# Rhabdomyolysis, Hypothyroidism, and Fatty Acid Oxidation: More Related Than You Think

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# Rhabdomyolysis, Hypothyroidism, and Fatty Acid Oxidation: More Related Than You Think

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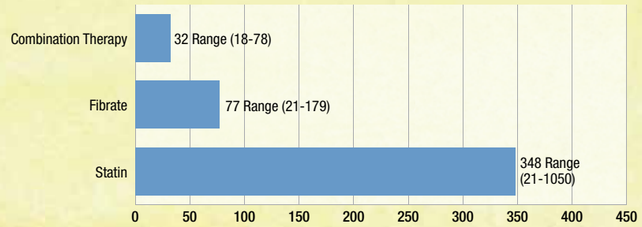
## Introduction

Rhabdomyolysis secondary to fenofibrate monotherapy is a rare, recently described event.[1] More often described is rhabdomyolysis during statin or statin-fibrate combination therapy.[1] Based on case report evidence, its incidence is increased in patients with hypothyroidism.[1,2] Our patient presented in rhabdomyolysis, secondary to fenofibrate monotherapy, with recently diagnosed hypothyroidism. We suggest identifying hypothyroidism when implementing statin or fibrate therapy and close monitoring during initiation. Reports of mean days of treatment before onset can guide monitoring length: 348 for statin, 77 for fibrate and 32 for combination therapy.[2] These incidence rates were greatest within the first six months and after 24 months of treatment; however they found no statistically significant difference in incidence rates over this time period.[2]

**Mean Days Of Treatment Before Rhabdomyolysis[2]**



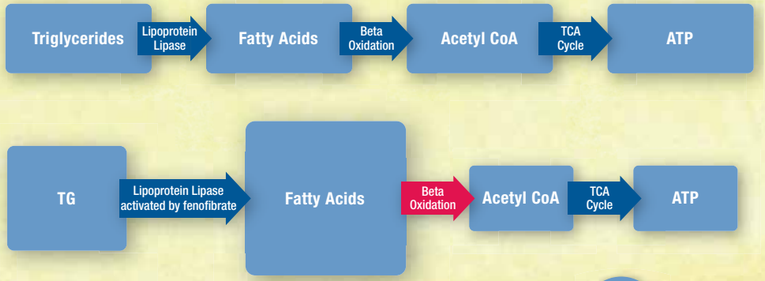

## Case

A 48 year old female patient presented with severe myalgia and dark colored urine for one week. Two days earlier she developed sore throat and right flank pain. Three weeks prior, patient was diagnosed with hypothyroidism and hypertriglyceridemia and began fenofibrate monotherapy 160mg. Laboratory values on admission revealed acute renal failure: BUN 87, Cr 4.2. Patient also had transaminitis but an otherwise normal liver function panel: AST 1983, ALT 844. Given the patient's symptomology, our differential diagnosis included glomerulonephritis secondary to post-streptococcal or IgA nephropathy and rhabdomyolysis. Antistreptolysin O titer and rapid streptococcus antigen test were negative. Complement values were normal (C3 123, C4 23.9). Rhabdomyolysis best explained the doubled AST versus ALT transaminitis. Creatine kinase of 45,510 and a urinalysis showing a large amount of blood with no red blood cells confirmed diagnosis of rhabdomyolysis. Urine microanalysis revealed muddy brown casts consistent with acute tubular necrosis, and urine myoglobin was positive. Patient was diagnosed with rhabdomyolysis secondary to fenofibrate. The fenofibrate was stopped, and she responded quickly to aggressive volume resuscitation.

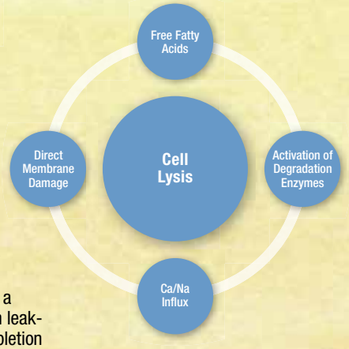
| Admission Laboratory Data | |
|---|---|
| AST | 1983.0 |
| ALT | 844.0 |
| CPK | 45,510.0 |
| BUN | 87.0 |
| Cr | 4.2 |
| C3 | 123.0 |
| C4 | 23.9 |

## Pathophysiology

Why is there an increased risk of rhabdomyolysis during fibrate therapy in hypothyroidism? The answer may lie in fatty acid oxidation (beta oxidation). Triglycerides are hydrolyzed into free fatty acids and glycerol.[3] Fatty acids then enter mitochondria and are oxidized into acetyl CoA and converted to ATP.[3] Hypothyroidism impairs beta oxidation and ATP turnover in myocytes.[4] Fatty acid oxidation impairment is also associated with rhabdomyolysis.[5] Fenofibrates activate lipoprotein lipase, which hydrolyzes triglycerides into fatty acids.[6] Thus, adding fenofibrate increases the amount of fatty acids to be oxidized and stresses a pathway impaired in hypothyroidism and rhabdomyolysis.[5,6]




- Hypothyroidism affects myocyte mitochondria. Impaired processes include myosin ATPase activity, oxidative metabolism, and fatty acid break-down, leading to low ATP turn-over.[4] ATP depletion can be a initiating factor in cell lysis.[7]
- Rhabdomyolysis involves skeletal myocyte lysis resulting in cellular content entering circulation.[5] Fatty acid oxidation impairment can predispose individuals to rhabdomyolysis.[5] One specific gene deficiency implicated is CPT which transfers fatty acids from cytosol to matrix within mitochondria for beta oxidation.[5]
- Free fatty acids play a role in causing cell lysis.[7] They can act as a detergent to membranes and damage mitochondria resulting in leakage of apoptotic factors.[7] Both membrane damage and ATP depletion decreases activity of Na/K ATPase and Ca membrane pumps leading to intracellular accumulation of Na and Ca.[4,7] Sodium influx leads to cellular swelling and calcium influx leads to activation of proteolytic enzymes.[7] This has many deleterious effects including leading to release of more free fatty acids.[7] **This is how free fatty acids, associated with fibrate use, and ATP depletion in hypothyroidism can propagate cell lysis in rhabdomyolysis.** [4,5,7]




## Summary Questions

Why is this important? Lipid lowering agents are the most prescribed class of drugs in the United States.[8]

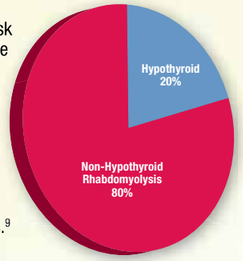
How does this risk compare among lipid-lowering agents? Increased risk of rhabdomyolysis compared to statin monotherapy is 5.5 fold for fibrate monotherapy and 12-fold for combination therapy.[2] Among the statins, simvastatin, atorvastatin, and pravastatin there was no statistically significant difference in incidence.[2]

What are the incidence rates of rhabdomyolysis? Two large JAMA trials report incidence of rhabdomyolysis during lipid lowering therapy. [2,9]

In the A to Z trial, incidence rates of myopathy for 80mg of simvastatin was .4%; these 9 cases included 3 of which developed rhabdomyolysis.[9]

This risk is further increased in hypothyroidism: a large cohort study showed that 20% of rhabdomyolysis cases during statin or fibrate treatment were on thyroid replacement therapy.[2]

**Percent of Rhabdomyolysis Cases With Hypothyroidism[2]**




## Conclusion

- Rhabdomyolysis incidence is increased in hypothyroidism and fibrate use.[4]
- There are pathophysiologic reasons why hypothyroidism increases risk of rhabdomyolysis during fibrate use. [4,5,7]
- Since rhabdomyolysis is considered extremely rare in absence of statin or fibrate use, screening patients for hypothyroidism during initiation could powerfully affect the incidence of this life-threatening adverse effect.[1]

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