Bone scintigraphy of severe hypercalcemia following simvastatin induced rhabdomyolysis

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Summary
Simvastatin induced rhabdomyolysis with renal failure is a well reported clinical entity with hyperkalemia recognized as a life threatening risk. The risk of delayed hypercalcemia during the recovery of renal function is not well appreciated as this varies in severity and can be caused by multiple mechanisms. We present a patient with high dose simvastatin induced rhabdomyolysis leading to late onset of severe hypercalcemia due to calcium phosphate deposition in muscles diagnosed by distinctive bone scintigraphy.

A 60-year-old Asian male was admitted to the hospital for profound weakness one week following the initiation of simvastatin 80 mg daily due to coronary artery disease requiring stent placement. His post cardiac catheterization period was complicated with contrast induced nephropathy.

One week later, he developed progressively worsening weakness in proximal upper and lower extremity, inability to raise his head and dysphagia. Simvastatin was discontinued at this point. He became oliguric and emergent hemodialysis was initiated. Electromyography showed diffuse myopathy. Left shoulder MRI showed increased T2 signal involving almost all muscles of the shoulder, consistent with myositis.

Right leg muscle biopsy showed findings consistent with statin-associated myofiber lesions, severe myonecrosis, partial deficiency of myophosphorylase and myofiber type 2 atrophy (with no foci of calcium deposits). Electron microscopy revealed mitochondrial degeneration.

His muscle weakness improved but he remained oliguric and hemodialysis was continued.

Table 1 - Laboratory data.

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>on admission</th>
<th>1 week later</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>6-23 mg/dl</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.5-1.2 mg/dl</td>
<td>2.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.5 mEq/L</td>
<td>6.2</td>
<td>6.5</td>
</tr>
<tr>
<td>CPK</td>
<td>25-210 U/L</td>
<td>153</td>
<td>426,270</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.6-10.4 mg/dL</td>
<td>8.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.5-4.5 mg/dL</td>
<td>2.7</td>
<td>7.6</td>
</tr>
<tr>
<td>Intact PTH</td>
<td>9-76 pg/mL</td>
<td>144</td>
<td>---</td>
</tr>
<tr>
<td>25(OH)D</td>
<td>25-80 ng/mL</td>
<td>20</td>
<td>---</td>
</tr>
<tr>
<td>Ionized Ca</td>
<td>4.6-5.3 mg/dL</td>
<td>---</td>
<td>3.0</td>
</tr>
<tr>
<td>AST</td>
<td>10-40 U/L</td>
<td>---</td>
<td>4489</td>
</tr>
<tr>
<td>ALT</td>
<td>7-56 U/L</td>
<td>---</td>
<td>667</td>
</tr>
<tr>
<td>Urine myoglobin</td>
<td>Negative</td>
<td>---</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Introduction
Rhabdomyolysis is a syndrome of severe muscle cell damage with release of myoglobin and other toxic intracellular contents leading to acute renal failure with marked changes in calcium and phosphate (1, 2). Simvastatin is the most common statin medication associated with rhabdomyolysis (3). Statin induced rhabdomyolysis occurs in 0.3-13.5 cases per 1,000,000 statin prescriptions (4).

In the recovery diuretic phase of acute renal failure, delayed hypercalcemia may occur by multiple mechanisms including secondary hyperparathyroidism and elevated 1, 25(OH) D levels. Myocellular calcium phosphate complexes begin to dissolve and result in marked hypercalcemia which has been reported in the past (10, 11).

Case report
A 60-year-old Asian male with past medical history of diabetes mellitus and hypertension was admitted to the hospital for profound weakness one week following the initiation of simvastatin 80 mg daily due to coronary artery disease requiring stent placement. His post cardiac catheterization period was complicated with contrast induced nephropathy.

One week later, he developed progressively worsening weakness in proximal upper and lower extremity, inability to raise his head and dysphagia. Simvastatin was discontinued at this point. He became oliguric and emergent hemodialysis was initiated. Electromyography showed diffuse myopathy. Left shoulder MRI showed increased T2 signal involving almost all muscles of the shoulder, consistent with myositis.

Right leg muscle biopsy showed findings consistent with statin-associated myofiber lesions, severe myonecrosis, partial deficiency of myophosphorylase and myofiber type 2 atrophy (with no foci of calcium deposits). Electron microscopy revealed mitochondrial degeneration.

His muscle weakness improved but he remained oliguric and hemodialysis was continued.

KEY WORDS: bone scintigraphy; statins; rhabdomyolysis; myocellular calcium phosphate deposits; hypercalcemia.
One month later, he developed nausea, vomiting and abdominal pain. His calcium level was 13.7 mg/dL peaking at 14.1 mg/dL. Creatinine was 2.5 mg/dL. EKG was unremarkable for any acute changes. There was no history of any vitamin D or calcium supplements intake. Evaluation for humoral hypercalcemia of malignancy, sarcoidosis, and thyroid abnormality was negative. He had no history of exposure to tuberculosis.

Two doses of calcitonin and one dose of zoledronic acid were given. Whole body bone scintigraphy showed diffuse uptake of technetium-99m MDP in soft tissues and muscles of the chest wall, shoulders, proximal upper and lower extremities, pelvis and hips (Figure 1). Hemodialysis was continued and normalization of his calcium to 8.2 mg/dL was achieved eight days later.

### Discussion

Calcium is a cation which is tightly regulated under normal conditions by Na+/Ca+2 exchanger and Ca+2 ATPase pump. In muscle fibers, calcium is stored primarily in sarcoplasmic reticulum.

<table>
<thead>
<tr>
<th>Normal Range</th>
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<tr>
<td>Calcium</td>
<td>8.6-10.4 mg/dL</td>
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<td>2.5-4.5 mg/dL</td>
</tr>
<tr>
<td>Intact PTH</td>
<td>9-76 pg/mL</td>
</tr>
<tr>
<td>1,25(OH)2D</td>
<td>18-64 pg/mL</td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td>4.6-5.3 mg/dL</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>25-100 U/L</td>
</tr>
<tr>
<td>TSH</td>
<td>0.35-5.5 mIU/L</td>
</tr>
<tr>
<td>Free T4</td>
<td>0.9-1.8 ng/dL</td>
</tr>
</tbody>
</table>

Table 2 - Labs 1 month later.

Figure 1 - Whole body bone scintigraphy showed diffuse uptake of technetium-99m MDP in soft tissues and muscles of the chest wall, shoulders, proximal upper and lower extremities, pelvis and hips.
Bone scintigraphy of severe hypercalcemia following simvastatin induced rhabdomyolysis

Figure 2 - Graphical representation of Calcium, Phosphorus and intact PTH during the course of illness.
Intracellular ionized calcium concentration is 10,000 times lower than the extracellular ionized calcium concentration (1, 2). De- 
regulation of calcium metabolism is frequently associated with 
rhabdomyolysis and especially when induced by statins. 
Statins are the preferred and most prescribed drugs for treatment 
of hypercholesterolemia and thereby primary and secondary pre-
vention of atherosclerotic cardiovascular disease. Our patient was 
of Asian descent and had contrast induced nephropathy which is 
proposed risk factors for statin induced muscle injury (1, 2). Sim-
vastatin is the most common statin medication associated with 
rhabdomyolysis (3).

Hypocalcaemia during the oliguric phase of acute renal failure is 
due to multiple underlying mechanisms: inhibition of kidney 1, alpha 
hydroxylase which results in impaired production of 1,25(OH)2D (2); hyperphosphatemia leading to precipitation of extensive cal-
cium phosphate deposits in damaged muscles (5) and skeletal re-
sistance to parathyroid hormone (5, 6).

Prior to the widespread application of the intact PTH assay to re-
nal failure, the hypercalcemia of the diuretic phase following rhab-
domyolysis was thought to be the result of the persisting increase 
in PTH in reaction to the marked hyperphosphatemia during the 
oliguric phase. The finding of suppressed PTH during the diu-
retic phase in this patient is consistent with flux of calcium back 
into the systemic circulation as serum phosphate levels are clea-
red by diuresis (5). Hypercalcemia due to elevated 1, 25-(OH)2D 
levels (7, 8) and secondary hyperparathyroidism (9) has been re-
ported. Calcium deposition in injured muscles is marked in patients 
with acute renal failure induced by rhabdomyolysis than those in-
duced by other causes (8). Immobilization induces bone calcium 
resorption which in combination with impaired renal excretion in 
rhabdomyolysis with renal failure can also contribute to hyper-
calcemia late in the course. Serial technetium-99m MDP scans show 
take of calcium by the injured muscle cells during hypocalcaea-
ia followed by release of calcium from those cells during the re-
covery phase (10). There has been histological evidence of ac-
tive calcium phosphate deposits dissolution on muscle biopsy (11).

Hypercalcemia occurring after immobilization with normal to low 
PTH levels and low 1,25(OH)2D levels in patients with renal fail-
ure (12) has been demonstrated. So far the exact mechanism of statin induced rhabdomyolysis is not clear. It appears to be multifactorial. Deficiencies of synthe-
pic products of the HMG (3-hydroxy-3-methylglutaryl) CoA reductase 
pathway have been implicated as possible mechanisms. Abnormal 
membrane integrity secondary to cholesterol deficiency, abnor-
mal mitochondrial respiratory function secondary to coenzyme 
Q, deficiency and abnormality in cell signaling cascades invol-
ving Rho, Ras and Rap-1a, apoptosis secondary to prenylated protein deficiency are the proposed mechanisms (13, 14).

Simvastatin has been shown to increasing cytosolic calcium by 
direct diffusion through sarcolemna and impairing membrane in-
tegrity due to prenylated protein deficiency which is a class effect.

In addition, it induced altered mitochondrial function and thereby 
mitochondrial calcium efflux through the Na+/Ca2+ exchanger or 
Ca2+ ATPase pump dysfunction due to ATP depletion. 
Our patient had Type 2 fiber atrophy with mitochondrial degene-
ration on muscle biopsy. Also the type of muscle fiber affected is 
based on its metabolic nature. Type 1 muscle fibers are predomi-
nantly oxidative in nature where as Type 2 fibers are glycoly-
tic in nature. Early involvement of mitochondria in selective glycoly-
colic muscle fiber necrosis following inhibition of the enzyme HMG-
CoA reductase has been shown in rats (15). Pathogenesis of delayed hypercalcemia in our patient could be 
due to calcium mobilization from the muscles and interstitium along 
with immobilization due to weakness. Appropriately suppressed intact PTH and 1, 25(OH)2D levels indicate that the hypercalcemia was likely the result of dis-
solution of calcium phosphate complexes in injured muscles or 
their interstitium. The patient’s profound weakness associated with 
myopathy likely resulted in a component of immobilization hy-
percalcemia as well. Moreover, our patient was still on hemodialysis. It is important for health care providers to understand this parti-
cular mechanism of delayed severe hypercalcemia in order to treat 
such patients in an appropriate and timely manner.

Summary points

• Delayed hypercalcemia during the recovery phase of renal func-
tion is not always due to secondary hyperparathyroidism and 
elevated 1,25(OH)2D levels.
• Mobilization and dissolution of calcium phosphate deposits in 
the injured muscle sites lead to delayed hypercalcemia as il-
ustrated in our patient.
• Bone scintigraphy is the imaging of choice to demonstrate the 
calcium phosphate deposits in the body.
• Recognition of this mechanism is important for appropriate fol-
low up and treatment of hypercalcemia to prevent life threate-
nings complications.

Financial disclosure and conflict of interest

None to disclose by any of the Authors.

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