Tendon, tendon healing, hyperlipidemia and statins

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Summary

Both hyperlipidemia and metabolic syndrome have adverse effect on tendon structure. Atorvastatin is most widely used antihyperlipidemic drug. Statins have adverse effects on the tendon. Many studies have analyzed the relationship between atorvastatin and skeletal muscles. Atorvastatin administered after the surgical repair of a ruptured tendon appears to affect revascularization, collagenization, inflammatory cell infiltration, and collagen construction. Therefore, further investigations on the effects of atorvastatin on tendon healing are needed.

Key words: tendon, tendon healing, hyperlipidemia, statins

Introduction

The current increase in obesity in the population is paralleled by increased blood lipid levels, which have direct affects on coronary heart disease. Antihyperlipidemic drugs should be used to decrease blood lipid levels. Atorvastatin is one of the most widely used antihyperlipidemic drugs (1). The side effects of atorvastatin on the musculoskeletal system include myalgia, muscle weakness, myositis, rhabdomyolysis, tendinopathy, and spontaneous tendon rupture (2, 3). Statins have adverse affects on the tendon unit (4). Do these affects manifest only as tendon rupture? Does the tendon healing process require the integrity of the tendon? How does atorvastatin influence the tendon healing process?

Statins and tendons

Muscle effects are the most common reported adverse effects of statins. Statin users were more likely to report musculoskeletal pain (5). Hypolipidemic therapy leads to diminution in the size of Achilles tendon xanthomas in patients with heterozygous familial hypercholesterolemia. Statin treatment reduces Achilles tendon thickness in hypercholesterolemia patients with normal Achilles tendon echostructure (6). Hypolipidemic therapy is associated with mobilization of tissue stores of cholesterol in these patients (7). Physiological repair of an injured tendon requires degradation and remodeling of the extracellular matrix through matrix metalloproteinases. Statins may increase the risk of tendon rupture by altering matrix metalloproteinases activity (8). Adverse effects of statins mainly occurred during the first year of treatment and appeared to be more frequent in patients with diabetes, hyperuricaemia or a history of tendon disorders, and in persons engaging in strenuous sports (9). The therapeutic effect of mixed loading exercises for the Achilles tendon may not be adequate to overcome the predisposition to rupture caused by hyperlipidaemia and statin medication (10).

Hyperlipidemia and tendons

High cholesterol could increase the likelihood of tendon tears. Tendon tears are indicative of high cholesterol could provide orthopedic clinicians with an additional preventive treatment opportunity for patients with undiagnosed hypercholesterolemia (11). Hyperlipidemia showed an abnormal stippled signal pattern on MRI with or without enlargement or abnormal configuration of the tendon (12). The presence of tendon xanthomas in hypercholesterolaemia patients is associated with genetic variation in the verse cholesterol transport and low-density lipoprotein oxidation pathways. Xanthomas and atherosclerosis share pathophysiological mechanisms (13). It may become worthwhile to consider the presentation of tendinopathy as a trigger to measure serum cholesterol (14). Tendon xanthomas are characteristic of familial hypercholesterolemia. Tendon xanthomas and cardiovascular disease may share etiology. Xanthomas are associated with a 3 times higher risk of cardiovascular disease among hypercholesterolemia patients (15).

Metabolic syndrome and skeletal muscle

Hyperlipidemia with insulin resistance is common in the metabolic syndrome. Tendinopathy has been associated with greater waist circumference, as has the metabolic syndrome and insulin resistance has been associated with intracellular fat deposition in muscle (16). Metabolic syndrome contribute to a loss of skeletal muscle microvessels, leading to impaired muscle perfusion with elevated metabolic demand (17).

Statins and skeletal muscle

Many studies have analyzed the relationship between atorvastatin and skeletal muscles (18-25). The use of atorvas-

tatin may give rise to muscle pain, tenderness or weakness, and elevated creatine kinase levels with myopathy. If the myopathy is missed and the statin use not stopped, rhabdomyolysis, myoglobinuria, and acute renal necrosis can develop. Myopathy can develop in patients who have complex medical diseases or in patients who use many drugs, especially elderly patients (1-4, 18-26).

Tendon healing

Tendon healing after acute injury begins with inflammation. The second stage is the formation of granulation tissue (proliferative or repair stage), and the last stage is the remodeling of the matrix (Tab. 1) (24, 27).

Table 1. The stages of tendon healing.

Repair stage	Days	Histology	Tensile strength	Comments
Inflammation	0-5	Cell proliferation	None	Neoangiogenesis
Fibroblastic	5-28	Fibroblastic proliferation, non-organized collagen	Increased	Fibronectin knockdown fibroblasts
Remodeling	>28	Linear collagen organization	Controlled active motion	Collagen cross-linking

Statins and tendon rupture

Statin myotoxicity involves a series of complex phenomena and various mechanisms. Impaired cell membranes and cell functions attributable to mitochondrial dysfunction and damage to myocyte duplication have been reported (28). Statins affect the synthesis of membrane glycoproteins, decrease Cl^2 channel activation in the muscle membrane, and increase intracellular Ca concentrations, leading to impaired membrane function. All of these actions can result in myocyte injury (25).

What should the question be?

"Do statins influence tendon healing?" This question does not really set out the issue fully. The real question should be, "Although statins have adverse effects on the muscle belly and tendon strength, do they have any adverse effects on tendon healing?"
Hypercholesterolemia may be the cause of the tendinopathy (21, 29). Statins, hypercholesterolemia, and tendinopathy constitute a controversial triad. Therefore, the relationship between the tendon and the mechanism of hypercholesterolemia should be investigated. Do the statins or the hypercholesterolemia influence tendon healing?

The possible relationship between statins and tendon healing

Myoblasts and fibroblasts play important roles in the healing of skeletal muscle (20). Statins alter the segmentation of myocytes, which stimulates myotoxicity. Normally, membrane and plasma lipids are in balance, and there is a relationship between decreased intracellular cholesterol and decreased plasma cholesterol. Consequently, decreased membrane viscosity and reduced cell proliferation have been reported with statin use (22).
Statins have adverse effects on angiogenesis. The antiangiogenic effects of statins at high concentrations are associated with decreased endothelial release of vascular endothelial growth factor and increased endothelial apoptosis (30).
Atorvastatin administered after the surgical repair of a ruptured tendon appears to affect revascularization, collagenization, inflammatory cell infiltration, and collagen construction (4). Therefore, further investigations on the effects of atorvastatin on tendon healing are needed. Nevertheless, atorvastatin may not be completely without negative impact in terms of the skeletal muscles.

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