

Statin Therapy and Tendon Disorders

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Statins are considered first-line therapy for the prevention and treatment of atherosclerotic vascular disease. They are highly effective agents in reducing low-density lipoprotein (LDL) cholesterol and demonstrated to reduce morbidity and mortality in patients with cardiovascular disease [1].

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is an enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid, a precursor of cholesterol. This enzyme is a target for pharmacological intervention since it acts on cholesterol biosynthesis. At the cellular level, statins inhibit the conversion of HMG-CoA to mevalonic acid, and as a result, inhibit cholesterol synthesis in the liver [2].

Due to the reduction of the intracellular cholesterol there is a stimulus to the cell to increase the production of LDL receptors. With the increase in the number of LDL receptors, cells can capture a larger amount of circulating LDL-cholesterol, and therefore lower plasma levels of this lipoprotein [1].

Even being quite effective drugs they have some adverse effects, among which we can mention constipation, headaches, sleep disturbances, and other more serious complications such as liver and musculoskeletal toxicity [3,4].

Although the incidence of myopathy is very low (about 0.01%), it increases proportionally to the concentrations of statins [5]. More rarely an extreme elevation of creatine phosphokinase may occur and can be associated with rhabdomyolysis and renal failure, especially in elderly patients that use statins in combination with certain types of drugs, such as fibrates and niacin [5,6].

Recently, cases of tendonitis and tendon ruptures have been associated with the use of statins [7]. These complications are observed in tendons in different sites, for example, the distal biceps tendon [8], the patellar tendon [9], the quadriceps tendon [10,11] and the Achilles tendon [9,12,13] which seems to be more affected by injuries [14].

Simvastatin and atorvastatin are some of the most frequently used statins in the treatment of hypercholesterolemia, they have high efficacy and tolerability [15] and however, these statins are the main involved in tendinopathy [14]. These adverse effects in the tendons are related to the effect of statins on metalloproteinase's (MMPs) activity and are often unreported to the pharmacovigilance centers [12,16].

Biochemical analyzes in tendons of rats after chronic treatment with statins, showed significant alterations in the extracellular matrix of tendons, such as, reduced content of collagen I and augmented activity of MMPs [17]. Type I collagen is the major structural component of tendons, form highly oriented fibers that give strength and resistance to the tissue [18]. MMPs are important enzymes responsible for maintaining homeostasis of the tendon extracellular matrix; and these enzymes are required for the repair and remodeling of injured tendons [19]. Therefore, changes in the collagen I and in the MMPs can cause serious damage to the tendons.

Changes in the extracellular matrix of the tendons, after treatment with statins, possibly cause micro damage and ruptures in this tissue. Therefore, during treatment with any drug of this class of lipid-lowering drugs, the patients should be carefully monitored for signs

and symptoms related to tendinopathy and tendon rupture. When tendon injury is detected the prescriber will assess whether the patient should continue the treatment with statins.

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Received September 12, 2013; Accepted September 12, 2013; Published September 22, 2013

Citation: Oliveira LP, Vieira CP, Guerra FR, Almeida MS, Pimentel ER (2013) Statin Therapy and Tendon Disorders. *J Glycomics Lipidomics* 3: e115. doi:10.4172/2153-0637.1000e115

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