0.39	
				Relapse percentage: 62.01 ± 28.94	**Relapse percentage:** 75.83 ± 20.33	
Dolci et al.[26]	21	7, 14, 21	ATV[2]	**Magnitude of movement (mm):** NM[3]	**Magnitude of movement (mm):** NM	Impressions recorded on days 7, 14 and

Author	Duration of tooth movement (day)	Duration of relapse phase (day)	Type of statin	Experimental (statin) group Mean±SD	Control group Mean±SD	relapse evaluation method
				Magnitude of relapse (mm): NM	**Magnitude of relapse (mm):** NM	21 after appliance removal.
				Relapse percentage: Day 7: 9.59 Day 14: 20.59 Day 21: 7.94	**Relapse percentage:** Day7: 31.91 Day 14: 29.36 Day 21: 28.40	
Han et al.[20]	21	7, 28	Sim	**Magnitude of movement (mm):** NM	**Magnitude of movement (mm):** NM	Distance was measured on the scanned stone models 4 weeks after 21 days of orthodontic force application
				Magnitude of relapse (mm): Day 7: 0.099±0.02 Day28: 0.195±0.032	**Magnitude of relapse (mm):** Day 7: 0.256±0.034 Day 28: 0.395±0.051	
				Relapse percentage : Day 7: 26.81 Day 28: 53.38	**Relapse percentage:** Day 7: 74.77 Day 28: 93.65	
Vieira et al.[37]	18	20	Sim	**Magnitude of movement (mm):** Initial micro CT: 0.154 (0.142-0.186) Final micro CT: 0.0041	**Magnitude of movement (mm):** Initial micro CT: 0.125 (0.109-0.154) Final micro CT: 0.0040	Micro CT images on: 1) Days 4–7 (spring installation). 2) After 18 days of OTM. 3) After 20 days of drug administration
				Magnitude of relapse (mm): NM	**Magnitude of relapse (mm):** NM	
				Relapse percentage : NM	**Relapse percentage:** NM	
Vieira et al.[38]			Sim	**Magnitude of movement (mm):** 0.35	**Magnitude of movement (mm):** 0.35	Micro-CT images were analyzed on the 7th and 18th days following spring fixation and finally, 20 days after treatment

Author	Duration of tooth movement (day)	Duration of relapse phase (day)	Type of statin	Experimental (statin) group Mean±SD	Control group Mean±SD	relapse evaluation method
				Magnitude of relapse (mm): initial 0.35 final:0.15	**Magnitude of relapse (mm):** initial 0.35 final:0.05 (The authors reported their results in the form of graphs and the numbers are not accurate)	
				Relapse percentage: NM	**Relapse percentage**: NM	
Chen et al.[36]	21	7, 28	Sim	**Magnitude of movement (mm** : L.D[4]: Day 7: 0.099±0.02 Day 28: 0.195±0.032 M.D : Day 7:0.161±0.033 Day28: 0.252±0.038 H.D : Day7:0.191±0.021 Day28: 0.271±0.027	**Magnitude of movement (mm):** Day 7: 0.256±0.034 Day 28: 0.395±0.051	Distance was measured on the scanned stone models 4 weeks after 21 days of orthodontic force application.
				Magnitude of relapse (mm): L.D : Day 7: 0.099±0.02 Day 28: 0.195±0.032 M.D : Day 7:0.161±0.033 Day28: 0.252±0.038 H.D : Day7:0.191±0.021 Day28: 0.271±0.027	**Magnitude of relapse (mm) :** Day7: 0.256±0.034 Day 28: 0.395±0.051	
				Relapse percentage:	**Relapse percentage :** Day 7: 74.77	

Author	Duration of tooth movement (day)	Duration of relapse phase (day)	Type of statin	Experimental (statin) group Mean±SD	Control group Mean±SD	relapse evaluation method
				L.D: Day 7:26.81 Day 28: 53.38 M.D: Day 7:38.23 Day 28: 65.36 H.D: Day 7: 53.54 Day 28:77.43	Day 28: 93.65	
Cao et al.[35]	21	3, 7, 14	Sim	**Magnitude of movement (mm):** 0.54±0.04	**Magnitude of movement (mm) :** 0.54±0.04	Electronic cursor Caliper (accurate to 0.01 mm)
				Magnitude of relapse (mm) : Day 3: 0.10±0.02 Day 7: 0.16±0.02 Day 14: 0.23±0.02	**Magnitude of relapse (mm):** Day 3: 0.11±0.02 Day 7: 0.22±0.02 Day 14: 0.30±0.04	
				Relapse percentage: NM	**Relapse percentage: NM**	
			ATV	**Magnitude of movement (mm) :** 0.54±0.04	**Magnitude of movement (mm) :** 0.54±0.04	
				Magnitude of relapse (mm): Day 3: 0.10±0.03 Day 7: 0.14±0.03 Day 14: 0.17±0.03	**Magnitude of relapse (mm):** Day 3: 0.11±0.02 Day 7: 0.22±0.02 Day 14: 0.30±0.04	
				Relapse percentage: NM	**Relapse percentage: NM**	

1. Simvastatin
2. Atorvastatin
3. Not mentioned
4: L.D: low dose group/M.D: medium dose group/ H.D: high dose group.

Quality assessment of included studies is presented in Table 6.

Risk of bias within studies

A summary of the risk of bias in the included studies is presented in Figure 2.

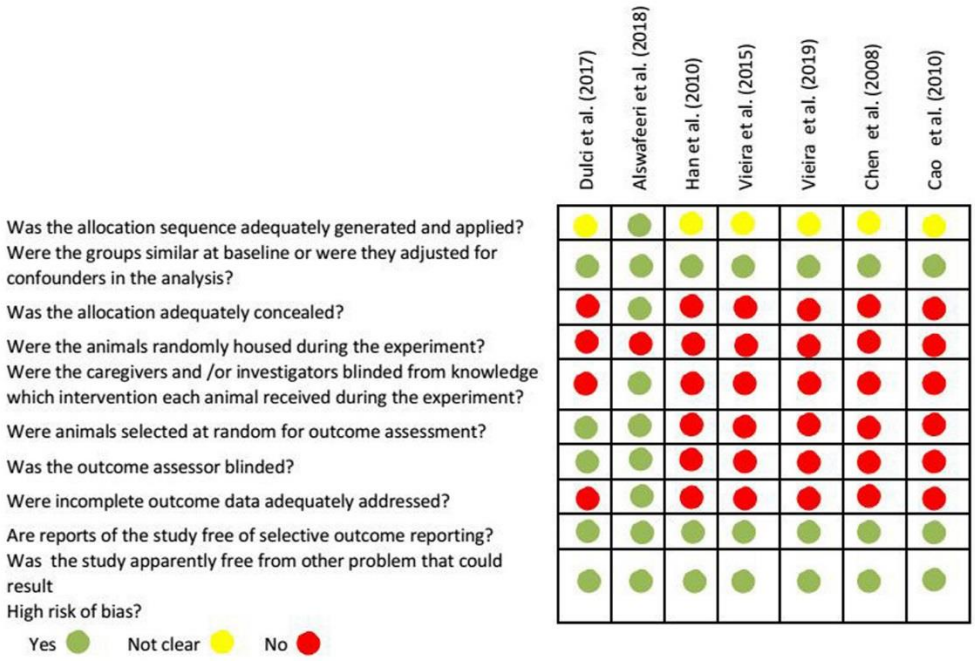

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Although this study included seven animal trials, each of these trials had at least one domain at high risk of bias.

Six of the studies did not report the method of sequence generation (selection bias).[20,23,34-38] All of the studies reported similar groups at baseline (selection bias).[20,23,34-38] In terms of assessing allocation concealment, only one trial clearly reported an adequate means of allocation concealment.[34] None of the studies reported about random housing (performance bias).[20,23,34-38] Only two studies reported about blinding of caregivers, outcome assessors or investigators (performance and detection bias).[23,34] Two studies reported about random outcome assessment (detection bias).[23,34] Only one study adequately addressed incomplete outcome (attrition bias).[34] None of the trials had selective reporting bias. Quality assessment of included studies (CAMARADES checklist) showed in (Table 6).

Table 6. Quality assessment of included studies (CAMARADES checklist)

	Alswafeeri et al. (2019)	**Dolci et al. (2018)**	**Han et al. 2010**	**Vieira et al. 2015**	**Vieira et al. 2019**	**Chen. et al. 2008**	**Cao. et al. 2010**
Publication in peer-reviewed journal	Y	Y	Y	Y	Y	N	N
Statement of control of temperature	N	Y	Y	Y	Y	N	N
Randomization of treatment or control	Y	Y	Y	N	N	Y	Y
Allocation concealment	Y	N	N	N	N	N	N
Blinded assessment of outcome	Y	Y	N	N	N	N	N
Avoidance of anesthetics with	N	N	N	N	N	N	N

marked intrinsic properties							
Use of animals with hypertension or diabetes	N	N	N	N	N	N	N
Sample size calculation	Y	N	N	N	N	N	N
Statement of compliance with regulatory requirements	Y	Y	Y	Y	Y	Y	Y
Statement regarding possible conflict of interest	N	N	N	N	N	Y	Y
Total (on 10)	6	5	4	3	3	3	3

Results of individual studies and synthesis of results

Most of the included studies reported the reduction of relapse amount by Statin administration.[20,23,35,36] The others reported insignificant reduction in their trials.[34,37]

Also, lower dose of Stains inhibited the relapse more than other doses and control group according to Chen et al.[36]

One of the included studies reported their results in the form of graphs. The corresponding author was contacted three times via e-mail for requesting the missing data but the e-mails were not responded.[38]

The results of this systematic review are based on a limited number of studies and the methodological heterogeneity and non-comparability of original outcomes made it difficult to conduct a meta-analysis. Although, most of included studies reported reduction of relapse amount by statin administration, more high quality studies needed for accurate conclusion.

Discussion

Orthodontists try to minimize orthodontic relapse and it is an important phase of treatment. Mechanisms of orthodontic relapse would seem to be a complex multifactorial process. Remodeling of the periodontal ligament and surrounding alveolar bone, normalization of the periodontal vasculature after orthodontic force, increase in elasticity of the gingival fibers and stretching of transseptal fibers are elements in the relapse process.[34,39-42]

Summary of evidence

Overall, founded on the information provided from the eligible studies in the present animal systematic review, the efficacy of commonly prescribed statins on postorthodontic relapse. remains debatable. Four studies reported that statins may reduce orthodontic relapse.[20,23,35,36] Simvastatin by interaction with metalloproteinase- 9 participates in the catabolic phase and regulates the differentiation of osteoclasts. Metalloproteinase- 9 is essential for osteoclast recruitment. Furthermore, Simvastatin prevents osteoclasts activity by regulating the ratio of local osteoprotegerin to RANKL in the periodontal tissue.[20,43] Statins could stimulate new bone regeneration by an increased expression of bone morphogenic protein-2 level in osteogenic cells.[11] Also, the effect of Simvastatin is most obvious at lower doses.[36] Simvastatin in low concentrations exhibited a positive effect on reproduction and differentiation of PDL cells to osteoblasts.[44] Atorvastatin may have a longer half-life than Simvastatin and the effect of Atorvastatin on orthodontic relapse increases more than Simvastatin as the time passes.[35]

Three studies demonstrated insignificant decrease in the postorthodontic relapse after Simvastatin administration.[34,37,38] This relapse after orthodontic tooth movement was predictable because in this

initial period after appliance removal, the tooth undergoes a rebound shift in the tooth socket. AlSwafeeri et al selected rabbits to test the hypothesis of their study.[34] Rabbits have sufficient periodontal width than rats used in the studies with significant reduction in orthodontic relapse.[45]

AlSwafeeri et al., showed a significant reduction in the area of bone resorption and a significant increase in the area of newly formed bone in Simvastatin group in histological analysis.[34] Simvastatin decreased osteoclastogenesis and a positive correlation was found between orthodontic relapse and osteoclast count which highlights osteoclastogenesis.[23] Simvastatin inhibited relapse by stimulating PDL remodeling and increasing alveolar bone formation.[20]

The results from this animal systematic review cannot be directly extrapolated to a clinical situation. Due to short periods of time administration of statins and different dosage of substance in humans.[46]

Strengths and limitations

The strengths of the present systematic review comprise the use of a well-established guidelines methodology. The search strategy employed was exhaustive, electronic and manual search irrespective of language and date up to 20stFebruary 2020. Study selection, confirmation of eligibility, data extraction, assessment of risk of bias and the quality of evidence were performed in duplicate, and any disagreement was resolved by discussion or consultation with the third co-author until a final consensus was achieved.

Previous review included four relapse-related articles. However, the current study has included 7 studies irrespective of language. Furthermore, their assessment of the quality and risk of bias were different.[47] They used ARRIVE criteria to assess risk of bias and study quality while in our review SYRCLE and COMARADES tools were used.

There are some limitations to the present systematic review, arising primarily from the characteristics of the included studies. One of the included studies reported their results in the form of graphs and Data were not retrieved although the corresponding author was contacted three times via e-mail for requesting the missing data.[38] One of the studies also reported their results by percentage and we contacted the corresponding author via e-mail for three times to request the amount of relapse in mm. The e-mails were unfortunately not responded.[23]

Most studies have at least one domain at unclear or high risk of bias because of methodological characteristics. Moreover, the quality of the most of included studies was low.

In addition, the data retrieved in the present review is related to animal studies and cannot be directly extrapolated to clinical situation. Only one human study was conducted regarding the effect of statins on orthodontic relapse.[48]

Based on the findings of a study, it might be safe to suggest that local, or even systemic use of statins, should be considered as a available therapeutic agent with which to improve various aspects of overall dental and oral health,[49] so it is strongly suggested that clinical trials be conducted to assess the effects of statins on orthodontic relapse.

Conclusions

Although, most of included studies reported reduction of relapse amount by statin administration, Reliable conclusion could not be drawn with the insufficient evidence based on humans. The effect of statins on postorthodontic relapse in humans is lacking. Investigations on animals cannot currently give plausible explanations for statins effects.

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