

# Statin Effects on Muscle and Kidney

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## ABSTRACT

HMG-CoA reductase inhibitors (statins) have shown benefits in preventing some cardiac events. Initial studies indicated very few adverse effects including rhabdomyolysis. However, significant evidence has accumulated to suggest that statin-induced muscle injury is an under-reported cause of significant morbidity and mortality. Statin-induced rhabdomyolysis can be acute, subacute, or chronic, and may be permanent despite dose reduction or substitutions. Diabetes and acute and chronic renal failure are also increased in statin users. Because of a genetic polymorphism, one-quarter of the population may have higher-than-expected blood levels and thus be at increased risk for these complications.

## Adverse Drug Reports of Rhabdomyolysis

In 2006 the FDA provided my office all the atorvastatin-associated MedWatch Adverse Drug Reports for the period 1997 to 2006 in a text file in a CD ROM. From this resource, using the search mechanism on our computers, we counted 2,731 cases of rhabdomyolysis hospitalizations in 1997–2006 from atorvastatin alone. Ardati et al.<sup>1</sup> had previously estimated the death rate from statin-associated rhabdomyolysis to be 12 percent, suggesting an estimated 307 deaths during this time period.

A compilation of our review of the FDA Adverse Event Reporting System (FAERS) reports is found at [www.spacedoc.com](http://www.spacedoc.com), along with other information and articles. Since 2000, more than 30,000 email messages have been sent to the website by people reporting adverse effects while taking statins.

FDA *MedWatch* records from Jul 1, 2005, to Mar 31, 2011, were reviewed by Hoffman et al.,<sup>2</sup> who found 8,111 reports of all statin-associated rhabdomyolysis hospitalizations during this period. If the death rate is 12 percent, there were about 972 deaths, averaging 135 deaths yearly. Combining 1997–2006 data from Ardati et al. with 2005–2011 data from Hoffman et al. suggests that the use of statins may have resulted in an excess of 1,279 deaths. Bringing these calculations forward 4 years to the present (2011–2015) adds 540 deaths, bringing the current estimate of statin-associated rhabdomyolysis-related deaths in the U.S. to 1,819.

Numbers of this magnitude should have come to the attention of the medical community much sooner than now. During the Baycol crisis of 2004, only 60 deaths caused the FDA to request Bayer to recall its problematic product. Six years later, an excess of 1,800 deaths has not prompted any apparent concern. What's different at the FDA and in the medical

community that now accepts this level of risk? Where is the media uproar that we had back in 2004?

## Statins and Muscles

Hoffman's review has also permitted a comparison of the relative risks of muscle problems with the use of the individual statin drugs. He found that, with the exception of uncommonly used statins, the risk of muscle adverse effects varies with the statin potency and its ability to reduce cholesterol levels. Rosuvastatin (Crestor), perhaps the strongest statin, was linked to higher adverse muscle events relative to the others. Atorvastatin (Lipitor) and simvastatin (Zocor) showed intermediate risks, and lovastatin (Mevacor) and pravastatin (Pravachol) had the lowest risk rates. Using rosuvastatin as an index, relative rates of all-category adverse muscle events for atorvastatin, simvastatin, pravastatin, and lovastatin were, respectively, 55%, 26%, 17%, and 7.5%.

Mohaupt et al.<sup>3</sup> reported that structural muscle injury does not necessarily lead to elevated levels of creatine phosphokinase (CPK). Persistent myopathy in patients taking statins reflects structural muscle damage, and lack of elevated levels of circulating CPK does not rule out structural muscle injury. Mohaupt et al. found no correlation of muscle injury to the statin dose or type. Draeger et al.<sup>4</sup> found statins caused extensive changes in the expression of genes of the calcium regulatory and the membrane repair machinery, whereas the expression of genes responsible for mitochondrial function or myocyte remodeling was unaffected. Draeger et al. found that lipophilic statins impair mitochondrial function in skeletal muscle.

## Statins and Diabetes

Although the medical community's awareness of increased diabetes risk with statin use appears recent, Siddals et al.<sup>5</sup> raised the alarm in 2004. They reported that statins caused the "abrogation of insulin action." HMG-CoA (3-hydroxy-3-methylglutaryl-Coenzyme A) reductase inhibitors disrupt cellular processes by the depletion of isoprenoids and dolichols that are intimately involved with insulin and insulin-like growth factor (IGF) signaling, including receptor functions.

Reports of increasing diabetes Type 2 associated with statins were not long in coming after 2004. At first the diabetes incidence was modest, but it rapidly increased. One of the more influential studies, the Women's Health Initiative of 2012,<sup>6</sup> concluded that statin medication use in postmenopausal women is associated with an increased

risk for diabetes mellitus. The response of FDA was almost immediate,<sup>7</sup> demanding new labeling on statin medication and opening the floodgates for litigation. South Carolina soon found it necessary to use the class-action mechanism to handle the litigation load.<sup>8</sup> But it was the study of Cederberg et al.,<sup>9</sup> published in 2015, that has truly alarmed the medical community. They reported: "Our population-based METSIM study including 8,749 non-diabetic individuals at baseline showed that statin therapy was associated with a 46% increase in the risk of incident diabetes after adjustment for confounding factors." They found in their 6-year follow-up study that the increased risk of Type 2 diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion.

### Statins and Renal Failure

Rhabdomyolysis has long been recognized as a significant cause of acute renal failure. Shortly after the bombing of London began in 1940, a new type of acute renal failure was noticed in some of those rescued from fallen buildings. Typically the patient had been buried for several hours with pressure on a limb. At autopsy brown pigmented casts containing myoglobin were found in the kidney tubules along with changes we now call acute tubular necrosis. Many of these early rhabdomyolysis patients died because dialysis had not yet been invented. Subsequently, many different causes of rhabdomyolysis other than crush injuries have been identified, including electrical shock, thermal imbalance, cocaine, certain toxins, electrolyte and endocrine disorders, and more recently statin drug use.

Despite numerous studies, the exact nature of acute renal failure (ARF) related to muscle injury remains to be identified. Classically, the cause of ARF from rhabdomyolysis has been attributed to mechanical obstruction by myoglobin and particles of muscle tissue obstructing tubular flow. But, early studies indicated that even a localized myopathic process such as a crush injury to arm or leg can trigger acute renal failure without tubular obstruction.

Safety concerns related to potential toxic effects of high-dose statins in patients with reduced renal clearance have definitely limited the use of statins in the chronic kidney disease (CKD) population. In the SHARP study (Study of Heart and Renal Protection), Baigent et al.<sup>10</sup> reported that 33% initiated dialysis during the trial, many of those within the first year. It appeared that the combination of simvastatin and ezetimibe, an inhibitor of cholesterol absorption and trafficking, accelerated the CKD process.

New information cited by Floyd et al. in *JAMA*<sup>11</sup> dramatically points attention to simvastatin as a primary contributor to rhabdomyolysis today. With its rate of rhabdomyolysis reports of 4.7 per one million prescriptions filled, it is second only to rosuvastatin. Floyd et al. failed to address any specific cause for simvastatin's preeminent association with rhabdomyolysis.

Furthermore, chronic myalgia without CPK elevations may be an indicator of subclinical myopathy and a major

contributor to progressive renal failure. The higher incidence of myalgia and myopathy, now much closer to 20% than the 2% originally cited, especially when combined with the risk factor of statin-related diabetes, can make a major contribution to progressive renal failure.

### Genetic Polymorphisms and Statin Levels

With the advent of increasingly sophisticated and available genetic screening, much has been learned in these past few years directly bearing on statin toxicity. It appears that some of us are born with various genetic combinations that greatly increase our sensitivity to the various statin drugs. The question now is just how significant this factor is. A large Finnish study comparing Finns with the rest of the world has provided insight chilling in its implications.

The relevant factor is a genetic combination known as the *SLCO1B1* polymorphism,<sup>12</sup> specifically the variant c.521CC genotype called "SNIPS" by workers in the field. This variant form has some rather remarkable effects on the pharmacokinetics of different statins. Its greatest effect is on the plasma concentration of simvastatin. It also increased the plasma concentration of atorvastatin, pravastatin, and rosuvastatin, but to a lesser degree.

Large differences in frequency of these genetic combinations exist between different populations. The highest frequency of these variant genotypes was found in America (24% average, 18%-32% range) with similar but slightly smaller figures for Europe (18% average, 14%-23% range). The smallest frequency of this variant genotype was found in Sub-Saharan Africa (1.9% average, 0.7%-4.8% range).

In the United States 24% of our population is born with a supersensitivity to statins. In such patients, statin blood levels are far higher than expected with usual doses. This may be particularly evident with the use of simvastatin. It appears that nearly one-quarter of our population could be inadvertently overdosed with statins because of its genetically programmed predisposition. This observation should trigger an immediate review and, possibly, withholding of this statin until the population at risk can be identified. Note that simvastatin in 10 mg tablets is dispensed over the counter in the United Kingdom.

Rosuvastatin, the newest statin, first marketed in 2003 despite FDA's prohibition against marketing its 80 mg dose because of both rhabdomyolysis and kidney damage tendency, managed to achieve a rate of 13.1 rhabdomyolysis cases per million prescriptions filed. And this was the statin that replaced Baycol!

### Case Study

Generally, statin rhabdomyolysis is considered an acute crisis reaction requiring immediate hospitalization and aggressive therapy. Low-grade myopathy triggered by statin therapy may also lead to end-stage renal failure as seen in the following case. It may be a strong indication that this condition may actually be common. Boltan et al.<sup>13</sup> in 2007

reported a statin myopathy of this nature associated with the drug simvastatin.

A 59-year-old black man was in his usual state of good health until July 2004, when he was hospitalized for an acute myocardial infarction. He had been on simvastatin 20 mg daily for the previous 6 years. Coronary artery bypass grafting was performed on Jul 27, 2004, and the postoperative course was uncomplicated. At hospital discharge, the simvastatin was increased to 40 mg daily, and he was started on 81 mg of aspirin daily.

He did well until June 2005 (4 months before death), when he noticed bilateral muscle weakness in his legs. A biopsy of his deltoid muscle revealed a non-inflammatory myopathy, and the simvastatin therapy was discontinued in early July 2005.

He was transferred to specialty hospitals because of worsening bilateral muscle weakness, dysphagia, dysarthria, and dyspnea. No abnormalities were noted on examination of the lungs, heart, abdomen, cranial nerves, skin, or lymph nodes. The peripheral muscles were severely weak bilaterally. The deep tendon reflexes could not be elicited in the knees or ankles. He was unable to walk.

During his entire hospitalization he was alert, but there was never any improvement in the degree of muscle weakness. It progressed to the point where he was unable to lift either his arms or legs or move about in bed. A prednisone pulse was without benefit. Numerous studies were performed to rule out infectious, paraneoplastic, toxic, and rheumatologic causes of the myopathy, and appropriate tests for these were negative. On Oct 1, 2005, generalized tremors appeared, and he died.

At autopsy multiple muscle biopsies showed extensive myofibril loss, degeneration/regeneration, and calcific deposits. The cause of death was determined to be necrotizing bronchopneumonia associated with impaired respiratory function. Although muscle enzymes studies had been elevated they never reached the level common to the usual acute rhabdomyolysis cases.

This case report is an example of chronic progressive myopathy leading to death. At the present time my repository has received reports of about 250 cases of what I have called chronic myopathy associated with the use of statin drugs. Most have normal CPK, but moderate elevations are sometimes seen. These patients have been asymptomatic on statins until muscle aches and pains occur. From that point on there is inexorable progression of the condition despite stopping the statin. Sometimes CoQ10 supplementation is helpful in causing at least partial remission.

A neurologist consultant recently suggested to me that somatic mitochondrial mutations could be a cause of this statin reaction. A logical sequence of events would be that statin-associated CoQ10 inhibition allows greater exposure of mitochondria to the harmful effects of oxidation and free radical exposure, resulting in a much greater mutation rate. Once triggered, the mutation would be permanent as long as it is not so severe as to cause cell death. The suggestion seems worth considering.

## Conclusion

The incidence and prevalence of statin-associated rhabdomyolysis, myopathy, and diabetes is apparently much higher than previously thought, and can be present without elevation of CPK levels. Yet statins are being more widely used, and at increased doses, to achieve a 3% to 5% absolute risk reduction for cardiovascular events. The increased risk of diabetes and the collateral damage to muscle and kidneys is probably higher than most clinicians would consider acceptable. The evidence suggests restricting the use of statin drugs until we know more about the incidence and pathophysiology of statin-related myalgia, myopathy, and renal disease.

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