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Review

The influence of statins on osseointegration: a systematic review of animal model studies

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SUMMARY **Recent research data have suggested that the beneficial action of statins in bone tissue could improve osseointegration around titanium implants by increasing the bone implant contact (BIC), the expression of bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF). The aim of this systematic review was to evaluate the influence of statins on osseointegration of titanium implants in animal studies. Two reviewers searched independently four databases (MEDLINE, SCOPUS, WEB OF SCIENCE and the Cochrane Library), until March 15, 2016. The Cochrane Collaboration's Tool for Assessing Risk of Bias was used to assess the quality of the included studies. Papers that reported outcome data considering bone implant contact (BIC), mechanical tests or other histological evaluation were eligible for inclusion. 312 references were eletronically retrieved, 21 full-text papers were screened and 17 studies were included. Thirteen trials presented histomorphometry data on bone implant contact measures. All of them showed a significant improved BIC when using statins. Despite data from included studies point to beneficial effects, standardized studies and with less risk of bias, are needed to clarify the role of statins on osseointegration.**

KEYWORDS: **osseointegration, statin, simvastatin, fluvastatin, titanium implant, bone**

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Background

The increase in the use of immediately loaded dental implants and implant anchorage in low-density bone tissue has led to a need for accelerating and improving the osseointegration process. In some groups, such as osteoporosis patients, this need may be even greater. Previous investigations have demonstrated that osteoporosis can impair the process of osseointegration in an experimental model (1, 2). In this context, several studies have reported strategies to enhance osseointegration, such as the use of growth factor and/or stem cells, hormone replacement, the development of nanosurfaces and nanotechnology, the use of new titanium alloys, surface chemistry and the use of drugs.

Due to their efficacy in reducing high levels of cholesterol in blood, the development of statins (HMG-CoA) as therapeutic agents in hypercholesterolaemia has been of great importance (3, 4). Recent research data have demonstrated the anabolic effect of statins on bone tissue (4, 5). *In vivo* and *in vitro* studies have revealed that statins reduce osteoclast activity, activate osteoblast differentiation and bone formation and have beneficial effects on bone density (2, 4–7). In particular, they increase the expression of bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF) (4, 8). Therefore,

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statins have been proposed as potential agents in the treatment of osteoporosis.

Some animal studies have suggested that the beneficial action of statins in bone tissue could improve osseointegration around titanium implants by increasing the bone implant contact ratio, bone area and bone density (2, 9). *In vitro* studies have suggested that statin-coated titanium surfaces can promote and stimulate osteoblast differentiation (10, 11). The aim of this systematic review was to evaluate the influence of statins on the osseointegration of titanium implants. A preliminary search revealed that to date, no related clinical trials conducted in humans have been published, only animal studies using different models. Thus, the following focused question was addressed: 'In animals that receive implants, is the systemic or local administration of statins more effective than control treatment (no use of statins) in the osseointegration process?'

Material and methods

This systematic review complies with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (12).

Inclusion and exclusion criteria

Studies were included in this systematic review if they met the following eligibility criteria: (i) original studies in English (clinical and animal trials); (ii) evaluation of titanium implants influenced by statins; (iii) presence of a control group; and (iv) outcome data considering bone implant contact (BIC), mechanical tests or other histological evaluation. Studies using implants inserted into the medullar cavity were excluded. Letters to the editor, reviews, case series, case reports and *in vitro* studies were not included.

Search strategy

A systematic literature search was conducted in MEDLINE, SCOPUS, WEB OF SCIENCE and the Cochrane Library database through 15 March 2016. Publications were searched using the following keywords with Boolean operators (OR, AND) to combine searches: #1: (simvastatin OR statin); #2: (osseointegration OR bone implant contact OR BIC); #3: (torque OR push in OR push out OR pull out AND implant); (#1 AND #3); and (#1 AND #4). After the initial electronic search, the authors manually searched for further potentially relevant published articles and examined the bibliographies of the identified studies.

In the first phase of the review, two independent reviewers (DIS and MCZD) independently screened the titles and abstracts identified by the search strategy. Disagreements were resolved by discussion and consensus. Studies that met the inclusion criteria or those with unclear information in the title and abstract were selected for assessment of the full paper in the second phase of the review, which was conducted by the same reviewers. The reasons for rejecting studies were recorded for each report.

Data extraction

Publications that met the inclusion criteria had their data extracted using standardised evaluation forms (13). If data were missing, the authors of the original reports were contacted and asked to provide further details.

Assessment of validity

The Cochrane Collaboration's Tool for Assessing Risk of Bias (14) was used to assess the quality of the studies included in this review. Briefly, the reviewers considered the following points and questions: selection bias (randomisation and allocation concealment), performance bias (blinding of study personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias and other biases; these were classified as adequate (+), inadequate (−) or unclear (?). Based on these domains, the risk of bias was judged as (i) a low risk of bias if all criteria were met (adequate randomisation and allocation concealment, a yes answer to all questions about the completeness of outcome data and blinding, and a no answer to selective reporting and other sources of bias); (ii) an unclear risk of bias if one or more criteria were partly met; or (iii) a high risk of bias if one or more criteria were not met.

Summary measures and synthesis of results

Analyses were performed using the Review Manager (RevMan) software [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

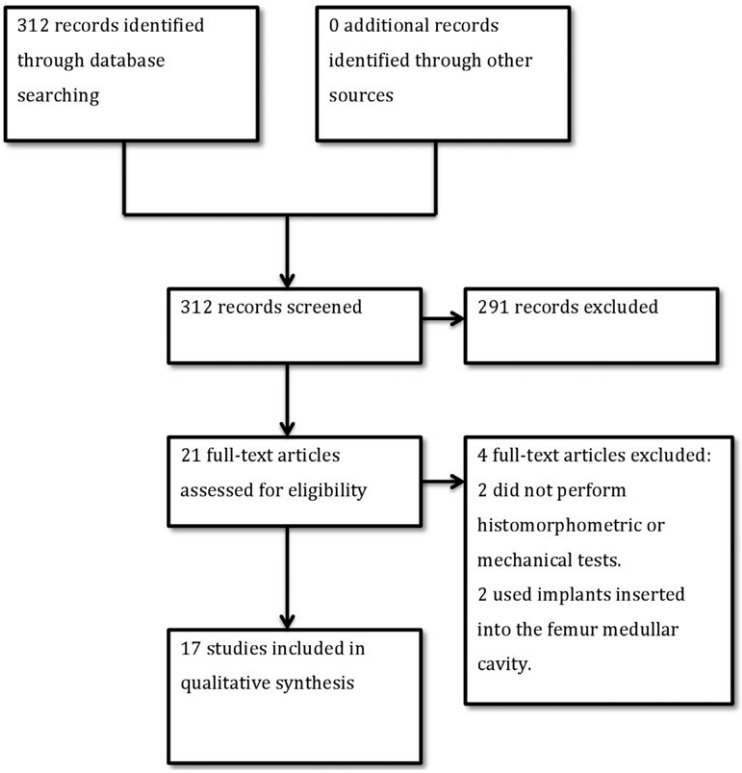

Fig. 1. Flow diagram of articles screened through the review process.

Results

Initially, 312 references were electronically retrieved. No additional references were identified manually. After title and abstract evaluation, 291 papers were excluded. The full texts of the remaining 21 articles were considered for detailed reading. Of these publications, 17 met the inclusion criteria and were included in the review (Fig. 1). The kappa agreement between examiners was 0·84.

Description of studies and experimental models

Data regarding the characteristics of the included papers are presented in Table 1. No randomised controlled clinical trials or controlled clinical studies were found. Ten studies were prospective animal trials, six studies were parallel and in one trial, any epidemiological classification was applicable. The studies were conducted in China (7), Brazil (1), Japan (6), Republic of Korea (1), Switzerland (1) and Turkey (1). Research foundations or university scholarship programmes supported thirteen studies totally or in part. One study (15) was supported by a manufacturer of dental implant systems and three (16–18) did not provide any funding information.

The studies tested different animal models: healthy and ovariectomised Wistar and Sprague Dawley rats, and New Zealand rabbits. The follow-up period ranged from 1 to 12 weeks. In total, 1458 implants were used in the studies. Only one study (17) reported the insertion torque value, between 10 and 15N in Wistar rats. The types of implant alloys were commercially pure titanium, grade 4 titanium and Ti-6A1-4V alloys. The types of surfaces tested were machined; grit-blasted; sand-blasted and acid-etched; and blasted with aluminium oxide and acid-etched and hydroxyapatite-coated. The occurrence of adverse effects and/or post-operative complications during the post-surgical period was reported in three trials due to wound healing complications (15) an anaesthetic accident (19) and infection (19, 20).

Route of administration

In seven trials, statins were administered systemically by subcutaneous injections, intra-peritoneal injections, posterior trunk dermal injections of

Table 1. Characteristic of included studies

Study	Methods	Animal model	Follow-up	Statin	Implant type and intervention	Outcomes
Ayukawa *et al.*, 2004 (24)	*In vivo* parallel study; one treatment group	10 female rats received titanium implants in both tibiae	30 days	Simvastatin	Commercially pure titanium implants with a diameter of 1·0 mm and a length of 1·5 mm. The experimental group was intra-peritoneally administered 10 mg kg^{-1} of simvastatin daily	Bone implant contact. Bone density
Ayukawa *et al.*, 2010 (25)	*In vivo* parallel study; four treatment groups	60 female rats received titanium implants in both tibiae	30 days	Simvastatin	Commercially pure titanium implants with a diameter of 1·0 mm and a length of 1·5 mm. The experimental groups were intra-peritoneally administered: 0·125 mg kg^{-1} 1 mg kg^{-1} 5 mg kg^{-1} 10 mg kg^{-1} of simvastatin daily	Bone implant contact. Bone density
Başarir *et al.*, 2009 (29)	*In vivo* parallel study; one treatment group	20 Male New Zealand rabbits received implants cylinders in both femurs	6 weeks	Simvastatin	Titanium alloy (Ti-6A1-4V) grit-blasted implants with a diameter of 5·0 mm and a length of 10 mm. The experimental group received 50 mg kg^{-1} subcutaneous injections of simvastatin daily	Percentage of bone growth Pull-out test
Du *et al.*, 2009 (2)	*In vivo* prospective study; one treatment group	54 female Sprague Dawley ovariectomised rats received titanium implants in left tibia	28 and 84 days	Simvastatin	Commercially pure titanium implants with a diameter of 2·0 mm and a length of 1·0 mm. The experimental group was orally administered 5 mg kg^{-1} of simvastatin daily	Bone implant contact. Bone area. Bone density
Fang *et al.*, 2015 (9)	*In vivo* prospective study; two treatment groups	36 female Sprague Dawley ovariectomised rats received titanium implants in both tibias	2, 4 and 12 weeks	Simvastatin	Titanium grit-blasted implants with a diameter of 2·2 mm and a length of 4·0 mm. The experimental groups received implants with deposit of simvastatin–nanohydroxyapatite coating on porous surfaces with varying concentration of: 10^{-7} M 10^{-6} M	Bone implant contact. Bone area
Faraco-Schwed *et al.*, 2014 (16)	*In vivo* prospective study; one treatment group	16 Male New Zealand rabbits received implants in right tibia	28 and 56 days	Simvastatin	Titanium blasted with aluminium oxide and acid attack implants with a diameter of 3·25 mm and a length of 8·5 mm. One of the surgical defect was injected with 30 mg mL^{-1} of simvastatin gel before implant placement	Removal torque analysis
Kwon *et al.*, 2015 (18)	*In vivo* study. Two treatment groups	4 Male New Zealand rabbits received implants in tibia and femoral head of both sides	4 weeks	Simvastatin	Titanium screws with a diameter of 3·5 mm and a length of 8·5 mm. In the experimental group, implants were coated with nano-sized hydroxyapatite and simvastatin (1 mg, 2·4 μmol)	Bone volume Removal torque analysis

(continued)

Table 1. (continued)

Study	Methods	Animal model	Follow-up	Statin	Implant type and intervention	Outcomes
Masuzaki *et al.*, 2010 (22)	*In vivo* prospective study; two treatment groups	40 female Sprague Dawley rats received titanium implants in both tibiae	2 and 4 weeks	Fluvastatin	Pure titanium rods with a diameter of 1·0 mm and a length of 1·5 mm. In the experimental groups, fluvastatin-impregnated microspheres (with 0·5 mg kg^{-1} or 1·0 mg kg^{-1}) were administrated to the back skin of the rats by a single transdermal injection	Bone volume Bone implant ratio Push-out test
Moriyama *et al.*, 2008 (21)	*In vivo* prospective study; three treatment groups	60 female Wistar rats, received rods in both tibias	1 and 2 weeks	Fluvastatin	Commercially pure titanium implants with a diameter of 1·0 mm and a length of 1·5 mm. In the experimental groups, surgical defect was injected with (before implant placement): 3 μg fluvastatin-containing PGA. 15 μg fluvastatin-containing PGA. 75 μg fluvastatin-containing PGA	Push-out test Bone implant contact. Bone volume
Moriyama *et al.*, 2010 (27)	*In vivo* prospective study; four treatment groups	126 female Wistar rats received implants in both tibias	1, 2 and 4 weeks	Fluvastatin	Commercially pure titanium implants with a diameter of 1·0 mm and a length of 1·5 mm. In the experimental groups, surgical defect was injected with (before implant placement): 3 μg fluvastatin-containing PGA. 15 μg fluvastatin-containing PGA. 75 μg fluvastatin-containing PGA. 300 μg fluvastatin-containing PGA	Push-in test Bone implant contact. Bone volume
Nyan *et al.*, 2014 (17)	*In vivo* prospective study; three treatment groups	36 male Wistar rats received implants in both tibias	2 and 4 weeks	Simvastatin	Titanium screws with a diameter of 1·8 mm and a length of 5·0 mm. Simvastatin was dissolved in ethanol and applied on the implant oxidised surface with concentration of: 25 μg 50 μg	Bone implant contact. Bone volume Mineral appositional rate
Standliger *et al.*, 2013 (15)	*In vivo* prospective study; four treatment groups	160 female Wistar ovariectomised rats and 64 female Wistar rats received titanium implants in left proximal tibia metaphysis	2 and 4 weeks	Simvastatin	Titanium (grade 4) sand-blasted and thermally acid-etched implants with a diameter of 1·1 mm and a length of 3·0 mm. In the experimental group, implants were coated with a simvastatin–chitosan complex using a modified spin-coating procedure, with 35 μg simvastatin per implant	Bone implant contact Bone area Removal torque analysis

(continued)

Table 1. (continued)

Study	Methods	Animal model	Follow-up	Statin	Implant type and intervention	Outcomes
Tan *et al.*, 2015 (28)	*In vivo* parallel study; two treatment groups	48 female Sprague Dawley ovariectomised rats received titanium implants in left tibiae	4 weeks	Simvastatin	Titanium alloy (Ti-6A1-4V) implants with a diameter of 1·5 mm and a length of 10·0 mm. In the experimental group, simvastatin was injected into the femurs at the intercondylar notch with varying concentration of: 5 mg 10 mg	Push-in test Bone density Bone volume Bone mineral apposition. Percentage of osseointegration
Tao *et al.*, 2015 (26)	*In vivo* parallel study; three treatment groups	50 female Sprague Dawley ovariectomised rats received titanium implants in both femurs (medullary canal)	12 weeks	Simvastatin	Titanium grit-blasted hydroxyapatite-coated implants with a diameter of 1·5 mm and a length of 20·0 mm. The experimental group was orally administered 5 mg kg^{-1} of simvastatin daily	Bone implant contact. Bone area ratio. Push-out test
Tao *et al.*, 2016 (19)	*In vivo* parallel study; three treatment groups	40 female Sprague Dawley osteopenic rats received titanium implants in both femurs (medullary canal)	12 weeks	Simvastatin	Titanium grit-blasted hydroxyapatite-coated implants with a diameter of 1·5 mm and a length of 20·0 mm. The experimental group was orally administered 25 mg kg^{-1} of simvastatin daily	Bone implant contact. Bone area ratio Push-out test
Yang *et al.*, 2012 (23)	*In vivo* prospective study; two treatment groups	50 female Sprague Dawley ovariectomised rats received titanium implants in both tibias	1, 2, 4 and 12 weeks	Simvastatin	Titanium grit-blasted screws with a diameter of 2·2 mm and a length of 4·0 mm. In the experimental group, simvastatin was dissolved in ethanol and applied on the implant surface with varying concentration of: 10^{-7} M 10^{-6} M	Bone implant contact Bone area
Zhao *et al.*, 2014 (20)	*In vivo* prospective study; four treatment groups	16 female Sprague Dawley ovariectomised rats received titanium implants in both tibias	4 and 12 weeks	Simvastatin	Commercially pure titanium implants with a diameter of 2·2 mm and a length of 4·0 mm. In the experimental group, simvastatin was prepared onto titanium porous surfaces by biomimetic calcium phosphate coating with varying concentration of: 10^{-7} M 10^{-6} M 10^{-5} M 10^{-4} M	Bone implant contact Bone area

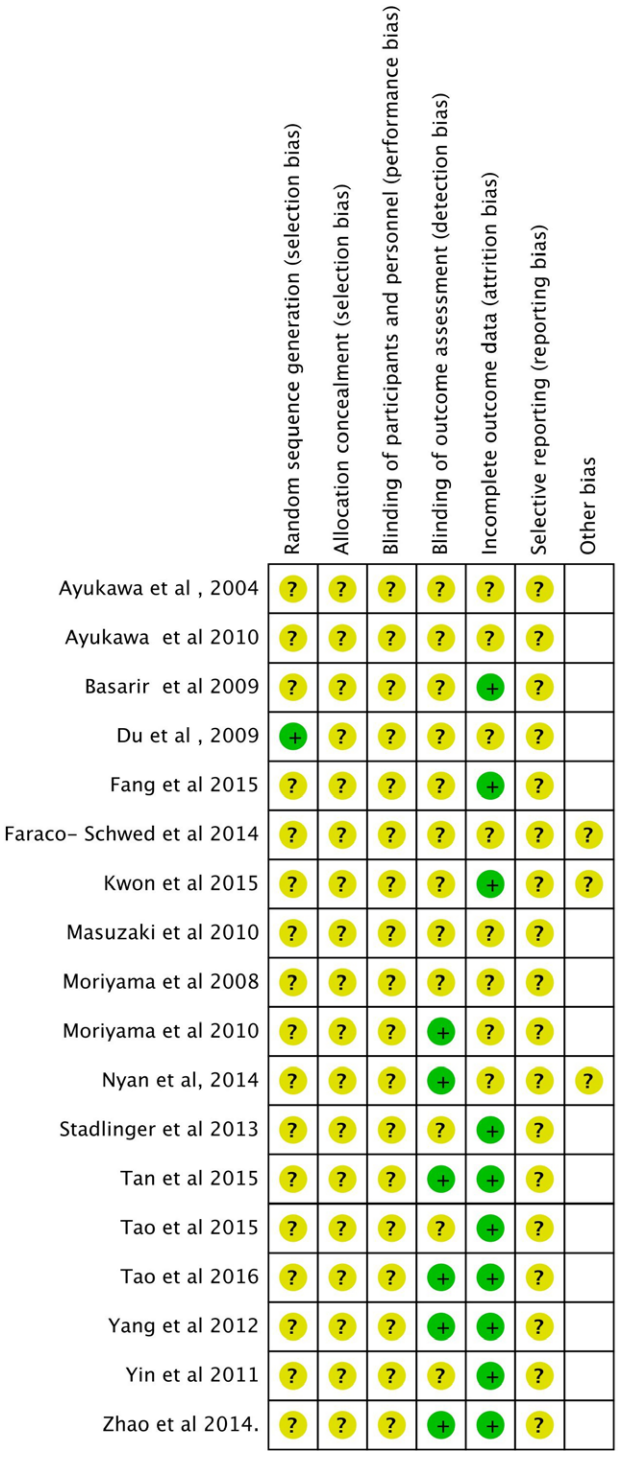

Fig. 2. Methodological quality of the included studies.

microspheres containing fluvastatin or orally. In ten studies, statins were administered locally, by injections into the surgical holes before implant placement, injection into the femur at the intercondylar notch or coated on the implant surfaces.

Quality assessment

Only one of the studies reported an adequate method of randomisation. None of the trials reported an adequate method of allocation concealment. Six articles conducted blinding of examiners with regard to the treatment procedures. The number of animals both at baseline and at the final examination was described in nine articles. Therefore, based on the criteria established by this review, all studies were considered to present a high risk of bias (Fig. 2).

Bone implant contact

Thirteen trials presented histomorphometry data on BIC measures. All of them showed a significant improved BIC when using statins. Five studies (9, 21–23) showed significant results for increased bone implant contact compared to control groups after at least 2 weeks of experimentation. Four trials (15, 20, 24, 25) showed significant differences within at least 4 weeks, and two studies (19, 26) showed such differences within 12 weeks. One trial (2) found a significant improvement in BIC only in cancellous bone within 28 and 84 days.

Bone volume

Only four trials presented histomorphometry data on bone volume (BV) measures; however, they all showed a significantly improved BV when using statins. Three studies (21, 22, 27) indicated a significant improvement in bone volume compared to the control group after at least 2 weeks. One trial (28) showed significant results within 4 weeks.

Bone area

Seven studies presented histomorphometry data on bone area (BA) measures. All of them showed a significantly improved BA when using statins. Two studies (9, 23) showed significantly increased bone compared to the control groups after at least 2 weeks. One trial (20) showed significant differences within 4 and 12 weeks, and two studies (19, 26) showed such

differences within 12 weeks. One trial (2) found significant differences only in cancellous bone within 28 and 84 days. One study (15) showed a higher BA in 2 weeks in the statin test group; however, after 4 weeks, differences between the groups were no longer detectable.

Bone density

Only four trials showed data on bone density (BD) measures by histomorphometry. All of them showed a significantly improved BD when using statins. Three studies (24, 25, 28) indicated statistically significant results compared to the control groups after at least 4 weeks. One trial (2) found statistically significant differences only in cancellous bone between 28 and 84 days of observation.

Mechanical tests

Ten studies presented some data on mechanical tests, including removal torque analysis, push-out test, pull-out test and push-in test, to assess the strength of the newly formed bone around implants. Eight studies (18, 19, 21, 22, 26–29) showed significant results for the groups with statins compared to the control groups after at least 2 weeks. One publication (16) showed significant results after 56 days. One trial (15) did not find any significant impact on the statins group's removal torque.

Discussion

To our knowledge, this is the first systematic review to assess the efficacy of statins for osseointegration *in vivo*. Although the 17 selected studies are very heterogeneous, it can be seen that both the systemic and local application of statins improved bone implant contact, bone volume, area and density for different concentrations and evaluation periods. No meta-analysis could be performed because the studies included different animal species, variable statins administration methods and concentrations. Furthermore, variable periods of observation and different approaches for analysing bone formation with measurement unit systems were found.

It is known that experimental studies are difficult to design, especially regarding standardised methodologies and analysis, including the appropriate allocation concealment in animal models. Despite the notable work performed by the authors of the studies included in this systematic review, only one trial reported an appropriate method of randomisation, and only six studies included blinding examiners regarding the analysis of the results, which increases the risk of bias and reduces the strength of scientific evidence.

With regard to bone implant contact ratio, some considerations should be highlighted. In the systemic administration studies, the positive results were directly related to a higher concentration of statins and longer observation periods. Little or no difference was found in the comparative groups with 1 week of follow-up or for applications less than 5 mg kg^{-1} daily. In contrast, statistically significant differences were found in all studies that evaluated 12 weeks of follow-up and with concentrations greater than or equal to 5 mg kg^{-1} daily. Although the systemic use of statins indicates positive results, a rapid liver metabolism requires higher concentrations of statins to express an osteogenic function (28, 30). Otherwise, topical statins that are associated with a vehicle that slows their metabolism can promote bone formation and improve the torque force required to remove the implant (16).

For local use, it was difficult to equalise the optimal range of doses/concentrations due to the widely varied applications found, which ranged from transoperative injections to coating of implants. Additionally, the animals used were from diverse species and presented different systemic conditions, which made it difficult to establish a unique optimal dose. However, as it occurred with the systemic use, the positive results also appear to be dose-dependent, suggesting that the most relevant effects occur at higher concentrations and over longer evaluation periods. Similar results were observed in bone volume and density. Regarding bone area, two studies (9, 23) compared the results obtained at 4 and 12 weeks with local use of statins and revealed no significant differences between these periods. One study (15) could not identify any differences between 2 and 4 weeks. These results suggest that the effect of locally applied statins on bone area occurred in the early stages of wound healing. Although none of the included studies reported any adverse effects using statins, publications have shown that the topical application of high-dose simvastatin can cause local inflammation (31, 32) and osteolysis (33).

Eight studies used ovariectomised rats as an animal model. In three trials, statins were administered systemically, and in five, they were administered locally. In all studies, statins improved osseointegration in the test group. The positive effect on models with osteoporosis and osteopenia reveals a possible clinical application of great interest.

The outcomes of mechanical tests showed a great variability in the measurement methods, but the results for bone implant contact were likewise dependent on the drug concentration and longer periods of evaluation. Only one study did not find significant differences compared to the control group (15).

The positive effects on osseointegration might be correlated with statin action on bone tissue. In addition to increasing the expression of the two important anabolic factors, bone morphogenetic protein-2 (BMP-2) (5) and vascular endothelial growth factor (VEGF) (8), statins are known to regulate osteoblast function by increasing the expression of bone sialoprotein, osteocalcin and type I collagen (2, 8) and to reduce osteoclast activity (5, 8).

Even with the difficulties faced in verifying the systemic and local administration patterns of statins that may provide clear evidence of their role in improving the osseointegration of titanium implants, the effects have been suggested to be positive. Researchers should be encouraged to implement more standardised studies with low risk of bias, aiming to reach an optimal dose for the development of a phase 1 clinical trial.

Conclusion

Despite data from included studies point to beneficial effects, standardised studies, and with less risk of bias, are needed to clarify the role of statins on osseointegration.

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