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Systematic Review
Dental Implants

The ability of topical and systemic statins to increase osteogenesis around dental implants: a systematic review of histomorphometric outcomes in animal studies

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Abstract. The purpose of this systematic review was to evaluate the quantitative histomorphometric outcomes of animal studies investigating statins as a pro-osteogenic agent to enhance the osseointegration of dental implants. Some animal studies have suggested a beneficial action of statins on bone tissue. Electronic and manual literature searches, without date or language restriction, were performed by two independent review authors up to February 2017. Eligibility criteria included animal trials quantitatively analysing the pro-osteogenic effect of statins on dental implants. The quality of the included studies was assessed using the ARRIVE guidelines. The search and selection process yielded 12 studies, published between 2004 and 2015. The experimental animals models used were rats and dogs. The statins used in the studies were simvastatin and fluvastatin, which were administered locally or systemically, or applied to the implant surface. All of the selected studies showed a statistically significant positive effect of statins on bone formation around implants. The mean quality assessment score (ARRIVE) of the studies was 11.5 ± 2.27 out of a possible total of 25 points. The histomorphometric data from available preclinical studies suggest a positive effect of statins on increasing osteogenesis around dental implants.

Key words: statins; osseointegration; dental implants.

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Endosseous implant therapy has become a widely accepted treatment modality for the replacement of missing teeth[1]. Spurred by the convenience of shorter treatments and the necessity of dealing with more challenging clinical situations, implants and implant therapies have undergone continuous improvement to increase osteogenesis around titanium implants.

Recently, several modified surface treatment techniques have been reported that shorten the period of bone healing, such as sand-blasting, acid-etching, grit-blasting, anodization, plasma-spraying, and coating with inorganic calcium phosphate, drugs, or biological molecules, and chemical modifications have been devised to improve the biological characteristics that promote osseointegration and bone formation and thus shorten the time required for implant loading[1–6].

Among the various factors that may adversely affect the osseointegration of implants are low bone mass, deterioration of the bone microarchitecture, extensive bone fragility, and increased risk of fracture, which are observed in patients with osteoporosis[7–11].

Hydroxymethylglutaryl-coenzyme A reductase inhibitors, the so-called statins, are used widely as cholesterol-lowering drugs. These drugs act by inhibiting hepatic cholesterol biosynthesis[12,13]. Previous studies have shown that a type of liposoluble statin, simvastatin (SIM), may increase the mRNA expression of bone morphogenetic protein 2 (BMP-2) in osteoblasts, promoting bone formation as a result[14]. They have also shown the beneficial effects of statins on bone mineral density (BMD)[15,16].

There are reports in the literature on different methods of statin administration in association with dental implant procedures, such as systemic administration (muscular or subcutaneous)[7,12,13], topical application (internal surgical site)[8,9,11,17–20], and continuous release from a treated implant surface[10,21–23]. In addition, a recent systematic review evaluated the effect of statins on osseointegration in animal models[24]. However, this previous review did not perform an assessment of the risk of bias and quality specific for animal studies and this may hinder the analysis and interpretation of the data.

The purpose of the current systematic review was to evaluate the quantitative histomorphometric outcomes of animal studies investigating statins as a pro-osteogenic agent to enhance the osseointegration of dental implants.

Materials and methods

The protocol of this review was based primarily on the PRISMA-P statement[25], and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42016039394). The methodology used followed the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*[26]. To increase the quality and transparency of the research, the methodology adhered to the PRISMA statement checklists[27].

The focused question was, ''Does the application of statins (topical or systemic) lead to enhanced osseointegration around dental implants?''

Search strategy

An electronic search without date or language restriction was performed in the MEDLINE/PubMed, Cochrane Central Register of Controlled Trials, Scopus, and LILACS databases (inception to February 2017). Furthermore, a 'manual search' of the electronically available material from the following relevant journals, including publications ahead of print, was performed: *Journal of Periodontology*, *Journal of Clinical Periodontology*, *International Journal of Periodontics and Restorative Dentistry*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *The International Journal of Oral and Maxillofacial Implants*, *Journal of Oral and Maxillofacial Surgery*, *Clinical Oral Investigations*, and *Journal of Dental Research*. Unpublished studies (grey literature) were sought through the Grey Literature Report and OpenGrey databases. Searches of the ClinicalTrials.gov database and the reference lists of the included studies (cross-referencing) were also conducted.

The search strategy included the terms ''statin'' and ''dental implant'' using Boolean operators in all databases: (''statin''[MeSH Terms] OR ''statin''[All Fields]) AND (''dental implants''[MeSH Terms] OR (''dental''[All Fields] AND ''implants''[All Fields]) OR ''dental implants''[All Fields] OR (''dental''[All Fields] AND ''implant''[All Fields]) OR ''dental implant''[All Fields]).

Outcome measures

The primary outcome measures were the bone-to-implant contact (BIC; the length of bone formation in direct contact with the implant, as a percentage, measured on histological slides) and mechanical stability. The secondary outcome variables were bone neoformation, inter-thread and peri-implant bone density, and cortical and medullary bone area ratio.

Selection criteria

The inclusion criteria were animal studies presenting BIC or bone area formation in healthy or osteoporotic bone, with the application of topical or systemic statins to enhance the osseointegration of dental implants.

With regard to exclusion criteria, in vitro studies, reviews, studies in systemically compromised animal models (e.g. diabetes mellitus), and studies in compromised implant host bone or soft tissue (e.g. peri-implantitis models, nicotine/smoking models, defects with the application of guided tissue regeneration or socket preservation) were excluded, as were studies dealing with the following aspects: influence of immunosuppressive therapy, influence of radiotherapy, influence of bisphosphonates, bone substitution materials, association between periodontal ligaments and implants.

Study selection and screening process

The titles of the articles retrieved were screened, and publications that fulfilled the inclusion criteria were identified. Abstracts of all titles that were agreed on were obtained and screened for the inclusion criteria. After screening the abstracts, the full texts of the selected articles were then obtained. If the title and abstract of an article did not provide sufficient information to make a decision regarding the inclusion criteria, the full text was obtained and examined. Finally, the full-text articles were selected based on the inclusion criteria by screening the materials and methods and results sections. This screening procedure was performed by two review authors (V.M. and M.D.C.M.). Disagreements between the review authors were resolved through careful discussion. When necessary, the authors of the studies included herein were contacted by e-mail for clarification of remaining doubts.

Data extraction

When available, the following data were extracted from the included studies by two review authors (V.M. and M.D.C.M.): authors, experimental animal model, randomization method, implant used (surface/brand), statins (type/administration/