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Review Article

Unleashing the potential of simvastatin to osteogenesis: A review role of simvastatin in bone formation

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Abstract

Owing to the efficiency of several regenerative procedures, the demand for effective biomaterials for bone augmentation procedures has gained a surge. In light of this, the newer material must have improved osteogenic properties combining pros of autologous bone grafts and eliminating their cons. On search, various anabolic drugs (bisphosphonates, calcitonin and simvastatin) aimed at upregulating intrinsic bone growth factors has been introduced. Simvastatin, a lipid lowering agent has been reported to promote osteoblastic activity and inhibit osteoclastic activity via various biological pathways. Several animal studies have demonstrated the bone- promoting effect of simvastatin when applied topically. Simvastatin is shown to increase cancellous bone volume, bone formation rate, and cancellous bone compressive strength.

Keywords: Simvastatin, Regeneration, Bone formation, Topical, Osteogenesis.

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1. Introduction

For comprehensive healing of periapical tissues and effective pain alleviation, efficient endodontic therapy is crucial. While non-surgical endodontic treatments generally lead to the resolution of periapical lesions, some cases, such as those involving extensive periapical bone loss, large cystic lesions, or persistent infections unresponsive to conventional therapy, necessitate surgical intervention. Various branches of dentistry have explored autogenous and autologous bone grafts to enhance tissue formation in lesion-induced defects post-surgery. Additionally, the integration of anabolic agents such as bisphosphonates, calcitonin, and statins has demonstrated promising results in promoting bone regeneration in medical and dental applications.[1,2]

Statins (Hydroxymethylglutaryl-CoA reductase inhibitors) are widely recognized for their cholesterol-lowering properties; however, their pleiotropic effects extend beyond lipid metabolism. Notably, they exhibit anti-inflammatory and connective tissue-proliferating properties that contribute to bone regeneration. These effects are mediated by the upregulation of bone morphogenic protein-2 (BMP-2), vascular endothelial growth factor (VEGF), and alkaline phosphatase expression, while simultaneously inhibiting osteoclastic activity via the blockade of the mevalonate pathway. Unlike hydrophilic statins such as atorvastatin and fluvastatin, which negatively affect bone metabolism, the lipophilic statin simvastatin has been recognized for its osteoinductive potential, enhancing bone mineral density and bone remodelling.[3]

Since the pioneering work of Munday et al. in 1991, which first identified the anabolic effects of statins on BMP-2 in rodents, extensive research has investigated their ability to stimulate osteoblast differentiation, enhance bone mineral density, and modulate inflammatory responses, making them a potential therapeutic option for osteoporosis and other bone-related conditions.[4] Multiple clinical trials have demonstrated that systemic and local administration of statins can improve periodontal health by reducing inflammatory cytokine levels, enhancing osteoblast differentiation, and promoting angiogenesis.[5,6] These effects contribute to reduced tooth mobility and increased alveolar bone

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regeneration, particularly in patients with type II diabetes mellitus and chronic periodontitis, conditions often associated with impaired bone healing and increased susceptibility to periodontal disease.[7] Additionally, statins exhibit antimicrobial, antifungal, antiviral, anti-inflammatory, immunomodulatory, and wound-healing properties, underscoring their relevance in regenerative dentistry.[8]

Despite these promising findings, a significant gap remains in understanding the role of statins in periapical tissue healing. While their impact on periodontal regeneration and implant osseointegration has been well-documented, limited studies have systematically reviewed their potential in treating periapical diseases.[9] This review aims to bridge this gap by critically assessing recent preclinical and clinical studies on simvastatin's effects in peri-apical disease management. Additionally, it will evaluate the optimal routes of drug administration, dosage parameters, and their translational significance in regenerative endodontics, ultimately contributing to evidence-based clinical advancements.

2. Materials and Methods

This umbrella review was conducted following established guidelines for comprehensive narrative reviews. A broad literature search was performed to synthesize all available literature, including systematic reviews, meta-analyses, and narrative reviews evaluating the osteogenic potential of simvastatin.

2.1. Search strategy

A systematic search of the following electronic databases was conducted: PubMed, Scopus, Web of Science, Embase, and Cochrane Library. The search was performed using a combination of Medical Subject Headings (MeSH) terms and free-text keywords to ensure comprehensive coverage of relevant literature. The search terms included:

"Simvastatin", "Bone regeneration", "Osteogenesis", "Periodontal regeneration", "Topical simvastatin", "Statins and bone healing", "Endodontic bone defects", "Simvastatin scaffolds", "Simvastatin controlled drug delivery".

Boolean operators (AND, OR) were used to refine the search strategy. Additionally, reference lists of retrieved articles were manually screened to identify additional relevant studies.

2.2. Inclusion criteria

Studies were included if they met the following criteria:

1. Published in peer-reviewed journals between [insert time frame, e.g., 2000-2024]
2. Systematic reviews, meta-analyses, and narrative reviews investigating the effect of simvastatin on bone regeneration, osteogenesis, or periodontal healing
3. Studies that provided a comprehensive synthesis of preclinical, clinical, and in vitro research.
4. Examined different modes of simvastatin administration (topical, systemic, scaffold-based delivery).
5. Reported conclusions related to bone formation or histological evidence of osteogenesis.

2.3. Exclusion criteria

1. Studies that did not focus on simvastatin's role in bone formation.
2. Primary experimental studies without review-based synthesis.
3. Review articles lacking systematic methodology.
4. Studies with insufficient or inconclusive data on osteogenic outcomes.

2.4. Data extraction & quality assessment

Two independent reviewers extracted key information from selected reviews, including study design, sample size, intervention details (dosage and administration route), control groups, follow-up duration, and primary outcomes related to bone regeneration. Any discrepancies were resolved through discussion or consultation with a third reviewer narrative reviews were evaluated based on clarity, comprehensiveness, and depth of analysis.

2.5. Synthesis of findings

Due to the nature of an umbrella review, no new statistical analyses were performed. Instead, overarching themes, consistent findings, and areas of controversy were highlighted to provide a holistic understanding of simvastatin's osteogenic potential. This umbrella review aims to offer a synthesized perspective on the therapeutic applications, dosage optimization, and route of administration for enhanced clinical outcomes.

3. Results

The database search yielded a total of [79] records. After removing duplicates, [49] studies remained for initial screening based on title and abstract. A further [37] studies were excluded after full-text screening, resulting in a final inclusion of [12] systematic reviews, meta-analyses, and narrative reviews.

The included studies comprised meta-analyses, systematic reviews, narrative reviews, etc]. The majority of studies focused on [e.g., topical vs. systemic administration, scaffold-based delivery, periodontal applications]. Key trends identified included [e.g., optimal dosage, duration of treatment, specific benefits in bone healing]. Areas of controversy and gaps in research were also noted, particularly regarding [e.g., inconsistent findings on systemic administration, lack of long-term clinical trials].

3.1. Simvastatin and osteogenic differentiation

Simvastatin upregulates BMP-2 expression via inhibition of the mevalonate pathway and suppresses osteoclasts by inhibiting prenylation of small GTPase proteins.[10] (**Figure 1**)

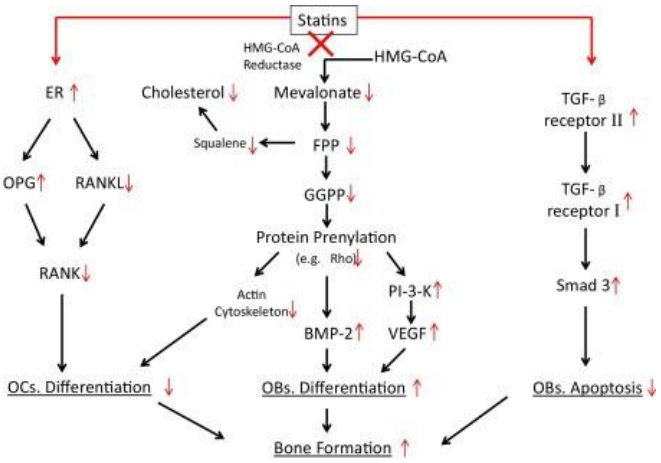

Figure 1: Highlights the mechanism of simvastatin in bone regeneration

Furthermore, studies demonstrate that simvastatin induces osteogenic differentiation of cells through pathways independent of inhibition of prenylation in small GTPase proteins. This includes modulating actin filament organization and cellular stiffness in BMSCs, thereby increasing BMP-2 and RUNX-2 expression via activation of the RhoA/actin/cell stiffness pathway.[11] According to Chen et al., activation of the Ras/Smad/Erk/BMP-2 signaling pathway is responsible for viability and differentiation of osteoblasts.[12] Simvastatin modulates Wnt/β-catenin pathway, which plays a role in BMSC proliferation and osteogenic differentiation. The regulation of lipid metabolism by simvastatin also contributes to osteogenic differentiation.[10]

3.2. Simvastatin- route of administration and dosage

To ensure osteogenesis in the oral cavity, dosage of simvastatin ranges as low as 1.2mg when applied topically to 10mg/kg/day on systemic application.[1]

The inconsistent findings from previous literature[1] indicate that statins administered orally may undergo liver degradation, resulting in limited availability of the drug to accumulate in bone.

By administering locally, hepatic degradation of statins can be bypassed, achieving therapeutic concentrations in bone while minimizing systemic side effects aforementioned. (**Figure 2**)

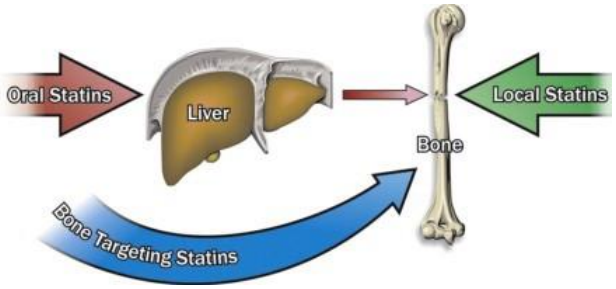

Figure 2: Highlights route of administration

The key factor in a local drug delivery system is ensuring the active ingredient reaches the intended site of action effectively.[1]

Mentioning the deleterious effects of high-dose orally administered simvastatin, exercising caution in optimal dosing of the medicine has become crucial. According to various studies, the dosage of the drug affects its inflammatory response as well as its capability to enhance bone volume.[1] At low to moderate dosages, simvastatin acts as an anti-inflammatory by inhibiting the mevalonate pathway, thereby reducing the release of inflammatory mediators. At high dosage, it has a potential pro-inflammatory effect with a high risk of myopathy. However, in terms of bone, the effect of dose is vice versa.

Study by Pradeep et al concluded, the topical simvastatin in humans did not result in any complications.[15]

Literature provide evidence that the local application of statins enhances bone healing and also have certain beneficial local effects.

Table 1 highlighting clinical studies and reviews reveal that topically applied simvastatin in forms of either gels, grafts or sub- gingivally and doses of 1.2mg – 10mg advances clinical outcomes, boosts bone formation, preserves alveolar bone and facilitates osteogenesis across different oral sites, including peri-apical defects, intra-alveolar regions, extraction sockets, maxillary sinus, and class II furcation defects. Thus, simvastatin could be considered a superior osteoinductive biomaterial.

The findings also report that the effectiveness of the drug is corelated to the duration of action, the specific cell type involved, and the level of cellular differentiation. For example, a study indicated that a dosage of 0.1μM has the greatest impact on the osteogenic potential of osteoblasts like MC3T3-E1 cells.

Studies yield consistent findings regarding the critical concentration at which simvastatin exhibits cytotoxicity. A concentration of 1μM appears to be critical for simvastatin-induced cytotoxicity.[10]

Table 1: Highlights studies, topical form of administration and dosage of simvastatin that boosts osteogenesis

Study (year)	Study design	Carrier used	Application method	Dose	Site of application	Outcomes
Gupta S et al[1] (2020)	Clinical Case-report	Gelatin sponge	Local	10mg	Peri-apical defects	Simvastatin indicated bone regeneration at faster rate.
Diniz JA et al[27] (2024)	Scoping review	Various	Topical	10mg, 2 mg	Intra-alveolar	Intra- alveolar simvastatin effectively and safely preserves alveolar bone with various concentrations and carriers, without significant adverse effects.
Betha H et al[28] (2024)	Clinico-radiographic study	Hydrogel	Gel	1%	Extraction socket	Post immediate implant, topical application of simvastatin enhances clinical outcomes and crestal preservation.
Nasr TA et al[26] (2024)	Comparative study	Ceramic cement	Topical	7.21mg	Maxillary sinus	The superiority in terms of bone formation Favors the drug as osteoinductive biomaterial
Harsha G et al[2] (2023)	RCT	Not specified	Topical	10mg	Extraction socket	Promoted osteogenesis
Esmaeili V et al[20] (2023)	Clinical & histological study	Polymer (graft)	Graft	10mg/ 1g of graft	Intra-alveolar	Simvastatin impregnated graft material demonstrated superior osteoinduction as compared to routine graft materials
Saleh N et al[21] (2023)	RCT	Hydrogel	Gel	1.2%	Infra- bony	Better bone fill can be appreciated radiographically.
Pradeep A R et al[15] (2021)	RCT	Not specified	Sub-gingivally	1.2mg	Class II furcation defects	Simvastatin, when administered locally, improves clinical parameters and facilitates osteogenesis.
Cruz R et al[9] (2021)	RCT	Hydrogel	Gel	1.2%	Extraction socket	There was reduction in dimensional changes i.e.; bone formation was seen.
Mahdi HS and Al-Adili SS[28] (2021)	RCT	Gel foam	Topical	10mg	Extraction socket	Bone formation was evident with increase in bone density.
Gupta S et al[1] (2019)	Systematic review & Meta - Analysis	Various	Topical + systemic	1.2mg topically to 10 mg systemically	Bone, soft tissues, TMJ cartilage	Simvastatin holds Great role in various oral therapies like periodontal infection control, bone formation, soft tissue grafting, TMJ cartilage repair.
Gouda A et al [29] (2017)	Systematic review	Gelatin sponge or collagen	Topical	0.2ml or 2.2mg, 0.5mg	Surgically created bone defects	Osteoinductive potential of simvastatin was highly appreciated.

3.3. Controlled release drug delivery system

The local drug delivery system faces several shortcomings. Primarily, drugs with low molecular weight tend to have a faster rate of release in comparison to higher molecular weight drugs. The effect of mesh size also favours faster release of the former. Although, in biomimetic materials, certain parameters (hydrophilicity/hydrophobicity, rate and mode of degradation, etc.) influencing the rate of release could be modified.[16] This section highlights the various simvastatin-loaded drug delivery systems.

3.3.1. Simvastatin- coated scaffolds

Simvastatin can create a coating laden with drugs on a scaffold surface by interacting with a transitional material that can bind the drug and scaffold at the same time. The most frequently employed material is Polydopamine (DOPA). The dopamine coating provides an amine group to the biomaterial surface, enabling simvastatin binding. Yang et al. created a medication delivery method by combining simvastatin acid with a β-tricalcium phosphate scaffold through a DOPA coating. The findings demonstrated that, despite a minor burst release on the first day, simvastatin was released constantly over the course of 28 days. This composite method enhanced ALP expression and MC3T3-E1 cell extracellular matrix deposition while exhibiting good biocompatibility. The alternate linker for simvastatin is β-cyclodextrin (βCD). β-CD can interact with simvastatin through an inclusion complexation. Simvastatin's release rate is considerably slowed by the presence of β-CD, enabling the medication to be released gradually. A simvastatin coating can be made via the addition of the drug into the matrix of the coating material. Simvastatin can be included to create a drug-loaded mixture while biodegradable polymer coating materials are being made. Additionally, simvastatin can be mixed with inorganic elements as calcium phosphate coatings to create new substances. Simvastatin may alter the crystal structure during calcium phosphate production; therefore, the right drug concentration and mixing technique are essential to resolving this issue. Additionally, the coating materials can serve as barriers that reduce the rate of drug release into the surrounding medium. To accomplish drug loading, the majority of scaffolds of this kind are submerged in a simvastatin solution. Because of the weak electrostatic contacts between simvastatin and the scaffolds, the medicine is usually delivered in bursts. Lai et al. used anodization to create titania nanotubes (TNTs) on a titanium scaffold's surface. After that, simvastatin was added to the TNTs, and chitosan/gelatin multilayers (TNTs-SV-LBL) were applied on top. Compared to uncoated scaffolds, simvastatin within TNTs-SV-LBL showed more sustained release and was more effective at suppressing osteoclasts and encouraging osteogenic differentiation. However, there may be drawbacks to such a barrier covering as well. Although the medicine is given more slowly, the coating on the surface may decrease the original material's capacity to connect to cells, reducing cell adhesion and perhaps affecting the amount of locally regenerated bone mass.

3.3.2. Simvastatin- embedded scaffolds

Hydrogels are always a favoured method for delivering drugs topically. Their use for delivering statin has also been explored. Literature is evidence stating that hydrogels are an excellent mode of delivering simvastatin topically due to their three-dimensional network structure, flexibility, and unique ability to swell with water, making them ideal for drug loading.[17] Hydrophilic hydrogels are better than hydrophobic, as the former induce a weak inflammatory response by adsorbing fewer proteins, hence creating a more favourable microenvironment for osteogenesis.[10] However, as simvastatin is hydrophobic, it tends to aggregate and precipitate with hydrophilic gels, thereby affecting drug release kinetics.[10] Ceramics and synthetic polymers have also been explored as potential carriers for simvastatin. FDA-approved formulations for ceramic bone cements act as scaffolds for osteogenesis. In some cases, they are even resorbable, allowing forming bone to replace them gradually. Studies have reported simvastatin-loaded calcium phosphate cements to heighten the osteogenic potential as well as the rate of degradation of simvastatin.[18]

The excellent biodegradability and biocompatibility of polymer materials make them ideal as biomaterials. Simvastatin-loaded polymer matrix is prepared via direct mixing it with polymer solution at the time of manufacturing.[10] Polymers with hydrophobicity create an ideal microenvironment for incorporating hydrophobic simvastatin. This also enables extended release of the drug by limiting water penetration into the carrier and minimizing the solubility of the drug.[19] The drug is released following diffusion and polymer degradation. The hydrophobic interaction between polymer and simvastatin facilitates controlled drug release at the site. The drug release follows either zero-order kinetics or an attenuated burst release followed by sustained release. They have an advantage over ceramic cements as the drug binds chemically to the polymer matrix.[20] Literatures demonstrate simvastatin-loaded polymer materials promote osteogenesis and favor drug release profiles. The widely used synthetic carrier for simvastatin is PLGA.

3.3.3. Simvastatin- containing microspheres

Microsphere scaffolds engineered through polymer material also serve as drug delivery platforms. According to researchers, the morphology (micrometer level) influences cell viability, response, and osteogenic gene expression of biomaterials.[15] Simvastatin-loaded microspheres exhibit exceptional biological activity and possess large surface areas.[21] Common techniques involved in the manufacturing are the water-oil-water emulsion method, electrospraying, and electrostatic spinning. Simvastatin-loaded PLAG microspheres, as per studies, can release drugs for a month,

enhancing bone formation and promoting healing significantly. However, the large surface area of the microspheres causes initial burst release, hence impairing their osteogenic potential.[15]

To address this, the drug-loaded microspheres can be distributed homogenously in either the polymer or inorganic matrix. The matrix would act as a temporary barrier and will decrease the burst release thereby.[22]

Another strategy uses devising core-shell microspheres where the outer core encloses the inner core. This design provides a stable, sustained release with the shell acting as a barrier. The structures have shown great biocompatibility and osteogenic potential. Nevertheless, certain agents like photoinitiators, cross-linking agents, and surfactants used in the manufacturing process could affect the biocompatibility of the scaffold, potentially diminishing the therapeutic potential.[10] Therefore, innovating microsphere manufacturing technology and producing cost-effective, highly biocompatible microspheres are crucial for the development of simvastatin-containing microspheres.

3.3.4. Simvastatin- containing nano- particles

In recent years, nanostructured biomaterials for bone regeneration in bone tissue engineering have garnered significant attention. Drug-coated nanoparticles are considered an ideal platform for simvastatin delivery due to their high surface area to volume ratios, sustained drug-releasing potential, high drug encapsulation rates, enhanced drug permeability, and stability. Simvastatin can be embedded in the nanoparticles either during electrospinning or the ionic gelation process. As the nanoparticles swell, the drug is released slowly at the site of action. The scaffold has demonstrated their potential to endorse in vitro mineralization and osteogenic differentiation.

Internal bone formation could be seen as nanoparticles invade cell walls easily.[10]

Recently, biodegradable nanopolymer micelles loaded with simvastatin have been engineered. These nanoscaffolds release simvastatin in a targeted manner, markedly boosting osteoinductive effect and biocompatibility.[23]

However, the complex preparation and application processes involving these nanoscaffolds hinder their clinical application in healing bone defects.

4. Conclusion

Topical simvastatin, a potential osteoinductive drug, has delivered promising results in terms of bone formation, wound healing, and alleviating peri-apical lesions. With inconsistent findings for systemic therapeutic doses, local simvastatin-carrying scaffolds appear as an appealing solution to manage therapeutic dosage at the required site. This review marks the potential of the drug in varying human studies of dental origin. The cost-effectiveness, ease of handling, and aseptic technique favour its use in clinical practice. However, the bone formation with simvastatin occurs in a dose-dependent fashion. Hence, encouraging use of simvastatin for osteogenesis in peri-apical lesions is highly recommended.

5. Source of Funding

None.

6. Conflict of Interest

None.

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