Author's response to reviews

Title: Rhabdomyolysis due to the additive effect of statin therapy and hypothyroidism.

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Abstract

We describe a patient with previously undiagnosed hypothyroidism who developed rhabdomyolysis while taking a statin without any other precipitating factors. The statin was stopped, intravenous fluids were started immediately and L-thyroxine was given after confirming the diagnosis of hypothyroidism. His symptoms improved progressively in a few days. Because rhabdomyolysis is rare but potentially life threatening disorder when complicated acute tubular necrosis and renal failure, the physicians must pay special attention when starting statins in patients with hyperlipidemia.
**Introduction**

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) have been widely used as the first choice for treatment of hyperlipidemia. Their side effects are relatively infrequent (1). **The most common side effects are** skeletal muscle complaints, including clinically important myositis and rhabdomyolysis, mild serum creatine kinase (CK) elevations, myalgia with and without elevated CK, muscle weakness, muscle cramps, and persistent myalgia (2). The risk of rhabdomyolysis and other adverse effects with statin use can be exacerbated by several factors, including compromised hepatic and renal function, hypothyroidism, diabetes, and concomitant medications (2). Herein, we report a case of **rhabdomyolysis due to atorvastatin in a patient without any other precipitating factors other than hypothyroidism.**

**Case report**

A 56-year-old man was admitted to the hospital with complaints of severe myalgia proximal muscle weakness of the extremities with difficulty in exercise and climbing stairs for two weeks. He denied vigorous physical exercise and **alcohol use.** His medication consisted of ramipril for hypertension and atorvastatin for hyperlipidemia for two weeks. He had no familial or prior personal history of thyroid disease and **muscle disorders. He had no** previous history of muscular toxicity with a statin or fibrate use.

On physical examination, he was afebrile, had periorbital puffiness, lip swelling and mild diffuse goitre, normal heart rate (89 beats/min). All the limbs were swollen and had pitting edema. Other systems were normal by examination.
On admission, laboratory measurements revealed: Hemoglobin 11.3 g/dl, total leucocyte count 7.7×10⁹/l, serum K 3.9 mEq/l, Na 137 mEq/l, urea 34 mg/dl, creatinin 1.4 mg/dl blood glucose 85 mg/dl. Serum muscle enzymes were markedly elevated; CK 3471 IU/l (normal up to 170), CK-MB 90 IU/l (normal up to 15), LDH 730 IU/l (150-500), Aspartate transaminase (AST) 91 IU/l, alanine transaminase (ALT) 50 IU/l. Urine analysis showed moderate blood with dipstick, but on microscopic examination there were no erythrocytes. Therefore, we assumed that this was due to myoglobulinuria. Thyroid function tests confirmed the diagnosis of hypothyroidism. Thyroid stimulating hormone (TSH) >75 uIU/ml (0.4-4), free T₃ (FT₃) 0.85pg/ml (1.57-4.71), free T₄ (FT₄) 0.3 pg/dl (0.85-1.78). The diagnosis was rhabdomyolysis secondary to additive effect hypothyroidism and atorvastatin. Atorvastatin was stopped, intravenous fluids were started immediately and L-thyroxine (100µg/day) was given after confirming the diagnosis of hypothyroidism. His symptoms progressively improved in a few days. On discharge, two week after admission, serum CK, AST, ALT measurements have decreased to 668 IU/l, 23 IU/l, 27 IU/l respectively. TSH level became normal range 6 weeks after starting treatment.

**Discussion**

The present report describes a patient with rhabdomyolysis due to additive effect of undiagnosed hypothyroidism and atorvastatin. Statins have been found to be effective in primary prevention as well as secondary prevention of coronary disease (3). Although statins are well tolerated by most of the patients, they may cause myopathy, rhabdomyolysis and elevated liver enzymes (4). Medications, that inhibit cytochrome P-450 (CYP) 3A4, such as macrolide antibiotics, antifungals, and cyclosporine, increase serum concentrations of statins and the risk of rhabdomyolysis (2). There have been several case reports of rhabdomyolysis induced by hypothyroidism (5) but most of the reported cases were precipitated with exercise (6). In a
previous report, 11.7% of patients with primary hypothyroidism accidentally received statins without diagnosis of hypothyroidism. Severity of hypothyroidism might be partially associated elevation of CK. Statins might be a risk factor for severe myopathy and rhabdomyolysis in patients with hypothyroidism (1).

**Conclusion**

We wish to alert the physicians to the importance of early recognition and treatment of hypothyroidism before starting statins, which is essential in reducing the mortality and complication of rhabdomyolysis. Finally, screening thyroid functions, before starting statins to avoid rare but serious complications is important.

**References**