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Review Article

Exercise And Statin Therapy Effect on Hypercholesterolemia, A Randomized Controlled Trial

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Introduction

Hypercholesterolemia and Pharmaceutical Therapies Statins are currently one of the most widely prescribed drugs on the market. Statins are indicated as an adjunct to diet to reduce hypercholesterolemia, a statin helpful if the person had heart attack in past or the lipid panel is high, for example LDL is above 190 mg/dL (4.92 mmol/L). Statins, however lower the blood level of cholesterol by increasing the number of high affinity receptors. Exercises have positive impacts on the symptomatology and physical fitness of individuals with hypercholesterolemia, and to reduce cholesterol levels [1-4].

Discussion

This enzymatic inhibition's main function is to prevent protease activation of sterol regulatory element binding proteins (SREBPs) from the endoplasmic reticulum, preventing nuclear translocation and upregulation of LDL gene expression and thus limiting hepatic cholesterol production. Statins have been linked to a slew of positive outcomes in addition to direct cholesterol reduction. However, vasculoprotective properties such as increased NO bioavailability, antioxidant, anti-inflammatory, and immunomodulatory properties that lead to an overall improvement in endothelial function have also been identified; however, identifying the discrete result in human hypercholesterolemic patients is difficult because the cholesterol-lowering benefits are similar. Furthermore, statin therapy has been shown to significantly improve endothelial function (as measured by flow-mediated dilator responses) in hypercholesterolemic patients with peripheral artery disease. While increased NO bioavailability may be responsible for this beneficial effect, the underlying mechanisms are unknown.

These various positive vascular outcomes are most easily identified when using a genetically modified murine model, as the lipid-lowering effects are null, leaving only the pleiotropic effects visible. While similar to the secondary benefits of direct cholesterol lowering, these independent effects described include reducing inflammation, decreasing ROS, increasing NO bioavailability and endothelial function, decreasing platelet activation and aggregation, decreasing coagulation, and decreasing cellular proliferation. Unfortunately, while the independent results are clear, the mechanisms of action that contribute to these changes are not completely understood at this time. Ezetimibe (Zetia) is a selective drug that works by targeting the Niemann-Pick C1-like 1 protein (NPC1L1), which is expressed on the intestinal cell surface and is a transporter with secretion signal and sterol-sensing domains. Ezetimibe inhibits this protein, preventing LDL absorption from the gut. The resulting decrease in cholesterol transport to the liver induces a compensatory increase in LDLR expression, boosting vascular clearance with no known significant adverse effects.

While cholesterol-lowering medications have been found to reduce cardiovascular events, ezetimibe has lately begun to exhibit pleiotropic effects such as decreased liver lipids, decreased lipid lesions, decreased ADMA levels, and increased eNOS mRNA expression. When used together, ezetimibe and statins (such as

Vytorin) inhibit cholesterol absorption from the gut and hepatic synthesis via complimentary mechanisms.

Long-term co-administration of these medications has been demonstrated to lower LDL blood cholesterol levels by 60% while simultaneously boosting HDL levels and reducing the liver damage, myotoxicity, and/or rhabdomyolysis that statin therapy alone causes. However, the adverse effects of the combination therapy are not fully documented at this time, and it is uncertain how effective these are in influencing the inflammatory profile.

Inflammation, oxidative stress, and pharmaceutical therapies

While reducing total cholesterol levels can reduce vascular oxidative stress and hence enhance endothelial function, certain studies have discovered that statins also have antioxidant capabilities. When cholesterol-lowering medicines were tested in a biologically active form, they were shown to boost the effectiveness of the NOS system while simultaneously inactivating oxygen radicals inside the system. These medications may not directly act on the radicals, but rather lower oxidative stress by reducing the availability of substrate for these radicals to act on or by enhancing antioxidant enzymatic activity, such as SOD.

Statins have been reported to act on the p21 Rac protein, disrupting the NOX subunit assembly and directly inhibiting the superoxide generation process via the NOX enzyme. Some research on lipid peroxidation has found good effects, such as an increase in an antioxidant effect leading to a decrease in ox-LDL with ezetimibe/statin therapy. Pharmaceutical therapies have been proven to impact inflammation by lowering systemic inflammatory indicators and increasing the stability of existing plaques, lowering the risk of thrombosis. Some groups are contemplating treating LDL as a method of regulating inflammation and avoiding atherosclerotic lesions, but the evaluations and results have been mixed. CRP has been frequently utilized as a clinical inflammatory measure since it has been linked to low-grade cardiovascular inflammation. Further research has revealed an interference with the inflammatory process, influencing the production of interleukins, adhesion molecules, platelet aggregation, and chemoattractant such as IL-1, IL-6, IL-8, NF-B, and TNF-, resulting in a drop in CRP. In animal studies, atorvastatin was found to lower inflammatory indicators like MCP-1 and the activation of the nuclear factor NF-B. As the pleiotropic effects of these therapies have been studied, some studies have discovered decreases in the adhesion molecules ICAM, VCAM, E-selectin, P-selectin, and platelet aggregation. These decreases have led some to believe that pharmacological interventions may be capable of minimizing or restrict the creation and instability of atherosclerotic plaques [5-10].

Exercise and Hypercholesterolemia

The American Heart Association (AHA) and the American College of Sports Medicine (ACSM) recently released joint guidelines recommending aerobic and resistance physical activities for people under the age of 65 in order to maintain health, reduce the risk of chronic disease states, and manage current risk factors such as hypercholesterolemia. Hypercholesterolemia has been known to reduce aerobic capacity by affecting dilator control, which is assumed to be caused by a lack of vascular responsiveness caused by a decrease in NO bioavailability. This decrease in vascular reactivity, however, might be owing to wall remodelling, as found in the LDLR mouse model of FH, or poor blood flow distribution due to micro vessel rarefaction, as seen in the ApoE mouse model of FCH. These may result in a reduction in oxygen delivery to working skeletal muscles during hyperaemic demand exercise, lowering aerobic capacity even more. There have been few studies that look at the dose-response relationships between exercise training and cholesterol changes.

Some have claimed that even at modest training volumes, exercise can affect blood lipids; however, the effects may not be significant until specific caloric thresholds are reached. Although exercise training has seldom been proved to have a direct effect on total cholesterol or LDL levels, substantial increases in HDL and reductions in triglycerides have been seen. This might be due to the intensity of the activity, since a 1200 - 2200 kcal/week exercise program conducted at moderate intensity has been demonstrated to lower total and LDL cholesterol levels. A variety of moderate-intensity exercise regimens have demonstrated gains in systemic aerobic capacity, successfully reversing early stage hypercholesterolemic alterations within the vasculature, such as increased vascular reactivity, NO bioavailability, and eNOS activity. Increases in NO bioavailability in humans and animal models of hypercholesterolemia have been linked to eNOS expression and NO generation as a result of a prolonged increase in shear stress with exercise, rather than an increase in SOD or a reduction in oxidant stress. Exercise and shear stress have also been found to promote endothelial vasodilation processes other than NO release. Exercise has also been proven to reduce increases in inflammatory and oxidative stress indicators over the course of a chronic disease, which would help many low-grade inflammatory disorders.

Exercise, Inflammation, and Oxidant Stress

Previously, it was acknowledged that inflammation caused by physical activity was caused by a series of recurring micro-traumas to the muscle. Muscle, on the other hand, has lately been identified as an endocrine organ, capable of producing and releasing humoral mediators directly into the system in response to muscle

contraction. This demonstrates a connection between skeletal muscle activation and anti-inflammatory benefits. The myokines generated include IL-6, IL-8, IL-15, brain-derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), FGF21, and follistatin-like-1, which are all controlled in some way by muscle contraction or contractility. According to the myokine theory, both type I and type II muscle fibers may create and release IL-6, which can act locally through AMPK signalling or systemically to increase hepatic glucose production and lipid metabolism. Acute exercise causes a rise in a number of anti-inflammatory cytokines, including IL-6, IL-1ra, sTNFR (soluble TNF- receptor), and IL-10. Pro-inflammatory cytokines TNF- (tumor necrosis factor-) and IL-1, on the other hand, are typically unaffected. Chronic exercise has been shown in the literature to reduce systemic and local indicators of inflammation within the vasculature.

Pro-inflammatory markers CRP, TNF-, IFN-, MCP-1, IL-6, IL-8, and MMP-9 have all been demonstrated to decline from initial baseline levels when exercise progresses to a chronic condition, whilst anti-inflammatory indicators IL-10 and TGF- rise, indicating the development of a less inflammatory phenotype.

The precise timing and procedures by which a sustained increase in physical activity leads to modest decreases in low-grade inflammation are uncertain. However, other groups are emphasizing the "long-term anti-inflammatory effects of exercise." As the source of muscular action, cellular respiration and metabolism are inextricably tied to physical activity and exercise. Aerobic respiration produces ATP in the presence of oxygen, where glucose is broken down to pyruvate and enters the mitochondria for further processing via Kreb's cycle and oxidation via the electron transport chain. Minor inefficiencies within the mitochondria, such as leaky membranes and restricted cofactor availability, result in decreased ATP synthesis and an excess of oxidants.

Because of the considerable amount of oxidative processing throughout the system, modifications to the mitochondrial electron transport chain are a direct source of oxidant stress during acute exercise. As a result, any inefficiencies within this system are amplified as mitochondrial requirements grow owing to increased activity, particularly during acute exercise, when whole-body oxygen demand increases, increasing the creation of ROS by active tissues. The pro-oxidant enzymes xanthine oxidase, myeloperoxidase, and NOX are all increased during the formation of these mitochondrial-derived radicals.

The activation of these enzymes results in an increase in plasma ROS indicators such as F2-isoprostanes.

While encouraging deleterious cardiovascular consequences, this enhanced oxidant stress has recently been demonstrated to occur in combination with elevations in antibodies against ox-LDL and antioxidant enzymes (catalase) after one week of exercise in mice.

These changes indicate that after only one week of moderate exercise, there is an improvement in hypercholesterolemia, a limitation in the course of foam cell growth, and an increase in antioxidant enzyme activity in both exercising and sedentary states. As exercise is continued, mitochondrial and antioxidant enzymes improve; particularly, increased production of Cu/Zn superoxide dismutase (SOD-1) and glutathione peroxidase leads to increased oxidant handling capacity and contributes to enhanced function.

As a result, the plasma oxidative stress indicators F2-isoprostane, myeloperoxidase, and malondialdehyde decrease. Exercise training has also been found to have a direct favorable effect on the activation of powerful antioxidants eNOS and ecSOD (endothelial cell SOD). These increases appear to be interdependent, since eNOS-/- mice appear unaffected by an increase in ecSOD. HO-1 (heme oxygenase-1) expression has also been demonstrated to be induced by exercise and NO increases. HO-1 products have antioxidant and anti-inflammatory properties, as well as the ability to suppress NF-KB, an oxidant stress sensitive transcription factor. Inhibiting NF-kB reduces the whole downstream signalling cascade, which might be the connection to many of the NO-mediated anti-inflammatory effects found with prolonged exercise, such as decreased leukocyte binding, chemotaxis, platelet aggregation, and smooth muscle cell proliferation [1, 9,11-14].

Conclusion

Given the severity of hypercholesterolemia as a risk factor for the advancement of severe CVD outcomes, successful interventional techniques to reduce cholesterol levels, increase vascular reactivity, and restore NO bioavailability merit sustained investigation. Pharmaceutical interventions have demonstrated a range of vasculoprotective effects that are not completely understood but entail a complicated interplay between vascular signalling systems, oxidative stress, and chronic inflammation. Furthermore, physical activity and exercise have long been proposed as ways to reduce CVD and regulate cholesterol. Current research also supports the hypothesis of long-term anti-inflammatory benefits via changes in the IL-6 and CRP pathways, as well as anti-oxidative effects via enhanced antioxidant enzyme expression and activity, resulting in a stronger oxidant handling capacity at rest and during exercise. These findings show that combining the pleiotropic effects of exercise and traditional pharmacological therapy may be most useful.

Conflict of Interest

None.

Acknowledgements

None.

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