Rhabdomyolysis in the Setting of Induced Hypothyroidism and Statin Therapy: A Case Report

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What Is Known about This Topic?
• The coexistence of statin therapy and hypothyroid states may synergistically increase the risk of myopathy.

What Does This Case Report Add?
• There are a few previously reported cases of statin-induced myopathy resulting from induced hypothyroidism.
• In the present case, substantial rhabdomyolysis caused acute kidney injury necessitating immediate treatment.

Key Words
Induced hypothyroidism · Rhabdomyolysis · Statin therapy · Recombinant human thyrotropin

Abstract
Mild elevation of creatine kinase (CK) is common in untreated hypothyroidism, but severe myositis and overt rhabdomyolysis are rare. Similarly, muscle pain and CK elevation are potential side effects of statin therapy, yet rhabdomyolysis is likewise rare in the absence of medication interactions adversely affecting statin metabolism. The coexistence of statin therapy and hypothyroid states may synergistically increase the risk of myopathy. We describe a case of rhabdomyolysis attributable to induced hypothyroidism in a patient on chronic statin medication who was anticipating adjuvant radioiodine (131I) therapy for a thyroid carcinoma.

Introduction
While muscle pain, myopathy and elevated creatine kinase (CK) are common findings in untreated hypothyroidism, severe myositis, profound elevation of CK and overt rhabdomyolysis are rare [1–6]. The degree of CK elevation may correlate with the severity and duration of hypothyroidism [7]. Similarly, potential side effects of statin therapy include muscle pain and CK elevation, but myositis and rhabdomyolysis are also rare in the absence of medication interactions adversely affecting CP450 metabolism of statins [8–10]. The coexistence of statin therapy and hypothyroid states may increase the risk of myopathy [11]. We describe a case of significant myositis and rhabdomyolysis likely attributed to thyroid hormone withdrawal in anticipation of adjuvant radioiodine (131I) therapy in a patient with well-differentiated thyroid can-
We know of only 2 other reported cases of statin-induced myopathy related to induced hypothyroidism. Neither of the previously reported cases resulted in overt rhabdomyolysis or the need for treatment of acute kidney injury, in contradistinction to our patient [3].

**Case Description**

A 70-year-old Caucasian man with a past medical history of coronary artery disease, diabetes mellitus type 2, hypertension, and hyperlipidemia was seen in the emergency department for diffusely distributed muscle pain with duration of a few days. He had undergone total thyroidectomy 2 months previously to treat a well-differentiated thyroid carcinoma (T1b, N0, M0, papillary carcinoma). Thyroid replacement (including T3 therapy) had been withdrawn 3 weeks previously in anticipation of adjuvant radioiodine (131 I) therapy. His medication included the following: aspirin 325 mg daily; atenolol 50 mg daily; atorvastatin 40 mg daily; clopidogrel 75 mg daily; insulin subcutaneously twice daily; metformin 500 mg daily, and amlodipine 5 mg daily. There were no apparent significant drug interactions known to increase the risk of statin myopathy and he had tolerated statin therapy for a number of years. He had no previous history of statin-induced myopathy. He denied any vigorous exercise, falls, trauma, recent infectious illness, or change in medication other than discontinuing lithium 3 weeks previously. His serum chemistries showed acute rhabdomyolysis requiring emergency treatment (table 1).

**Treatment**

At the time of presentation the patient was found to have symptoms, signs and laboratory results consistent with rhabdomyolysis (CK levels 5 times the upper limit together with abnormal renal function). His acute renal insufficiency was attributed to rhabdomyolysis which was treated in standard fashion – he received intravenous fluid hydration with a large volume of normal saline infusion (250 ml per hour). He urgently received intravenous calcium gluconate, as well as a bolus infusion of dextrose and insulin – treatments for potentially life-threatening hyperkalemia. Metformin was discontinued because of contraindication in acute renal insufficiency. Atorvastatin was discontinued because of potential causation of his myositis. His renal function and hyperkalemia improved quickly, allowing hospital discharge within 2 days. He completed radioiodine therapy 1 day after hospital discharge and resumed thyroid replacement 2 days after that. His renal function returned to normal within 1 week and serum CK levels were documented to be normal by 2 months after discharge.

**Discussion**

CK elevations are common in patients with hypothyroidism. Possible mechanisms include the downregulation of cellular metabolism, impaired glycogenolysis and impaired mitochondrial oxidative metabolism. These may result in direct cellular damage, yet severe myositis and rhabdomyolysis (CK elevations greater than 5 times the upper limit of normal together with renal insufficiency) are rare in hypothyroidism [2, 4].

Statins inhibit HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase, the rate-limiting enzyme in cholesterol synthesis [9]. They may also impair other biosynthetic pathways of cholesterol, including coenzyme Q10, a component of the mitochondrial respiratory chain, resulting in a toxic, noninflammatory myopathy leading to rhabdomyolysis [9, 10, 12, 13]. A similar mechanism has been reported by Chapman and Carrie [14], in which an imbalance occurred between muscle protein repair/synthesis and muscle protein degradation by means of gene expression within the mitochondria.

### Table 1. Serum chemistries

<table>
<thead>
<tr>
<th></th>
<th>Day 0 (hospital admission)</th>
<th>Day 1</th>
<th>Day 9</th>
<th>Day 62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>135 – 148 mmol/l</td>
<td>136</td>
<td>135</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>3.4 – 5.3 mmol/l</td>
<td>6.8</td>
<td>4.7</td>
<td></td>
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<tr>
<td>Chloride</td>
<td>96 – 110 mmol/l</td>
<td>96</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Carbon dioxide</td>
<td>19 – 32 mmol/l</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>3.89 – 5.55 mmol/l</td>
<td>6.11</td>
<td>8.49</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>38.1 – 106.8 μmol/l</td>
<td>229.8</td>
<td>141.4</td>
<td>91.5</td>
</tr>
<tr>
<td>TSH</td>
<td>0.40 – 4.0 mIU/l</td>
<td>65.0</td>
<td></td>
<td>16.6</td>
</tr>
<tr>
<td>fT4</td>
<td>10.30 – 23.17 pmol/l</td>
<td></td>
<td></td>
<td>12.87</td>
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<tr>
<td>Calcium</td>
<td>2.13 – 2.63 mmol/l</td>
<td>1.85</td>
<td>1.80</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>35.0 – 52.0 g/l</td>
<td>41.0</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td>0 – 4.18 μkat/l</td>
<td>84.79</td>
<td>78.79</td>
<td>19.52</td>
</tr>
</tbody>
</table>
Coexistent hypothyroidism and statin therapy may increase the risk of myopathy and rhabdomyolysis [11]. Several cases of hypothyroid patients taking statin therapy and resulting in rhabdomyolysis have been described [1, 4, 11]. In addition to these scenarios, a PubMed literature search identified 2 cases of statin-induced myopathy occurring in the setting of induced hypothyroidism. Neither of the previously reported cases resulted in overt rhabdomyolysis or the need for treatment of acute kidney injury, in contradistinction to our patient [3]. Possible explanations for how hypothyroidism might enhance statin myopathy include decreased clearance of CK or decreased drug catabolism, resulting in higher serum statin levels [3].

Although statins may lead to toxic effects on skeletal muscle, the overall incidence is low – typically 0.1% of patients receiving statin therapy [8]. Rhabdomyolysis associated with statin treatment is very rare, with less than 1 fatal case per 5 million patients [10].

Conclusion

The coexistence of hypothyroidism and statin therapy may increase the risk of myopathy and rhabdomyolysis. For this reason physicians should consider temporarily withholding statin therapy during periods of induced hypothyroidism (typically in anticipation of radioiodine 131I therapy). Alternatively, recombinant human TSH (thyrotropin) may be used to accomplish radioiodine remnant ablation in selected cases of differentiated thyroid cancer. Recombinant human Thyrogen allows patients to remain on thyroid replacement, possibly averting morbidities of induced hypothyroidism, including statin-related myopathy [15].

Disclosure Statement

The authors have no conflicts of interest to disclose.

References


3 Lando HM, Burman KD: Two cases of statin-induced myopathy caused by induced hypothyroidism. Endocr Pract 2008;14:726–731.


