STUDIA UBB EDUCATIO ARTIS GYMN., LXIII, 4, 2018, pp. 29 - 39
(RECOMMENDED CITATION)
DOI:10.24193/subbeag.63(4).31

STATINS, MYOPATHY AND PHYSICAL ACTIVITY

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ABSTRACT. Background: Cholesterol-lowering therapy (statins), associated with lifestyle modifications, have an important role in reducing atherosclerotic cardiovascular disease (ASCVD) events. **Methods**: We review the literature to explore the mechanisms of myopathy caused by statins and also to examine the effects of combining statin therapy with physical activity. **Results:** Although statins are usually well tolerated, dose dependent side effects including myopathy and others side effects were reported. Mechanism of myopathy caused by statins is unclear, but there are some theories to explain these. A large number of evidence suggests the protective effect of regular exercise against chronic diseases and this may be mediated trough their anti-inflammatory effect. There are a number of factors (age, genetic factors, vitamin D) influencing the interaction between statins, skeletal muscle and exercise. It is difficult to associate statin therapy with increased aerobic fitness, because of local adverse effects (muscular or hepatic), which tend to decrease patients' physical activity levels. **Conclusion**: Caution should be taken to the combination of the statin therapy with physical activity, especially in people with increased risk of local effects.

Key words: *exercise training, statins, musculoskeletal, cardiovascular*

REZUMAT. ***Statinele, miopatia şi activitatea fizică.*** **Introducere**: Terapia de reducere a colesterolului (statinele), asociată cu modificări ale stilului de viaţă, are un rol important în reducerea evenimentelor bolii cardiovasculare aterosclerotice. **Metode**: Am trecut în revistă datele din literatură pentru a explora mecanismele miopatiei cauzate de statine şi totodată pentru a examina efectele combinaţiei terapie cu statine – activitate fizică. **Rezultate:** Deşi statinele sunt în general bine tolerate, s-au raportat efecte adverse legate de doză, incluzând miopatia şi alte efecte adverse. Mecanismul miopatiei cauzate de statine este neclar, dar există câteva teorii care să-l explice. Un număr mare de evidenţe sugerează efectul protector al exerciţiilor fizice regulate împotriva bolilor cronice, iar acesta poate fi mediat prin intermediul efectului lor antiinflamator. Există un număr de factori (vârsta, factorii genetici, vitamina D) care influenţează interacţiunea

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dintre statine, mușchiul scheletic și exercițiile fizice. Este dificil de asociat terapia cu statine cu fitness-ul aerobic crescut, datorită efectelor adverse locale (musculare sau hepatice), care tind astfel să scadă nivelele de activitate fizică ale pacienților. **Concluzii**: Trebuie acordată o atenție deosebită combinării terapiei cu statine cu activitatea fizică, în special la persoanele cu risc crescut de efecte adverse locale.

Cuvinte cheie: *antrenament fizic, statine, musculoscheletal, cardiovascular*

Introduction

"The American College of Cardiology" (ACC) / "American Heart Association" (AHA) guidelines which was updated in 2013 recommended the reduction of cholesterol levels in order to reduce the risks of atherosclerotic cardiovascular disease (ASCVD) events. According to these guidelines ASCVD includes coronary heart disease (CHD), stroke and peripheral arterial diseases. Moreover, the guideline stated the importance of cholesterol-lowering therapy (statins) associated with lifestyle modifications in reducing ASCVD events (Stone et al., 2013).

With respect to the new recommendations statin therapy is recommended for individuals at increased ASCVD risk. There is a lower-intensity (lowering LDL-C by < 30%), moderate-intensity therapy (lowering LDL-C by approximately 30% to < 50%) or a high-intensity statin therapy (lowering LDL-C by approximately 50%).

The most common effects of statins include reducing inflammation, oxidative stress, changing the immunologic responses, improving endothelial function and suppressing platelet aggregation. Statins are usually well tolerated possessing a good safety profile, although dose dependent side effects of statins are associated with myopathy, diabetes mellitus, increased levels of transaminase, rhabdomyolysis, neurologic and kidney damage (Rosenson, Baker, Jacobson, Kopecky & Parker, 2014).

This review explores the mechanisms of statin-induced myopathy caused and also examines the effects of combining statin therapy with physical activity.

Mechanisms of statin-induced myopathy

Mechanism of myopathy caused by statins is unclear, but it seems that involves lowering sarcolemmal or endoplasmic reticulum cholesterol, decreased fat catabolism, decreased production of prenylated proteins, vitamin D deficiency,

increased myocellular concentrations of cholesterol and plant sterols, failure to repair damaged skeletal muscle, and inflammation (Thompson & Parker, 2013; Venero & Thompson, 2009).

Some data suggest a link between vitamin D deficiency (below 30 ng / mL of 25 hydroxyvitamin D) and statin-induced myopathy (Gupta & Thompson, 2011). They describe that the mechanism of vitamin D action on muscle include specific muscular receptors, with genomic and nongenomic effects. Vitamin D deficiency seems to cause, via this mechanism, myopathy in skeletal muscle and decrease muscle strength (Gupta & Thompson, 2011). Vitamine D deficiency may shunt the action of CYP3A4 from metabolizing statins, and also, can alter gene transcription, preventing translation of protein that repair muscle tissue structures (Gupta & Thompson, 2011; Lee, Greenfield & Campbell, 2009).

However, the relationship of vitamin D with statin-induced myopathy is questionable. Although statins should reduce serum levels of vitamin D, rather they do not influence this, or even increase these serum levels, in asymptomatic individuals (Gupta & Thompson, 2011).

On the basis of a large base of evidence 4 major statin therapies were identified, namely: 1) secondary prevention in individuals with clinical ASCVD, 2) primary prevention in individuals with primary elevations of LDL-C ≥ 190 mg/dL, 3) primary prevention in individuals with diabetes, 40 to 75 years of age, who have LDL-C 70 to 189 mg/dL and 4) primary prevention in individuals without diabetes, 40 to 75 years of age, who have LDL-C 70 to 189 mg/dL (Stone et al., 2013).

The secondary prevention in individuals with clinical ASCVD refers to subjects with acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.

For the primary prevention in individuals without clinical ASCVD or diabetes who have an LDL-C 70 to 189 mg/dL, as well as, in individuals with diabetes (diabetes mellitus type 1 and type 2) a 10-year ASCVD risk score should be estimated to guide the initiation of statin therapy. The 10-year ASCVD risk is defined as nonfatal MI, CHD death, or nonfatal and fatal stroke. It is demonstrated that high-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy in individuals with clinical ASCVD. Thus, high-intensity statin therapy should be initiated in adults (≤ 75 years) with clinical ASCVD who are not receiving statin therapy, or the intensity should be increased in those receiving a low- or moderate-intensity statin (Stone et al., 2013).

Lifestyle factors

The term lifestyle can denote the interests, opinions, behaviors, and behavioral orientations of an individual, group or culture. Health is as a state of complete physical, mental and social well-being, not simply just the absence of disease. A healthy lifestyle involves having a good state of mind, healthy living, balanced diet and regular exercise.

According to the World Health Organization (WHO) and the United Nations (UN) more than 70% of diseases (such as heart disease, type-2-diabetes, some forms of cancer, high blood pressure and obesity) worldwide are caused by lifestyle factors (such as bad nutrition, lack of physical activity and chronic psychological stress) (WHO, 2010).

Current treatment guidelines underlined the importance of lifestyle changes as early interventions in order to reduce the risk of CVD events. The lifestyle changes include a healthy diet, regular exercise habits, avoidance of tobacco products and maintenance of an ideal weight. Moreover, lifestyle changes should be complemented with medical treatments such as the use of statins (Lysty, Burell & Westerling, 2012).

Another widely debated topic was whether patients using statins realized the importance of CVD risk factors in a different way than non-statin users. Statin users patients had a tendency to underestimate several risk factors as important for the development of cardiovascular disease, including behavioral risk factors (poor exercise habits, smoking and poor eating habits). Previous research has shown that statin users make poor dietary choices and are more sedentary because of feeling safe and protected by taking lipid-lowering medications.

However, the administration of cholesterol-lowering therapy cannot replace healthy lifestyle changes and the lack of association induces poor dietary quality and a sedentary lifestyle, which attenuates the effectiveness of this medication (Lofgren et al., 2010).

Patients who adhere to preventive drug treatment are often assumed to also have a healthier lifestyle than those with poor adherence. Accordingly, a Finish study investigated the association between lifestyle factors (body mass index, smoking status, alcohol use and physical activity) and nonadherence to statin therapy among patients with and without cardiovascular comorbidities. In this study patients with a history of cardiovascular disease or diabetes had better adherence to statin therapy than those without these comorbidities. They found in individuals without cardiovascular diseases or diabetes that overweight, obesity and former smoking were associated with good adherence to statin therapy. Among participants with cardiovascular comorbidities, high alcohol consumption, extreme drinking occasions and having 3–4 lifestyle risk factors were predictors of nonadherence (Halava et al., 2014).

Physical activity and statins

Physical inactivity has been identified as the fourth leading risk factor for global mortality (6% of deaths globally) (WHO, 2010).

In Europe, physical inactivity is considered the second actual cause of death (Brønnum-Hansen, Juel, Davidsen & Sørensen, 2007) being responsible for the increased number of chronic disease (Mokdad, Marks, Stroup & Gerberding, 2004).

The association between regular physical activity and statin therapy may decrease cardiovascular mortality and morbidity. Besides the benefits of lowering cardiovascular disease risk, other effects are: reducing LDLc, increasing HDLc, lowering blood pressure, increasing aerobic fitness, decreasing the incidence of diabetes mellitus and achieving better control of blood glucose levels in patients who already have diabetes (Green, O'Driscoll, Joyner & Cable, 2008; Myers, 2005). Regular moderate intensity physical activity can reduce the risk of cardiovascular diseases, diabetes, colon and breast cancer, as well as depression. Moreover, regular exercises can attenuate the losses in bone mass and helps to control weight (WHO, 2010).

Physical inactivity is considered an independent and strong risk factor for the accumulation of visceral fat, which is a source of systemic inflammation. Chronic inflammation is associated with the development of insulin resistance, as well as with atherosclerosis, neurodegeneration and cognitive impairment.

A large number of evidence suggests the protective effect of regular exercise against chronic diseases and this may be mediated trough their anti-inflammatory effect (Handschin & Spiegelman, 2008; Zanchi et al., 2012).

Recently it has been demonstrated that myokines may contribute to exercise-induced protection against several chronic diseases. The theory that muscles produce and release myokines provides the understanding of mechanisms whereby exercise influences metabolism and exerts anti-inflammatory effects. According to this theory, skeletal muscle contraction release myokines which are muscle-derived humoral factors and therefore these muscles should be classified as “endocrine organs”. Also, other myokines exerts local effects within the muscle via paracrine mechanisms and may be involved in fat oxidation (Pedersen, 2009).

As a consequence of these studies, it was demonstrated that subjects submitted to 9 months of aerobic training showed reduced plasma levels of C-reactive protein (Mattusch, Dufaux, Heine, Mertens & Rost, 2000).

Moreover, regular resistance training has demonstrated significant anti-inflammatory effects confirmed by decreased TNF-α expression both in aerobic exercised rats, strength trained rats and in humans (Lira, et al., 2009; Zanchi, Lira, Seelaender & Lancha, 2010).

American College of Sports Medicine (ACSM) recommends regular exercises in older adults in order to prevent and treat CHD and CHD-related diseases. Healthy elderly persons should perform at least 30 minutes of moderate-intensity aerobic activity five days/week or vigorous activity for at least 20 minutes three days/week. Muscle-strengthening and flexibility exercises were also recommended at least two days/week as well as balance activities (Nelson et al., 2007). Patients at risk for CHD should attempt dietary and physical activity modifications for at least three months before starting lipid-lowering medications because some individuals can maintain normal lipid levels through these methods exclusively (NCEP-ATP III, 2001).

In literature there are relatively few studies about the effect of statins on muscle, and the findings are inconsistent. (Parker & Thompson, 2012) Some research suggests that patients with myopathy caused by statin therapy, developed this damage due to a prior disturbance in fat metabolism, which was exacerbated by statin therapy (Krishnan & Thompson, 2010).
However, statins have a beneficial effect on motor performance (muscle strength, aerobic contraction) in patients with heart failure and intermittent claudication, increasing the average walking distance and / or the walking time without pain (Parker & Thompson, 2012).

Considering the effects of statins on exercise training adaptations it has been suggested that the use of statins attenuates the increase in cardiorespiratory fitness and skeletal muscle citrate synthase after 12 weeks of aerobic exercise training. These date indicate that statins may reduce improvements in physical fitness in response to exercise training by impairment in skeletal muscle mitochondrial content and function. In support of these data, physiologic doses of simvastatin disrupt mitochondrial respiration, increase oxidative stress and activate mitochondrial apoptotic pathways in isolated skeletal muscle fibers after exercise training (Kwak et al., 2012).

There are a number of factors (age, genetic factors, vitamin D) influencing the interaction between statins, skeletal muscle and exercise. Age is a risk factor for skeletal muscle myopathy induced by statins, its incidence increasing with age. The explanation could be that the age increases serum or muscle concentration of statins and emphasizes their effect of increasing CK levels associated with exercises (Parker & Thompson, 2012).

Considering genetic factors, it was suggested that they may increase the individual susceptibility to statin-induced myopathy. (Parker & Thompson, 2012) Thus, myopathy is associated with the rs4363657 single nucleotide polymorphism (located in SLCO1B1), which encodes the organic anion-transporting polypeptide OATP1B1 and therefore regulates the hepatic uptake of statins (Parker & Thompson, 2012).

Unlike statins, increased aerobic fitness improves quality of life of patients including the psychic one. However, the prescribing of exercises by physicians is quite difficult (require more time for explaining the exercise program for patients, clinicians are rarely specialized in assessing the importance of exercises for various disorders, and also, there is a reluctance of the patients themselves, ignoring the causes of diseases and opting for the most comfortable solution for treatment (Myers, Kokkinos & de Araújo, 2014; Vuori, Lavie & Blair, 2013).

It is difficult to associate statin therapy with increased aerobic fitness, because of local adverse effects, muscular and hepatic, which tend to decrease patients' physical activity levels, decrease muscle strength and athletic performance, leading to fatigue and joint problems. (Deichmann et al., 2015; Myers, Kokkinos & de Araújo, 2014) Population at risk to these events is represented by: elderly, Asian race, the presence of certain genotypes, the presence of previous muscular or mitochondrial disorders, vitamin D deficiency, coenzyme Q10 deficiency (Deichmann, Lavie & Andrews, 2010; Deichmann et al., 2015; Meador & Huey, 2010; Vladutiu et al., 2006) (Table 1).

The association of statin therapy with physical training require a number of measures: adjustment of statin therapy (reassessment of the need to use statins, decreased dose of statins, changing medication with a hydrophilic statin, achieving of a pause in statin therapy), adjustment of physical training (decreasing the intensity and the length of physical training), restoring vitamin D deficiency, avoiding the combination of drugs that increase the statins toxicity (Deichmann et al., 2015).

Conclusions

In summary, statin therapy is recommended for individuals at increased ASCVD risk. Statins are usually well tolerated possessing a good safety profile, although dose dependent side effects of statins may occur. Patients at risk for CHD should attempt dietary and physical activity modifications for at least three months before starting lipid-lowering medications.

However, the prolonged use of statins may reduce improvements in physical fitness in response to exercise training by impairment in skeletal muscle mitochondrial content and function. In support of these data, physiologic doses of simvastatin induce myotube atrophy and cell loss associated with impaired mitochondrial respiratory capacity, mitochondrial oxidative stress, and apoptosis in isolated skeletal muscle fibers after exercise training, suggesting that mitochondrial dysfunction may underlie statin-induced myopathy.

Table 1. Review of the literature

Study	Methods	Results
Parker & Thompson, 2012	37 subjects treated with statins and 43 nonstatin-treated controls	Statins increase exercise-related muscle injury and this is related to age.
Krishnan & Thompson, 2010	Six studies examining the effect of statins on muscle strength and nine studies examining their effect on exercise tolerance.	Statins affect muscle strength and exercise performance (insufficient data). Also they may reduce muscle strength in older patients and alter energy metabolism during aerobic exercise.
Kwak et al., 2012	Differentiated primary human skeletal muscle cells (myotubes) were collected	Statin therapy induces myotube atrophy, decreased mitochondrial respiration, mitochondrial oxidative stress, and apoptosis in isolated skeletal muscle fibers after exercise training.
Myers, Kokkinos & de Araújo, 2014	Review of the literature	Statins attenuate the beneficial effects of exercise training by the occurrence of several side effects: liver damage, muscle pain, inflammation, and myopathy.
Deichmann et al., 2015	Review of the literature	The combination of statins and exercise training induce decreased athletic performance, muscle injury, myalgia, joint problems, decreased muscle strength and fatigue.
Vladutiu et al., 2006	110 patients with statin-induced myopathies were tested	Genetic factors may increase the individual susceptibility to statin-induced myopathy in 10% of these patients.
Deichmann, Lavie & Andrews, 2010	Review of the literature	Coenzyme Q10 deficiency, vitamin D deficiency, and underlying muscle diseases are among the factors that may predispose patients to intolerance of this combined statin therapy and exercise training.
Meador, & Huey, 2010	Review of the literature	The mechanisms for the combined statin-associated myopathy and physical activity include skeletal muscle fiber apoptosis, alterations in ubiquitin-proteasome pathway activity, mitochondrial dysfunction, and terpenoid depletion.

However, the prescribing of exercises by physicians is quite difficult. Also, it is difficult to associate statin therapy with increased aerobic fitness, because of local adverse effects, which tend to decrease patients' physical activity levels, decrease muscle strength and athletic performance. Although it has been proved that each of the two types of prescriptions, physical activity and statins, have beneficial effects in lowering the risk of cardiovascular disease, caution should be taken to the combination of these, especially in people with increased risk of local effects and cardiovascular events.

Acknowledgments

The authors have no financial or proprietary interest in the subject matter of this article.

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