Role of Atorvastatin on Endothelial Cells and Endothelial Progenitor Cells in Cardiovascular Disease

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ABSTRACT

The endothelium plays a key role in haemostatic balance. Endothelial progenitor cells (EPCs) are involved in the maintenance of endothelial haemostasis and in the process of blood vessel formation. Cardiovascular disease (CVD) is associated with reduced numbers and dysfunction of endothelial cells (ECs) and EPCs. Inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase helps in restoring of EPCs and improvement of vascular function. This review underlines the pleiotropic effects of atorvastatin on ECs and EPCs.

INTRODUCTION

Cardiovascular disease (CVD) is a most important health problem in the industrialized world for the past few decades (Vijaya Anand et al., 2008). Although there have been many research still people suffer from CVD. Atherosclerosis is a type of CVD and multifactorial disease determined by an inflammatory reaction, which is associated with endothelial dysfunction. It happen when there is impairment in endothelial cells (ECs) and endothelial progenitor cells (EPCs) which may be resulting in cardiovascular outcomes. Statins [3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co-A) reductase inhibitors] therapy is well established effective means of reducing risk of CVD (Vijaya Anand et al., 2009).

ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction contributes to several disease processes, as occurs in hypertension, hypercholesterolemia, diabetes and it can likewise result from exposure to environmental agents, such as smoking tobacco products and air pollutants. Endothelial dysfunction is one of the initial manifestations of coronary artery disease, occurring even in the lack of angiographic evidence of disease (Libby, 1995). The primary feature of endothelial dysfunction is the diminished synthesis, release and activity of endothelial derived nitric oxide (NO) and it has been demonstrated to inhibit several components of increasing vasodilators and NO factors on endothelial function of the atherogenic process. NO acts as an essential role which assists in the proper functioning of endothelial cells. Vascular relaxation can occur by NO derived from endothelium (Ignarro et al., 1987), but if there is impairment in endothelium may affect production of NO, results in decreased proliferation of vascular smooth muscle cells (Garg and Hassid, 1989), and also decreased inhibition of platelet aggregation (Radomski et al., 1992) and endothelial-leukocyte interactions with hypercholesterolemia subjects can induce microvascular dysfunction (Gauthier et al., 1995). Inactivation of NO by superoxide anion (O₂⁻) confines the bioavailability of NO and leads to nitrate tolerance, hypertension and vasoconstriction (Harrison et al., 1997).
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Statins could restore endothelial function, relatively, by lowering serum cholesterol levels. Conversely, in a few studies with statins, restoring of endothelial function occurs before significant reduction in serum cholesterol levels (Treasure et al., 1995 and O’Driscoll et al., 1997), which signifying that there are some more beneficial effects such as bioavailability of vasodilators, increase of NO other than that of cholesterol reduction. Certainly, statins increase endothelial NO formation by stimulating and upregulating endothelial nitric oxide synthase (eNOS) (Kureishi et al., 2000). Statins have been shown to restore the activity of eNOS in the presence of hypoxia, which shows better improvement in restoring of endothelial cells (Laufs et al., 1997) and ox-LDL cholesterol (Laufs et al., 1998). Additionally, statins increase the expression of tissue plasminogen activator antigen (Essig et al., 1998) which helps in breakdown of blood clots and also inhibit the expression of endothelin-1 as it cause vascular remodeling (Hernandez–Perera et al., 1998) thus helps in the production of EPCs.

Increase of blood glucose levels can damage endothelial function. Atorvastatin treatment with metformin for 6 weeks partially prevented the glucose-induced impairment of endothelium-dependent dilation in patients who received treatment (Tousoulis et al., 2010). Atorvastatin therapy was associated with significant reduction in plasma thiobarbituric acid reactive substances and lipid hydroperoxides levels, which was not noted in subjects treated with statins such as pravastatin (Murrow et al., 2012). A study by Zhang et al. (2010) demonstrated the complex mechanism of action of statins explaining their long-term beneficial effects in maintaining the morphological and functional integrity of vascular EC.

Another study demonstrates arterial stiffness and its relation to endothelial dysfunction. There was a reduction in the reflection index with treatment of N-acetylcysteine and atorvastatin signified the improvement of endothelial dysfunction. Further, decrease in high-sensitivity C-reactive protein (hsCRP) and malondialdehyde (MAD) was also observed with the above coupled treatment (Kudaravalli et al., 2011). Jaumdally et al. (2011) demonstrated that abnormal endothelial, angiogenesis and platelet functions were improved with atorvastatin treatment in diabetic patients. Treatment increased angiopoietin-2 in all groups, angiopoietin-2 increased 3-fold in non-diabetic subjects, it increased 2-fold in diabetic subjects. It has been suggested that other advantages of atorvastatin are to raise the levels of growth factor angiopoietin-2 to normal levels.

The pleiotropic effects of statins are partially mediated through up-regulation of small GTP-binding protein dissociation stimulator (SmgGDS) with a resulting Rac1 degradation and decreased oxidative stress. Atorvastatin helps in the enhanced SmgGDS expression in cultured human umbilical venous EC (HUVEC) and human aortic EC (Minami et al., 2016). Treatment of HUVEC with atorvastatin (1-10 microM) caused a clear increased expression of Tissue transglutaminase (tTgase) in both permeabilised and non-permeabilised HUVEC. By stimulating the expression of tTgase, statins may encourage tTgase-mediated stabilisation of the basement membrane (Soehnlein et al., 2004).

Plasminogen activator inhibitor type-1 (PAI-1) plays a critical role in vascular pathophysiology both at the intra- and extravascular levels. Atorvastatin and fluvastatin favorably modulate the expression of fibrinolytic factors produced by human EC (Izidoro-Toledo et al., 2011). Rosuvastatin and atorvastatin significantly reduced Rho-associated coiled-coil containing protein kinase (ROCK) activity. There was a significant relationship between ROCK activity and flow-mediated dilation for both statins. Short-term therapy of atorvastatin or rosuvastatin inhibits ROCK activity independent of decrease in the levels, cholesterol and also improves endothelial dysfunction in patients with atherosclerosis (Lopez et al., 2000).

Atorvastatin treatment of human umbilical vein EC produced a time-dependent increase in GTP loading of all Rho GTpases and influence the translocation of small Rho GTpases from the cell membrane into the cytoplasm. Atorvastatin significantly attenuates thrombin-induced human umbilical vein EC permeability, elevated VE-cadherin targeting to cell junctions and preserves junction integrity. Atorvastatin treatment also increases the activator protein-1 DNA binding mediated at the level of small GTp and also inhibits isoprenylation of Ras or Rho, accompanied by decreased in the inflammatory response. It also preserves the integrity of the cellular junction (Dichtl et al., 2003).

ENDOTHELIAL PROGENITOR CELLS

EPCs are hematopoietic stem cells, which are precursor cells that express some cell surface markers characteristic of mature endothelium (Liu et al., 2011). Vascular endothelium plays an essential role in maintaining and regulating vascular tone, structure, growth, fibrinolysis, and homeostasis, thus protecting the vessels from inflammation, immune response, thrombosis and CVD. Thus, alterations in EPCs may result in CVDs (Xiao et al., 2013)

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EPCs are a subtype of hematopoietic stem cells, which contribute to the restore of injured endothelium. EPCs enhance ischemia-induced revascularization (Fuyong Du et al., 2012), accelerate re-endothelialization following carotid balloon injury (Wan et al., 2010; Murohara et al., 2000) and enhance postschismic cardiac function (Walter et al., 2002). Landmesser et al. (2004) finding reveals that increased ENO availability is necessary for statin-induced enhancement of endothelial progenitor cell mobilization, neovascularization, left ventricular dysfunction, myocardial neovascularization and survival after myocardial infarction (MI). Bioavailability of ENO after MI possibly represents a significant therapeutic target in heart failure patients after MI and mediates positive effects of statin therapy.
after MI. In patients with stable coronary heart disease (CHD), administration of statins for four weeks improved the number of circulating EPCs and enhanced functional capacity in stable CHD patients (Kawamoto et al., 2001). Minami et al. (2009) study demonstrated that lipid lowering therapy with atorvastatin increased EPC numbers and decreased microRNA-221/222 levels in CHD patients. Atorvastatin pretreatment significantly increased the amount of EPCs after cardiopulmonary bypass surgery, by a mechanism independent of plasma levels of cytokines and cholesterol (Vasa et al., 2001).

Atorvastatin, also inhibited homocysteine-induced dysfunction and apoptosis in EPCs, which may be related to its effects on suppressing oxidative stress through up-regulation of Akt/eNOS and down-regulation of p38MAPK/caspase-3 signaling pathway (Minami et al., 2009). Atorvastatin also promoted homocysteine-induced activation of NADPH oxidase as well as the over expression of Nox4 mRNA and p-p38MAPK protein indicating, possibly favorable effects on EPCs function (Spadaccio et al., 2010). Atorvastatin improved proliferation of EPCs (Bao et al., 2010). Consumption of 40 mg dose of atorvastatin could also decrease the levels of circulating endothelial-derived microparticles and increase the number of circulating EPCs in ischemic cardiomyopathy patients when compared to a 10 mg dose of atorvastatin. This effect may be independent of the decrease of lipids, oxLDL and hsCRP (Hibbert et al., 2011). EPCs migrate from the bone marrow into the peripheral circulation to sites of injured endothelium and are involved in endothelial repair and vascular regeneration (Huang et al., 2012). During these processes, EPCs are exposed to oxidative stress condition, a crucial pathological condition, which occurs during vascular injury and limits the efficacy of EPCs in the repair of injured endothelium (Li et al., 2015).

CONCLUSION

Atorvastatin enhances the restoring of endothelial cells, which helps in improved vascularisation in patients with CVD. It augments the production of endothelial progenitor cells, thus helps in restoring endothelial cells for prevention of CVD. Atorvastatin may play a beneficial role in endothelial function and better clinical outcomes in patients undergoing coronary interventions.

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