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Statins as Potential Therapeutic Agents for Healing Disorders

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Abstract and Introduction

Abstract

Statins, HMG-CoA reductase inhibitors, are common cholesterol-lowering drugs. Recent studies suggest that statins may have potential as novel treatments for diverse conditions, ranging from sepsis and inflammatory diseases to chronic wounds and bone fractures. The diverse pleiotropic actions of statins are probably related to reduced isoprenylation of downstream targets of the mevalonate pathway and their binding to several nuclear hormone receptors. Statins exert their anti-inflammatory effect by inhibiting the release of C-reactive peptide, chemokines, cytokines and adhesion molecules, which may make them a powerful addition to the dermatologic anti-inflammatory medication arsenal. Along with reducing inflammation, statins have the potential to heal chronic wounds by decreasing farnesyl pyrophosphate, facilitating vascular relaxation, promoting neovascularization and reducing bacterial load. A review of the literature elucidates that route of administration, dose and type of statin appear to impact the outcome. A better understanding of their effects at the cellular and molecular level in skin is necessary for their future use.

Statins: Lipid-lowering Drugs

Statins, HMG-CoA reductase competitive inhibitors, are a class of drugs used to lower plasma cholesterol level. They are widely used medications commonly prescribed to patients suffering from high cholesterol levels. Cholesterol plays a critical role in the human body by maintaining cell membrane integrity and physiological functions, including steroid hormone synthesis. On the other hand, high cholesterol levels are associated with pathological conditions, such as atherosclerosis.[1]

There are two groups of statins: fermentation-derived and synthetic (Box 1). Naturally derived compounds are found in oyster mushrooms and red yeast rice. In addition, statins are classified as lipophilic (atorvastatin, lovastatin, simvastatin and fluvastatin) and lipophobic (pravastatin and rosuvastatin).[2]

Box 1. Naturally occurring (e.g., derived by fermentation) and chemically synthesized statins are shown.

Naturally occurring
• Mevastatin • Lovastatin • Simvastatin • Pravastatin
Chemically synthesized
• Pitavastatin • Fluvastatin • Rosuvastatin • Atorvastatin • Cerivastatin

Statins lower cholesterol by inhibiting the rate-limiting enzyme HMG-CoA reductase. Conversion of HMG-CoA to mevalonate by HMG-CoA reductase is one of the first steps in the mevalonate pathway of cholesterol biosynthesis. In the liver, inhibition of HMG-CoA reductase results in decreased cholesterol synthesis and increased synthesis of low-density

lipoprotein (LDL) receptors, leading to an increased clearance of LDL from the bloodstream. As stated above, statins act by specifically and competitively inhibiting HMG-CoA reductase, the first committed enzyme of the HMG-CoA reductase pathway. They substitute HMG-CoA in the enzyme and subsequently reduce the production rate of mevalonate, the next molecule in the pathway, as well as isoprenoid intermediates, such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate, thus affecting the production cascade of many other important downstream compounds in cholesterol biosynthesis.[3] These two intermediates of the cholesterol biosynthesis pathway play a role in post-translational modification of proteins such as nuclear laminins; Rho, Ras, Rac and Rap, important for the regulation of actin cytoskeleton and intracellular signaling athways.

It is not surprising that statins exert pleiotropic effects. It has been shown that in addition to reducing cholesterol levels, statins also decrease inflammation, atherogenesis and cardiovascular morbidity in hypercholesterolemic patients.[4] In addition to their lipid-lowering effect, a number of recent studies suggest potential effects of statins as a novel therapeutic modality for diverse pathologic conditions, ranging from sepsis, alopecia, psoriasis and other inflammatory diseases, to keloids and wound-healing disorders.[1–4] In recent years, the immunomodulatory, antibacterial and antioxidative activities of statins have been documented.[5]

Regardless of their pleiotropic beneficial effects, statins, similarly to every systemic medication in use, induce a number of side effects, among which myopathy and liver problems represent the most serious.[2] To date, reported skin reactions related to systemic statin treatment supported by literature include localized and generalized rashes, drug reaction with eosinophilia and systemic symptoms, dermatomyositis, lichenoid dermatitis, lichen planus pemphigoides and drug-induced lupus erythematosus.[6–9] However, basic and translational research supporting the pharmacological effects of statins in different tissues, in particular skin, is still missing sufficient mechanistic and clinical evidence.

The Wound-healing Process

Wound healing is a complex biological process that includes different cell types and multiple cellular processes. It is accomplished through highly orchestrated and precise phases, including hemostasis, inflammation, proliferation and remodeling, ultimately leading to barrier restoration.[10–12] Shortly after barrier disruption, pro-inflammatory cytokines, such as IL-1, IL-6 and IL-8, and TNF-α are upregulated. After wounding, IL-1 and TNF-α are released immediately from keratinocytes and disrupted endothelial cells. After approximately 24 h, IL-6 and IL-8 reach their peak levels, primarily attracting neutrophils.[12] The release of IL-1 by keratinocytes demarcates the pro-inflammatory phase of wound healing. However, an excess of inflammation is detrimental for wound healing, underscoring the importance of the balance and spatio–temporal regulation of these factors during the wound-healing process. Anti-inflammatory cytokines, such as IL-10, are also upregulated in acute wounds. These agents inhibit the expression of pro-inflammatory cytokines and the infiltration of neutrophils and macrophages toward the site of injury. Thus, among others, they serve to limit and terminate the inflammatory phase. Epithelialization, one of the defining parameters of wound healing, is governed by these extracellular signals. IL-1 plays a direct role in re-epithelialization by inducing the expression of keratin 6/16 (K6/K16) in keratinocytes to support migration and proliferation.[12] When the execution of the highly ordered process of wound healing fails, delayed acute or chronic wounds develop. The epidermis is an important site of cholesterol biosynthesis, which is regulated by barrier function. Wounding disrupts barrier function and thereafter, in murine epidermis, the basal activity of the enzyme HMG-CoA reductase increases, as early as 1.5 h after injury.[13]

Effects of Statins on Wound Healing

Because maintenance of barrier structure and function is the most important role of skin, the effect of statins on the different phases of the healing process has been the focus of many research studies.

Statins & Inflammation

It has been shown that high plasma cholesterol levels enhance the expression of pro-inflammatory genes and cytokines, thus promoting a low-grade inflammation.[14,15] Similarly, shortly after the injury, during acute wound healing, pro-inflammatory cytokines, such as IL-1, -6 and -8 and TNF-α, are upregulated.[16] Statins have been shown to exhibit anti-inflammatory properties (Figure 1) by reducing the release of C-reactive peptide, chemokines, cytokines and adhesion molecules, as well as modulating T-cell activity.[5] Statins inhibit the transendothelial migration of leukocytes by decreasing the expression of adhesion molecules, such as ICAM-1, lymphocyte function-associated antigen-1 and monocyte chemotactic protein-1. In addition to suppressing cell infiltration into sites of injury, statins inhibit antigen presentation and downregulate MHC class II. Moreover, statins further prevent inflammation by inhibiting chemokine

release and Th1-type chemokine receptors on T cells.[17,18]

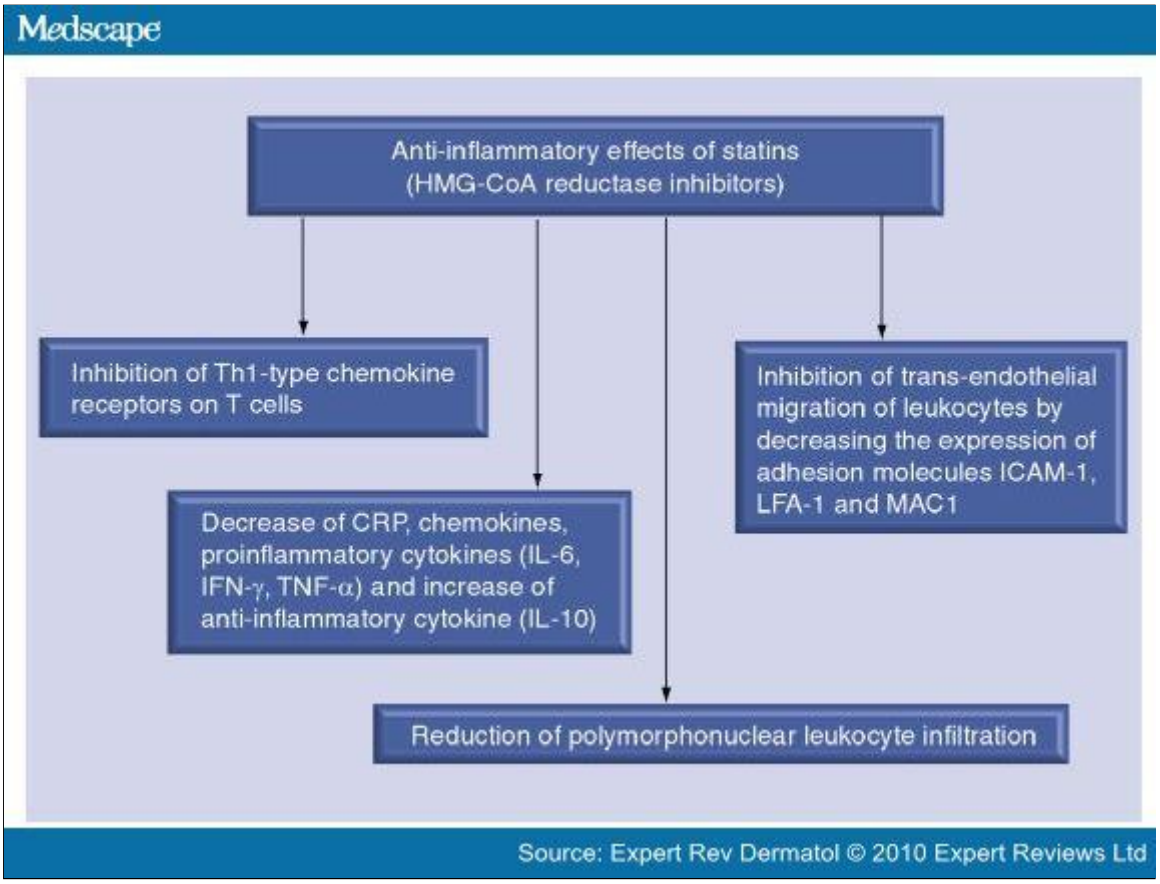

Figure 1. Mechanism of the anti-inflammatory effects of statins.
CRP: C-reactive protein.

The anti-inflammatory activity of statins results in reduced synovial inflammation and cartilage degradation in rabbit experimental osteoarthritis.[19] Studies on the immunomodulatory effects of lovastatin on rats with experimental autoimmune encephalitis found a decrease in IFN-γ and IL-6, with an increase in the anti-inflammatory cytokine IL-10. Further studies on neuro-inflammatory disorders found that statins inhibited the expression of inducible nitric oxide synthase and proinflammatory cytokines TNF-α and IFN-γ, suggesting promise for diseases such as multiple sclerosis.[20]

The anti-inflammatory properties of statins have also been translated to the dermatologic arena. It has been shown recently that simvastatin, dose-dependently and comparably to indomethacin, reduces polymorphonuclear leukocyte infiltration in a standard model of an acute local inflammation and enhances the regeneration of endothelial cells via VEGF secretion in injured arteries.[21] A study on the application of topical simvastatin to croton oil-induced contact dermatitis in male Swiss mice found reduced edema, polymorphonuclear leukocyte infiltration and erythema.[22] Additionally, there is some evidence that statins may be beneficial in reducing the severity of psoriasis. A recent abstract presented at the 2010 American Academy of Dermatology Annual Meeting (February 26–March 2, 2010, Miami, FL, USA) reported results from a retrospective chart review of 232 patients with psoriasis. Results indicated that the addition of statins to psoriasis medication (topical cortiocosteroids, topical vitamin D or ischemic treatment) tended to reverse the severity of the disease (body surface area of 5.21% with statins vs 7.43% for non-statin users; p = 0.1214). Although the results did not reach statistical significance, they are promising, especially considering the fact that psoriasis patients have increased cardiovascular risk.[23,24]

Because many dermatological disorders in addition to contact dermatitis and psoriasis, such as alopecia areata, bullous pemphigoid and lichen planus, are characterized by the presence of inflammation and excessive lymphocyte infiltration, statins may be a powerful addition to the dermatologic anti-inflammatory medication arsenal. Furthermore, chronic inflammation is a hallmark of recalcitrant chronic wounds, and therefore topical treatment with statins may represent a promising treatment approach given the fact that along with increasing inflammation, statins demonstrate a vast pleiotropic effect that can target multiple aspects of chronic wounds pathogenesis.

Statins & Epithelialization

Epithelialization is defined as a restoration of the epidermal barrier, and is often used as a major wound-healing parameter. Besides their lipid-lowering effects, statins have been shown to improve healing time and quality in different animal models of acute wound and impaired diabetic healing.[12,25,26]

The cholesterol independent pleiotropic actions of statins are diverse, and thought to be related to their binding to several nuclear hormone receptors,[27] as well as reduced isoprenylation of downstream targets of mevalonate. FPP is an important branch-point intermediate in the mevalonate pathway, essential for synthesis of sterols and isoprenylated cellular metabolites leading to cholesterol synthesis. FPP can act as a ligand for several nuclear receptors, which may participate in mediating some of the pleiotropic effects of statins.[27,28] Importantly, FPP acts as a bonafide ligand for glucocorticopid receptor, thus acting as an anti-inflammatory agent.[12,27,28] Data from our laboratory confirm a beneficial role of statins on wound epithelialization.[12] The mechanism by which statins regulate wound healing is by regulating FPP synthesis (Figure 2). We have shown that decreased levels of endogenous FPP promoted keratinocyte migration *in vitro* and epithelialization and wound closure in an *ex vivo* human culture wound-healing model, acting as an agonist for glucocorticoid receptor, and that this inhibition is mediated, in part, by keratin 6 repression.[12] Likewise, topical application of mevastatin, a HMG-CoA reductase inhibitor, promotes epithelialization in an *ex vivo* human culture wound-healing model.[12] Therefore, decreasing epidermal FPP levels using statins may have beneficial effects on epithelialization and wound healing. Our study indicates that statin-stimulated epithelialization is not related to a decrease in cholesterol synthesis or protein farnesylation, but rather to effects of mevastatin on decreased FPP levels. This finding may be beneficial for the treatment of patients suffering from chronic wounds. However, whether patients suffering from chronic wounds treated with systemic statins show better healing outcomes is not known.

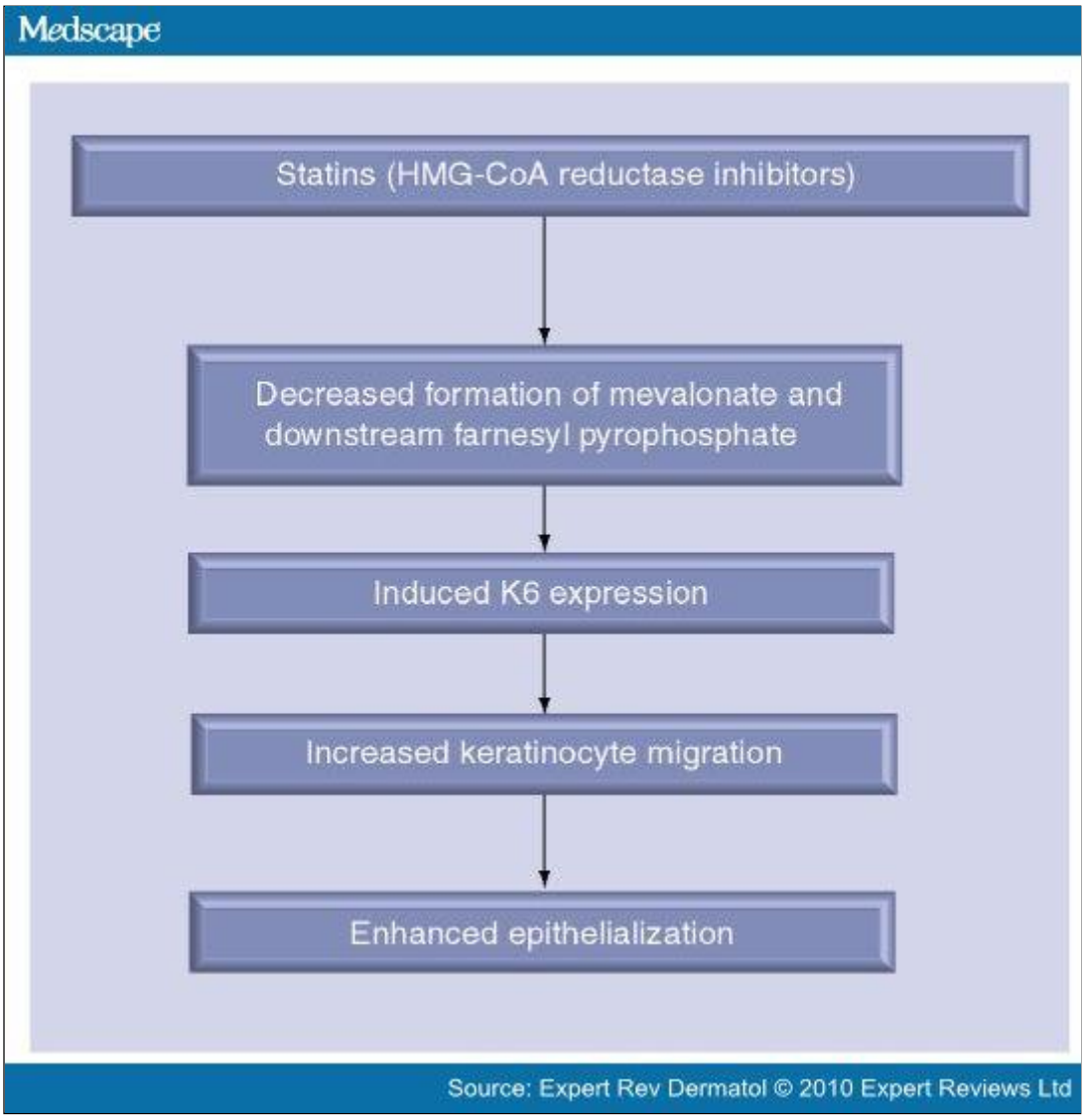

Figure 2. Positive effects of statins on epithelialization.

Another study investigating the effects of clinically relevant doses of simvastatin on colonic anastomosis in rats reported improved healing outcomes. Researchers found increased re-epithelialization, and a reduction in granuloma formation,

ischemic necrosis and inflammatory infiltration to the muscle layer in these animals.[29,30]

However, further experimental and clinical studies are needed to determine the optimal doses and develop sufficient preclinical evidence to bring these findings to clinical use for wound-healing disorders.

Statins, Angiogenesis & Diabetes

Statins have been shown to reduce cardiovascular disease in patients with diabetes, which is thought to be due to their pleiotropic effects on the vasculature. The pathogenesis of diabetic foot ulcers is complex, involving mechanical, vascular, inflammatory, oxidative, endothelial and nutritive factors.[31] The micro- and macro-vascular complications associated with diabetes mellitus have led many scientists to research the effects of statins in the treatment of impaired diabetic healing.

Statins reduce vasoconstriction by decreasing response to angiotensin-2 and by downregulating the pre-proendothelin-1 mRNA, thereby decreasing the synthesis of endothelin-1.[32,33] They facilitate vascular relaxation by blocking Rho geranyl-geranylation, which enhances the expression of endothelial nitric oxide synthase.[34,35] Statins also promote neovascularization in ischemic tissue by increasing endothelial progenitor cell activity.[36] Increasing vascular perfusion may make statins potent inhibitors of diabetic wound pathogenesis and promoters of impaired diabetic healing. Statins may stimulate angiogenesis by modulating the serine/threonine protein kinase Akt pathway, which stimulates the generation of nitric oxide.[37] In a model of severe hindlimb ischemia in streptozotocin-induced diabetic mice, treatment with statins enhanced endothelial nitric oxide synthase expression, significantly preventing auto-amputation.[38] Full-thickness wounds in streptozotocin-induced diabetic rats treated with topical atorvastatin have significantly faster wound-healing rates in comparison with control groups. The mean histopathologic and angiogenesis scores were significantly different at day 14 between statin and control groups.[25] Rates of wound healing were found to be significantly higher in the streptozotocin-induced diabetic rats treated topically with atorvastatin compared with those treated with a mixture of lanolin–vaseline and the untreated group.[25]

Impaired VEGF production in diabetic wounds is thought to be responsible for delayed healing,[39] and statins may represent a potential remedy. Other exploratory therapies that restored impaired diabetic VEGF production ameliorated delayed diabetic healing.[40] *In vitro* data show a biphasic dose-dependent effect of statins on angiogenesis associated with endothelial apoptosis and VEGF signaling. At low concentrations, HMG-CoA reductase inhibitors enhanced endothelial cell proliferation, migration and differentiation which were, by contrast, inhibited by high doses of statins.[41] In animal diabetic models, simvastatin restored the impaired wound-healing process in diabetic mice (db/db) compared with their normo-glycemic littermates. Incisional wounds on diabetic db/db mice treated with intraperitoneal simvastatin (5 mg/kg) had increased VEGF expression, enhanced nitric oxide wound content, augmented breaking strength and improved wound healing in comparison with controls.[26] Additionally, treatment with simvastatin led to enhanced quality of healed skin, with increased elasticity and decreased fibrosis. These results were verified to be the consequence of simvastatin acting through VEGF, as immunization with anti-VEGF antibody reversed the beneficial effects of simvastatin. Additionally, a slight increase in serum VEGF has been reported in hypercholesterolemic patients treated with simvastatin 20 mg/day for 4 weeks.[42] By contrast, another study reported a decrease of serum VEGF levels in hypercholesterolemic patients treated with 20 and 40 mg/day for 6 months.[43] Other studies have also demonstrated the opposite effects on VEGF with statin treatment. Higher doses of statins have been shown to inhibit angiogenesis.[44] In a study investigating wounded ob/ob mice treated with simvastatin (40 mg/kg injected intraperitoneally), researchers found a marked reduction in VEGF protein levels of wound keratinocytes.[45] This is a very high dose, considering the average dose for LDL lowering in humans is 40 mg per day, with the maximum being 80 mg per day.[101] It seems that the ability of simvastatin to enhance VEGF synthesis is dose- and time-dependent, as high doses and prolonged treatment with simvastatin did not result in an increase in VEGF.

Conversely, a small pilot study demonstrated that all diabetic foot ulcers in a group receiving 10-mg atorvastatin healed, whereas in a group receiving 80-mg atorvastatin, only 66% of ulcers healed.[46] In patients suffering from diabetic foot ulcers, daily treatment with high-dose (80 mg) atorvastatin resulted in a reduction of recurrence and the development of new neuropathic diabetic foot ulcers compared with the treatment with low-dose (10 mg) atorvastatin. A possible explanation may suggest a preventive effect of high-dose statins in diabetic foot ulcer development.

Interestingly, in another study, treatment of patients with systemic sclerosis with 10 mg of oral atorvastatin for 12 weeks showed no development of new digital ulcers after the treatment, but one patient developed a new ulcer 2 weeks after the drug discontinuation.[47] The authors suggest that atorvastatin exerts its beneficial effects by increasing the proliferation and mobilization of bone-marrow-derived circulating endothelial precursors. Although in both studies administration of

statins showed protective effects against ulcer development, it is clear that statin effects on impaired diabetic wound healing proceeded through different mechanisms, and is still to be fully explored.

In addition to ulcer development, preliminary observational data suggested that therapy with statins may protect against the development of diabetic peripheral sensory neuropathy. However, this data needs further confirmatory evidence, preferably randomized clinical trials.[48]

In summary, statins may play a role in the prevention and treatment of diabetic foot ulcers, and possibly other non-healing chronic wounds, by decreasing development of neuropathy, and increasing neovascularization, perfusion and, ultimately, oxygenation to ischemic diabetic wound tissue (Figure 3).

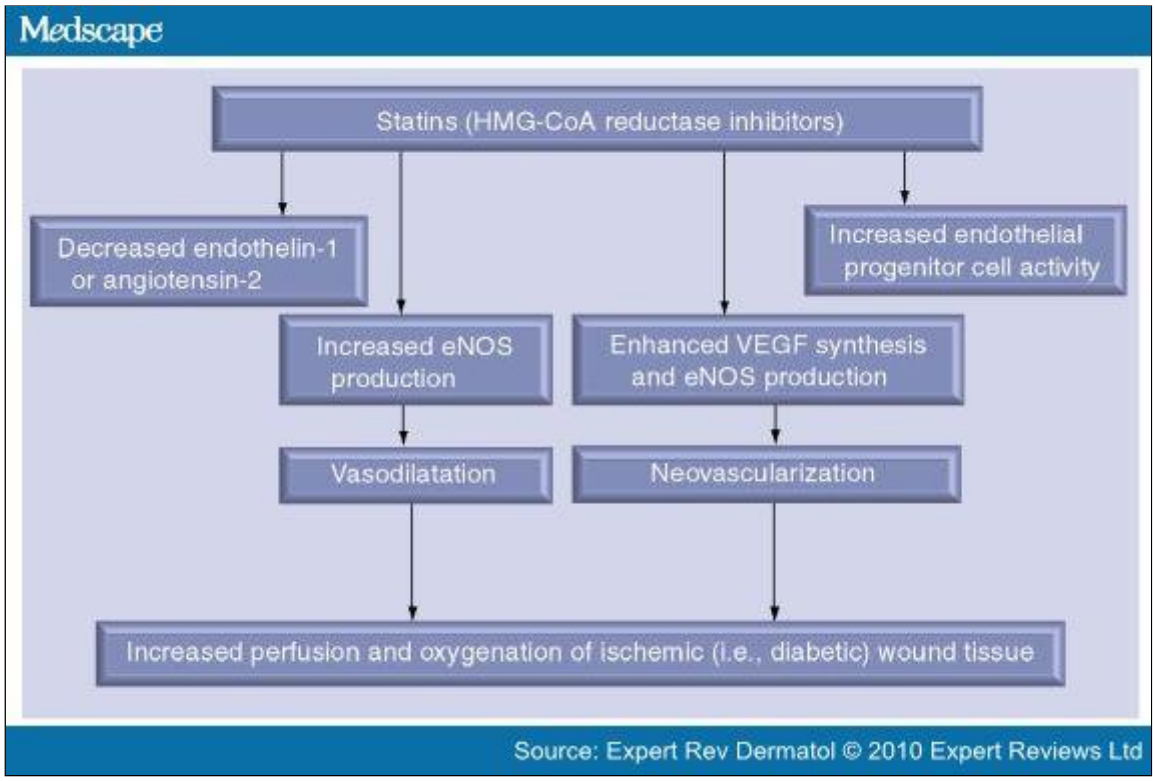

Figure 3. The effect of statins on perfusion and oxygenation of ischemic wounds.

Statins & Bone Healing

Studies employed in the last few years have shown that statins may have a beneficial effect on bone healing. In preclinical animal models, statins were found to increase fracture healing by reducing structural defects and increasing mineralization.[49–51] They have been shown to have anabolic effects on bone metabolism (Figure 4), likely through activation of bone morphogenic protein, a growth factor targeting bone formation,[52] and TGF-β1.[53] Statins decreased osteoblast apoptosis and inhibited osteoclast activity, thus controlling the bone remodeling process.[54,55] A study on the use of simvastatin-coated titanium stabilization wires in rat tibial fractures showed an improvement in fracture healing at high doses.[29] Another study investigating topical application of fluvastatin around titanium implants placed in rat tibiae demonstrated increased bone formation around implants.[56] However, a prospective, double-blind, randomized controlled trial on trauma patients receiving simvastatin 20 mg per day for 12 weeks found no effect on the rate of fracture healing.[57] As with wound healing, the effect of statins on fracture healing is likely dose- or route-dependent. A study examining the difference between transdermal (0.1–5 mg/kg/day) or oral (5–25 mg/kg/day) for 5 days after the fracture found that low doses of transdermal lovastatin accelerated healing. However, oral doses of statins required to produce any effect on fracture healing were tenfold higher.[51] Another study found that daily subcutaneous simvastatin injections had no effect on mouse femur fracture healing, but a dramatic effect on the biomechanical parameters of fracture healing when simvastatin was applied directly to the fracture area.[58] Local application of a nanobead preparation of lovastatin was also shown to be beneficial in hastening fracture healing in rats.[59] However, orally administered simvastatin at 10 and 30 mg/kg/day had a negative anabolic effect on callus formation in rabbits' fracture healing, whereas lower doses did not show any effect in the early stages of fracture healing.[60] Research conducted so far indicates that lipophilic statins are more effective in enhancing the bone healing.

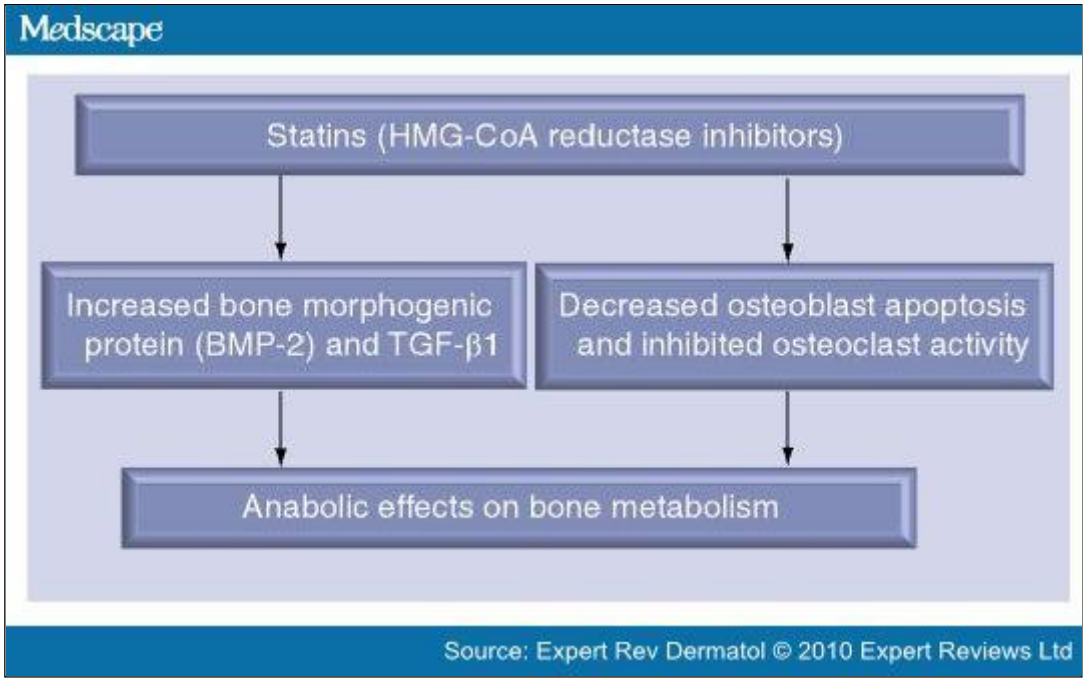

Figure 4. An anabolic effect of statins on bone metabolism.

Although the effects of statins on bone healing are inconsistent, the differences in outcomes can be explained by different types of statins being used, a different route of administration and different concentrations. Taken together, statins show a beneficial effect on fracture healing; however, further preclinical and clinical trials are needed in order to determine a route and time of application, optimal dose, and duration that will lead to faster bone healing.

Statins & Bacterial Infection

Bacterial infection of skin wounds is a common problem that causes an acute inflammatory response and contributes to delayed acute and chronic wound healing. Emerging evidence suggests that statins may exert beneficial effects in treating and preventing different infections.[61] Patients treated with statins had a decreased rate of severe sepsis and infection, along with decreased mortality.[62,63] Recent findings showed surprising antimicrobial effects of statins *in vitro*.[64]

The latest evidence suggests that statins have antibacterial effects, in addition to their pleiotropic roles in promoting healing and combating inflammation. Studies have found that statins reduce perioperative sepsis, a major cause of death in intensive care units.[2] Mice pretreated with simvastatin for 3 and 18 h before induction of sepsis had a fourfold increased survival rate.[65] Additionally, statin treatment at 6 and 18 h after sepsis induction also increased survival rates.[66] Although prospective data is lacking in humans, a retrospective study on patients prescribed statins before hospital admission found decreased septicemia-related mortality rates.[67]

Besides protecting from bacteria in the circulation, statins have also been shown to have additional antibacterial properties. Rat open skin wounds infected with Gram-positive and -negative bacteria were treated with topical simvastatin (10 mg/ml) or saline. Along with lower expression of TNF-α and IL-1β, researchers found infection in only one out of seven rats in the simvastatin treated group, while all rats in the saline group showed polymicrobial infections.[68] The ability of statins to reduce infection was also apparent in a study assessing the use of statins on methicillin-susceptible and -resistant *Staphylococcus aureus*, and vancomycin-sensitive and -resistant enterococci blood culture isolates. Researchers treated isolates with simvastatin and fluvastatin and found that both demonstrated antimicrobial activity. They found a significant antimicrobial effect of simvastatin, whereas fluvastatin showed a lower effect.[64] However, they noted that prokaryote HMG-CoA reductase has approximately 10,000-times less affinity for statins than human/eukaryote HMG-CoA reductase,[69] so it is unlikely that the antimicrobial effect works through this mechanism. Additionally, the MICs achieved in this study (29.2 mg/l for simvastatin against methicillin-susceptible *S. aureus*) were much higher than the concentration attained in adults taking a 40-mg oral dose of simvastatin, which is approximately 0.0209 mg/l.[70] In patients suffering from chronic wounds, bacterial burden adds to the pathogenesis of non-healing, and treatment with statins may be helpful for combating bacterial load, in addition to enhancing epithelialization and healing. Therefore, the *in vitro* antimicrobial effect of statins, especially simvastatin, may be applicable to patients, but future *in vivo* testing is necessary.

Expert Commentary

It is clear that statins have the potential to make a tremendous impact on the medical field. In addition to their lipid-lowering effects, statins have pleiotropic effects that extend far beyond the cardiovascular system. Along with their immunomodulatory and antibacterial properties, statins have been shown to decrease oxidative stress, improve endothelial and microvascular function, combat inflammation and improve healing outcomes.[5,12,71–73] However, a review of the literature published so far elucidates the fact that the route of administration, dose and type of statin used to treat the same pathological condition appear to have different impacts on the outcome. The low doses of topically applied statins seem to have beneficial effects, whereas topical statins applied in high doses appear to be detrimental. On the other hand, higher doses of systemically administered statins show longer-lasting beneficial effects. In addition, proper timing of treatment seems to be important in targeting specific pathological processes for any given disease, thus achieving the maximal effects.

Statins are not only shown to enhance healing in both skin and bone, but are also shown to reduce scar formation.[12,26,45,68] They inhibit the expression of connective tissue growth factor (CTGF), a downstream mediator of TGF-β-induced fibrosis, which is known to play a role in scar formation by inducing the conversion of fibroblasts into myofibroblasts.[74] In addition to *in vitro* data, an *in vivo* model of rabbit-ear wounding treated with simvastatin, lovastatin and pravastatin also had reduced CTGF expression and hypertrophic scar formation, but only at low doses. A study examining the effects of lovastatin treatment on cultured human tendon fibroblasts found decreased CTGF transcription, α-smooth muscle actin expression and collagen gel contraction.[75] Simvastatin at different concentrations (5, 10 and 20 μM) has also been effective in reducing CTGF protein expression in TGF-β1-stimulated human corneal fibroblasts.[76]

Because of their positive safety profile and relative inexpensiveness, statins may prove to be important across many medical specialties, in addition to cardiology (Table 1). Before we employ statins as a novel treatment strategy, a better understanding of the effects of different statins at the cellular and molecular level in skin may allow for the development of new and more specific drugs for a medical intervention. A combination of mechanistic and clinical studies are needed for further evidence that statins can be added as a new therapeutic option for wound-healing disorders, keeping in mind their positive effects on all phases of wound healing, as well as for other dermatological conditions.

Table 1. Articles investigating the effects of statin therapy on multiple healing outcomes in human subjects.

Author	Methods	Conclusions	Ref.
Anti-inflammatory			
Brauser	Retrospective chart review of 232 patients with psoriasis	Addition of statins to psoriasis medication tended to reverse the severity of the disease (BSA of 5.21% with statins vs 7.43% for nonstatin users; p = 0.1214)	[24]
Angiogenesis/wound healing			
Park *et al.*	22 hypercholesterolemic patients treated with simvastatin 20 mg/day for 4 weeks	Slight increase in VEGF	[42]
Giurgea *et al.*	107 hypercholesterolemic patients treated with 20 and 40 mg/day for 6 months	Significant decrease in VEGF after 6 months (-79.7%; p < 0.001)	[43]
Johansen *et al.*	13 diabetic patients with neuropathic DFUs <4 months randomized to receive either 10 or 80 mg atorvastatin for 6 months in addition to conventional DFU care	All ulcers healed in group receiving 10 mg of atorvastatin compared with six out of nine ulcers in the group receiving 80 mg. However, there were fewer recurrences and new ulcers in the 80-mg dose group	[46]
Kuwana *et al.*	Prospective study of 14 patients with systemic sclerosis treated with 10 mg per day of atorvastatin for 12 weeks	No new ulcer development during treatment	[47]

Davis *et al.*	Observational cohort study of Fremantle Diabetes Study participants taking fibrates and statins	Statins or fibrates may protect against the development of diabetic peripheral sensory neuropathy	[48]
Fracture healing			
Patil *et al.*	Prospective, double-blind, randomized controlled trial on 62 trauma patients receiving simvastatin 20 mg per day for 12 weeks	No significant difference between bone mineral density or bone biochemical markers; no effect on fracture healing	[57]
Sepsis			
Dobesh *et al.*	Retrospective cohort study on 188 patients with severe sepsis	Mortality reduction with APACHE II scores higher than 24 (mortality rate 32.3% in statin group vs 57.5% in non-statin group, p = 0.031). Multivariable regression model showed statin had a protective effect (odds ratio: 0.42; 95% CI: 0.21–0.84; p = 0.014)	[62]
Donnino *et al.*	Secondary analysis of a prospective, observational cohort study in ED with approximately 50,000 annual visits	Hospitalized patients with infection who received statin therapy had a significantly lower in-hospital mortality compared with patients who did not receive a statin	[63]
Kruger *et al.*	Retrospective cohort analysis of 438 patients requiring hospital care for an episode of bacteremia	Reduction in all-cause hospital mortality (1.8 vs 23.1%; p = 0.0002) and death attributable to bacteremia (1.8 vs 18.3%; p = 0.0018) in patients on statins	[67]

BSA: Body surface area; DFU: Diabetic foot ulcer; ED: Emergency department.

Five-year View

Although statins are used systemically as lipid-lowering drugs, there is an unexplored but high potential for their topical use as a treatment modality in wound healing and a variety of skin-related diseases. Systemic therapy with statins has shown beneficial effects on different diseases, but the therapeutic dose for long-term treatment of healing and other skin disorders, where statins can exert their positive effects, is still unknown. Topical application of statins shows promising results, and hopefully will be explored further in the next 5 years. However, there are still a lot of questions that need to be addressed with regard to use of statins. For example, do all statins have the same effect on skin cholesterol metabolism? It is clear that statins also exert cholesterol-independent effects on skin, and it would be important to elucidate which statins exert a cholesterol-dependent effect, and which exert a cholesterol-independent effect. Additionally, what is the optimal statin drug to be used that will lead to the best outcome in regard to a specific disease or state of disease? What would be the optimal time for treatment, best dose and duration of the treatment in order to achieve maximal effect? High-quality and evidence-based *in vitro* and *in vivo* studies are needed to address the best statin drug, appropriate dose, the best administration route and duration of treatment, and to determine to what extent different pleiotropic effects of statins contribute to the clinical benefits of statin therapy.

Future research endeavors should focus on exploring the mechanism of action by which HMG-CoA reductase inhibitors may act to ameliorate skin conditions and promote wound healing. Thus, in the future, topical application of statins may be safe and clinically useful as drugs for the treatment of patients suffering from inflammatory skin diseases and chronic refractory wounds that do not respond to standard modes of treatment. Furthermore, it will be important to learn if statins, in addition to already known therapy, can help ameliorate different inflammatory diseases. Understanding the mechanisms through which statins exhibit their effects may lead to the identification of potential new therapeutic targets to promote wound healing, fight skin infection and treat acute and chronic inflammatory skin disorders.

The addition of statins to the armory of medications used to treat diverse skin conditions will impact acute and acquired diseases either mediated or not mediated by cholesterol.

It is important to mention that a recently published study demonstrated corrected hair and skin abnormalities in Epi-Insig

DKO mice treated with simvastatin. These mice have epidermal specific ablation of genes encoding Insig-1 and -2, proteins required for the feedback inhibition of cholesterol synthesis.[77] In respect to this data, it seems that statins will also have a beneficial effect on genetic diseases, in which mutations in enzymes involved in cholesterol biosynthesis lead to multiple cutaneous abnormalities.

Sidebar

Key Issues

- Statins, in addition to reducing cholesterol levels, exert pleiotropic effects.
- The anti-inflammatory properties of statins includes reducing C-reactive peptide release and decreasing in chemokines, cytokines and adhesion molecules, as well as modulating of T-cell activity.
- Skin is a site of cholesterol synthesis, and therefore statins may play a role in the treatment of healing disorders and diverse skin conditions where the skin barrier is disrupted.
- Recent studies support the role of statins in diseases that are not mediated by cholesterol, inflammatory diseases and diseases with excessive lymphocyte infiltration, as well as hereditary diseases involving genes important for cholesterol biosynthesis.
- Statins promote epithelialization of cutaneous wounds by decreasing epidermal levels of farnesyl pyrophosphate, an intermediate in the cholesterol biosynthesis pathway, thus increasing keratinocyte migration *in vitro*and *ex vivo*.
- Statins promote vascular perfusion by restoring VEFG production. They have been shown to have a beneficial effect on delayed wound healing in diabetic animals, as well as in diabetic patients suffering from non-healing ulcers.
- There are conflicting data on the role of statins with regard to bone healing, most of which supports the role of statins in acceleration of fracture healing.
- The latest evidence suggests that statins have antibacterial effects that can be beneficial for wound healing and other skin disorders where superinfection with different bacterial strains is a common complication that leads to delayed healing.
- Statins represent a promising future therapy for various skin disorders. However, the role of statins on different cell types present in skin is yet to be explored, and the effects of different statins, the appropriate dose, duration and route of administration demands thorough further investigation.

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