Mitohormesis: another pleiotropic effect of statins?

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This editorial refers to ‘Opposite effects of statins on mitochondria of cardiac and skeletal muscles: a ‘mitohormesis’ mechanism involving reactive oxygen species and PGC-1‘, by J. Bouitbir et al., on page 1397

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are some of the most widely prescribed drugs in the world for the primary and secondary prevention of cardiovascular disease. Most, if not all, of the benefits of statins could be attributed to the reduction in serum cholesterol levels. Indeed, decreases in LDL-cholesterol with statin therapy correlate almost linearly with reductions in cardiovascular events. In addition, recent experimental studies and clinical trials suggest that statins may exert some of their cardiovascular benefits beyond cholesterol lowering, i.e. pleiotropic effects. Some of these non-cholesterol benefits include improvement in endothelial function, anti-inflammatory and antioxidative effects. Whether these pleiotropic effects of statins actually contribute to cardiovascular risk reduction in clinical trials, however, remains to be determined.

Bouitbir et al. have now described yet another potential mechanism by which statins could exert both their beneficial and detrimental effects. They observed that statin-treated patients, who were undergoing aortic valvular heart surgery without coronary artery disease, have decreased oxidative stress in atrial muscle biopsies compared with patients not on statins. This correlated with increased expression of antioxidant enzymes such as copper–zinc (CuZn) and manganese (Mn) superoxide dismutase (SOD1 and SOD2, respectively). The expression of peroxisome proliferator-activated receptor gamma co-activators (PGC-1α and PGC-1β), which are important regulators of MnSOD expression and mitochondrial biogenesis, was also increased in atrial muscle biopsies of patients on statin therapy. To determine the potential mechanism of PGC-1 up-regulation by statins, cardiomyocytes were treated in vitro with the statin, atorvastatin, in the presence or absence of the antioxidant, N-acetylcysteine (NAC). NAC was found to block the increase in PGC-1α and MnSOD expression by atorvastatin. These findings suggest that atorvastatin-induced generation of mitochondrial reactive oxygen species (ROS) mediates the increase in PGC-1 and mitochondria-associated genes, which could then later serve to protect the mitochondria and cardiomyocytes from further oxidative damage, such as in response to doxorubicin. Indeed, atorvastatin increased the levels of mitochondrial ROS in both cardiac and skeletal muscle.

The pre-conditioning or adaptive response of the mitochondria to low levels of oxidative stress induced by physical exercise, reduced caloric uptake, and glucose restriction, is referred to as mitochondrial hormesis or mitohormesis (Figure 1). This leads to increased resistance to subsequent higher levels of oxidative stress and damage. Therefore, abrogation of statin-induced mitochondrial oxidative stress by antioxidants may prevent statin-induced mitohormesis. Indeed, in the High-density Lipoprotein Atherosclerosis Treatment Study (HATS), addition of antioxidant vitamins reduces the clinical benefits of statin–niacin therapy in patients with coronary artery disease and low HDL levels. Thus, statin-induced mitohormesis could serve as a cardiovascular protective mechanism underlying some of the pleiotropic effects of statins.

While increased PGC-1 and decreased intracellular oxidative stress in cardiac muscle were observed in patients on statin therapy, in contrast, patients with statin-induced myopathy exhibited increased intracellular oxidative stress and lower PGC-1 and SOD expression in skeletal muscle compared with that of untreated normal volunteers. It is unclear why mitohormesis as an adaptive response does not occur in skeletal muscles of patients with statin-induced myopathy. Unfortunately, skeletal muscles from statin-treated patients who did not develop myopathy were not examined. Furthermore, experimental studies in statin-treated animals may not accurately reflect whether statin-induced mitohormesis occurs in skeletal muscle of humans. Nevertheless, the increased intracellular oxidative stress and the decreased PGC-1 expression and mitochondrial biogenesis in rat skeletal muscle by atorvastatin were reversed by co-treatment with the flavonoid/
antioxidant, quercetin. Treatment with quercetin alone had no effect on PGC-1 expression or mitochondrial biogenesis, suggesting that antioxidants do not affect mitohormesis.

Interestingly, atorvastatin produced a greater increase in mitochondrial oxidative stress in rat skeletal muscle compared with cardiac muscle, although total intracellular ROS production was similar between these two tissues. These findings suggest that statin-induced generation of mitochondrial ROS may lead to paradoxical effects in cardiac and skeletal muscle, possibly due to differences in the levels of mitochondrial ROS generated. Although this is a plausible explanation for the dichotomous effect of statins on skeletal and cardiac muscle, these results still do not explain why only some statin-treated patients develop myopathy. Perhaps only patients with statin-induced myopathy exhibit higher mitochondrial ROS generation in skeletal muscle, possibly due to differences in the levels of mitochondrial ROS generated. Alternatively, calorie/glucose restriction or physical exercise can activate AMP kinase and leads to increased oxidative phosphorylation.

Although this study did not address the mechanism by which statins could increase mitochondrial ROS generation, it is likely that by blocking the conversion of HMG-CoA to mevalonate, statins inhibit the production of isoprenoid intermediates, which are important precursors for the synthesis of ubiquinone or co-enzyme Q₁₀ (CoQ₁₀) (Figure 1). Most of the CoQ₁₀ is localized to the inner mitochondrial membrane, where it functions primarily as an electron carrier between complex I and complex III of the electron transport chain. Depletion of CoQ₁₀ by statins leads to increased generation of mitochondrial reactive oxygen species (ROS). Increased mitochondrial oxidative stress then induces PGC-1 expression, mitochondria biogenesis, and mitochondrial antioxidant enzymes such as manganese superoxide dismutase (MnSOD or SOD2). This pre-conditioning or adaptive response called mitochondrial hormesis or mitohormesis increases stress defence against subsequent oxidative damage to mitochondria and tissues. Alternatively, calorie/glucose restriction or physical exercise can activate AMP kinase and leads to increased oxidative phosphorylation. This increase in mitochondrial metabolism generates ROS, which could also induce mitohormesis.

![Diagram of mitochondrial hormesis](https://example.com/diagram.png)  
*Figure 1* Induction of mitohormesis by statins. Inhibition of 3-hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase by statins leads to decreased ubiquinone or coenzyme Q₁₀ (CoQ₁₀) levels in the mitochondria. CoQ₁₀ functions as an important antioxidant and serves as an electron carrier between complex I and complex III of the electron transport chain. Depletion of CoQ₁₀ by statins leads to increased generation of mitochondrial reactive oxygen species (ROS). Increased mitochondrial oxidative stress then induces PGC-1 expression, mitochondria biogenesis, and mitochondrial antioxidant enzymes such as manganese superoxide dismutase (MnSOD or SOD2). This pre-conditioning or adaptive response called mitochondrial hormesis or mitohormesis increases stress defence against subsequent oxidative damage to mitochondria and tissues. Alternatively, calorie/glucose restriction or physical exercise can activate AMP kinase and leads to increased oxidative phosphorylation. This increase in mitochondrial metabolism generates ROS, which could also induce mitohormesis.
mitochondrial biogenesis are offset by the concomitant decrease in CoQ$_{10}$-associated mitochondrial respiration, resulting in no net improvement in mitochondrial respiration. Furthermore, increased mitochondrial biogenesis by statins should lead to improved myocardial function, especially in patients with heart failure. Although short-term statin therapy has been shown to improve heart function, exercise endurance, and symptoms in patients with heart failure, large prospective clinical trials have failed to demonstrate outcome benefits with statin therapy in patients with chronic heart failure. Because CoQ$_{10}$ deficiency has been linked to the development of heart failure, it is possible that CoQ$_{10}$ depletion by statins may negate the potential benefits of statin-induced mitohormesis. Finally, it is unclear why statin-induced mitochondrial oxidative stress is required for mitohormesis when cardiac risk factors, atherosclerotic disease, and ischaemic injury could all potentially lead to ROS-mediated mitohormesis in the absence of statin therapy. Perhaps if the atrial muscle biopsy specimens in this study were obtained from patients with coronary artery disease, mitohormesis would be observed regardless of whether patients were on statin therapy. Thus, until these issues are resolved, it remains to be determined whether statin-induced mitohormesis is a clinically relevant mechanism which could contribute to some of the beneficial effects of statin therapy in cardiovascular disease.

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**References**