A REVIEW ON THE HEALING EFFECT OF STATINS IN DIABETIC WOUND

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ABSTRACT
Statins, a HMG CoA reductase inhibitor, have a vital role in diabetic wound healing which is a dynamic and complex biological process including coordinated events such as haemostasis, inflammation, proliferation, revascularisation and remodelling. Complications of diabetic wound healing includes neuropathy, corns, calluses, foot-ulcer, infections, poor circulation, dry and cracked skin, nail disorders, hammer toes, bunions, charcot foot and amputation. Statins have the potential to heal diabetic wounds via pleotropic effects. Pleotropic effects of statin include anti-inflammatory, anti-oxidative, immunomodulatory, anti-proliferative, antithrombotic, antibacterial activities, improving endothelial dysfunction, improving microvascular function and reperfusion.

Keywords: Diabetic wound; Farnesylpyrophosphate; Healing; Neovascularisation; Pleotropic effects; Statins

INTRODUCTION
Diabetic wound is the major complication of diabetes mellitus, a metabolic disorder characterized by hyperglycemia. Many clinical trials have proved that statins have beneficial effect on diabetic wound healing. Statins are a class of drugs whose primary action is to lower cholesterol levels by inhibiting the enzyme HMG CoA reductase. Diabetic wound healing is accelerated by the pleotropic effects of statins, the phenomena of one gene being responsible for or affecting more than one phenotype characteristic. Pleotropic actions are related to reduce isoprenylation of downstream targets of the mevalonate pathway and their binding to several nuclear hormone receptors.

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Epidemiology
The prevalence of diabetes is rapidly increasing all over the world. Over the past three decades, the status of diabetes has changed from mild disorder of the elderly to the major cause of mortality and morbidity affecting youth and middle-aged. Among persons diagnosed as having diabetes mellitus, the lifetime risk of developing a diabetic wound is estimated to be 15 per cent.
Based on recent studies, the annual population based incidence ranges from 1 percent to 4.1 per cent and prevalence ranges from 4 per cent to 10 percent. This suggests that the lifetime incidence may be as high as 25%. The major increase in mortality among diabetic patients over the past 20 years is considered to be due to the development of macro and micro vascular complications, including of the wound healing process. Important risk factors for diabetic wound include age (≥ 50 years), duration of diabetes (4 to 8 years), rural location, oral hypoglycemic treatment, insulin treatment and tobacco use.

**Pleotropic Effects of Statin**

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. Studies revealed that statins such as atorvastatin, simvastatin, mevastatin and pravastatin have positive effect on diabetic wound healing.

**Role of Farnesyl Pyrophosphate in Wound Healing**

Statins have the potential to heal chronic wounds by decreasing farnesyl pyrophosphate (FPP), facilitating vascular relaxation, promoting neovascularization and reducing bacterial load. Farnesyl pyrophosphate, a key intermediate in the mevalonate pathway and protein farnesylation, can act as an agonist for several nuclear hormone receptors. FPP inhibits wound healing by acting as an agonist for glucocorticoid receptor (GR). Elevation of endogenous FPP by squalene synthetase inhibitor Zaragozic acid A(ZGA) results in activation and nuclear translocation of GR, a known wound healing inhibitor.

**Statin and Endothelial Dysfunction**

An important characteristic of endothelial dysfunction is the impaired synthesis, release and activity of endothelial derived nitric oxide(NO). NO released from nitrosothiols in haemoglobin or from endothelial cells, diffuses into smooth muscle cells and binds to guanylatecyclase (GC), which results in GC activation. Activated GC cleaves two phosphate groups from guanosine triphosphate (GTP) and forms cyclic guanosine monophosphate (cGMP). cGMP phosphorylate proteins include the smooth muscle contractile protein called myosin. Relaxation of myosin results in vasodilation.
Statins are able to increase NO synthesis and improve blood flow dependent upon on endothelium. Endothelium derived NO mediates vascular relaxation, vascular smooth muscle proliferation and inhibits platelet aggregation.

**Statins and Anti-Inflammatory Effects**

Statins produce anti-inflammatory effects by inhibiting the release of C reactive peptides, chemokines, cytokines and adhesion molecules as well as modulating T-cell activity. It inhibits trans-endothelial migration of leukocytes by decreasing the expression of adhesion molecules such as Intercellular Adhesion Molecule-1 (ICAM-1), lymphocyte function–associated antigen-1 and monocyte chemotactic protein-1.

**Statins and Neovascularisation**

Statins promote neovascularisation in ischemic tissue by increasing endothelial progenitor cell activity. Statins may stimulate angiogenesis by modulating the serine threonine protein kinase Akt pathway which stimulate the generation of NO. Statins increase the level of angiopoietin.

**Statins and Thrombosis**

The fibrinolytic system is involved in parts of wound healing process and deficiency of thrombin–activatable fibrinolysis inhibitor (TAFI) results in delayed wound closure. Statins enhance antifibrinolytic effect through TAFI. It have the capacity to decrease global fibrinolytic activity of the blood to decrease activity of Plasminogen Activator Inhibitor-1 (PAI-1) and inhibit thrombin generation.

**Statins and Platelet Function**

Statins inhibit platelet expression of the protease activated receptor -1(PAR-1) thrombin receptor, thus inhibit platelet activation and thrombin generation. It increases the synthesis of nitric oxide which is an inhibitor of platelet aggregation. Additional mechanism is the reduction in Thromboxane A2(TXA2) synthesis, thus inhibit activation of new platelets and also platelet aggregation.
Statins and Antibacterial Action

In patients suffering from chronic wounds, bacterial burden adds to the pathogenesis of non-healing of diabetic wound and treatment with statins may be helpful for combating bacterial load in addition to enhancing epithelialisation and healing. Statins mediate the reduction of cholesterol level within phagosomal membrane, and promote phagosomal maturation and autophagy.

Statins and Wound Healing

Impaired production and release of VEGF (Vascular Endothelial Growth Factor) in DM causes altered angiogenesis and thereby impaired wound healing. Recent studies clearly showed that simvastatin was able to improve the pattern of VEGF production by hypoxia-inducible factor-1alpha upregulation in endothelial cells and significantly ameliorate wound repair by measurement of VEGF mRNA, protein expression and enhanced NO wound content.

Statins and Ages

Advanced glycation end products(AGEs) worsen diabetes by speeding up oxidative damage to cells and blood vessel complication. AGEs and their receptor (RAGE) play an important role in the pathogenesis of diabetic complication. Statins, due to their cholesterol lowering effects, increase the soluble RAGE level by inducing RAGE shedding and prevent the development of RAGE-mediated pathogenesis.

Atorvastatin

Atorvastatin display pleiotropic properties and exert their benefits through the inhibition of vascular smooth muscle cell (VSMC) proliferation. In high doses (80 mg) it inhibits synthesis of prenyl radicals which results in the inhibition of cell proliferation. It also inhibits the production of Monocyte Chemoattractant Protein (MCP-1) and Interleukin-8 (IL-8) and these effects were attributed to the inhibition of protein prenylation.

In low doses (10 mg) itself atorvastatin produces anti-inflammatory effect by inhibiting the production of cytokines, adhesion molecule and fibronectin. It cause down regulation of endothelial Intercellular Adhesion Molecule-1 (ICAM-1). Statins are capable of increasing the expression and activity of endothelial nitric oxide synthase (eNOS).

Administration of high dose atorvastatin was associated with significant decrease in C reactive protein (CRP). Statins reduce IL-6 - induced CRP production directly in hepatocytes via inhibition of protein geranylgeranylation. Statins reduce the interleukin-6 induced activation and phosphorylation of Signal Transducer and Activator of Transcription-3 (STAT-3).

Simvastatin

Simvastatin improve the VEGF production and secretion enhances angiogenesis and thereby wound healing. It also improves the NO wound content. It decreases the leukocyte endothelial cell interaction by reducing leucocyte infiltration.
and provides an endothelium protective effect. It increases reepithelialisation, decreases granuloma formation and inflammatory infiltration and thus decreases ischaemic necrosis. In vivo administration of simvastatin inhibits leucocyte rolling, adherence and transmigration in acute inflammatory states. This effect was found to be mediated by down-regulation of P-selectin expression on endothelial cells and is also consistent with the down-regulation of CD-18 on stimulated polymorphonuclear cells. It causes up-regulation of thrombomodulin, decreases blood coagulation and thereby microthrombus formation. It also increases dermal blood flow.

**Mevastatin**

Mevastatin reverses the effect of zaragozic acid, a squalene synthase inhibitor. It decreases endogenous Farnesyl pyrophosphate and inhibits glucocorticoid receptor, thus promoting wound healing. It also enhances epithelialisation.

**Pravastatin**

Pravastatin mainly exhibits anti-inflammatory and antioxidant properties. It limits expression of adhesion of adhesion molecule and maintains endothelial function.

**CONCLUSION**

Statins, HMG-CoA reductase inhibitor, the cholesterol lowering agent possess diabetic wound healing effect due to its pleotrophic action. Statins have the same mode of action via inhibition of HMG-CoA reductase activity but differ between each other in the extent of this inhibition, which leads to different levels of LDL cholesterol lowering. Due to this fact, not only cholesterol synthesis is inhibited, but also formation of inflammatory proteins, substances associated with smooth muscle cells proliferation etc. Since pleotrophic effects of statins is expanding rapidly, it is essential to establish their relative biological significance and clinical relevance. Pleotrophic effect may vary among statins. Clinical studies were performed on atorvastatin, simvastatin, mevastatin and pravastatin. These results revealed that simvastatin possesses more healing effect in a diabetic wound.

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