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Short Article

Statin Therapy and the Risk of Rhabdomyolysis in Physically Active Individuals: Implications for Sports Medicine

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Abstract

Background. Statins are widely prescribed for cardiovascular prevention and generally have a favorable safety profile. However, skeletal muscle adverse effects occur and, rarely, may progress to rhabdomyolysis, which can lead to acute kidney injury and death.

Aim. To summarize current evidence on statin-induced rhabdomyolysis, including epidemiology, mechanisms, risk factors, and clinical management, with emphasis on physically active individuals and sports medicine practice.

Material and methods. Narrative review of clinical trials, observational studies, pharmacovigilance analyses, and case reports addressing statin-associated rhabdomyolysis, exercise-related risk, drug–drug interactions, and patient susceptibility factors.

Results. Rhabdomyolysis is rare in randomized trials but appears more frequently in real-world settings, especially with high-intensity statin regimens, interacting medications (e.g., CYP3A4 inhibitors), renal/hepatic dysfunction, and genetic predisposition. Strenuous or unaccustomed exercise may act synergistically with statin-related myotoxicity, complicating diagnosis in athletes due to overlap with post-exercise soreness and physiological CK elevations.

Conclusions. Although uncommon, statin-induced rhabdomyolysis is clinically important. Individualized risk assessment, patient education, early symptom recognition, prompt statin discontinuation when suspected, and supportive management are essential, particularly in physically active populations.

Key words: statins; rhabdomyolysis; statin-associated muscle symptoms; exercise; athletes; sports medicine; drug–drug interactions; lipid-lowering therapy.

Content

1. Introduction

Statins are a cornerstone of contemporary cardiovascular prevention and treatment. By inhibiting 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, they reduce hepatic cholesterol synthesis and upregulate LDL receptors, thereby lowering circulating LDL cholesterol and reducing major cardiovascular events. Despite proven benefits and broad guideline endorsement, statin therapy may be associated with skeletal muscle adverse effects, collectively termed statin-associated muscle symptoms (SAMS), ranging from myalgia to severe myopathy and, rarely, rhabdomyolysis. Although rhabdomyolysis is uncommon, its potential consequences—acute kidney injury, electrolyte disturbances, arrhythmias, and death—justify heightened clinical awareness, particularly in populations exposed to additional muscle stressors such as strenuous physical activity. [1,2]

2. Statin Therapy and Skeletal Muscle

Statins differ in chemical structure, lipophilicity, metabolic pathways, and transporter dependence, which may influence muscle exposure and toxicity. Lipophilic statins (e.g., simvastatin, atorvastatin, lovastatin) distribute more readily into extrahepatic tissues, including skeletal muscle, whereas hydrophilic agents (e.g., pravastatin, rosuvastatin) are more hepatoselective. Metabolism through cytochrome P450 enzymes is clinically important: statins primarily metabolized by CYP3A4 are vulnerable to interactions with macrolide antibiotics, azole antifungals, certain calcium-channel blockers, and other inhibitors, potentially increasing systemic statin concentrations. Hepatic uptake transporters (notably OATP1B1) also affect exposure; SLCO1B1 polymorphisms can increase plasma statin levels and myopathy risk. In practice, muscle toxicity often reflects the combined effects of dose, pharmacokinetics, comorbidities, and concomitant medications. [1,2,7,10]

3. Statin-Associated Rhabdomyolysis

Rhabdomyolysis is characterized by rapid breakdown of skeletal muscle fibers with release of intracellular contents into the circulation. It is typically diagnosed by markedly elevated creatine kinase (CK) and evidence of myoglobinuria, with risk of acute kidney injury. Statin-induced rhabdomyolysis represents the most severe end of the SAMS spectrum and is commonly associated with CK levels exceeding 10–40 times the upper limit of normal, although much higher levels may occur. Pathophysiological mechanisms include sarcolemmal disruption,

mitochondrial dysfunction, impaired cellular energy production, oxidative stress, and dysregulated calcium homeostasis. The classic triad of myalgia, weakness, and dark urine is not always present, and nonspecific symptoms can delay recognition. [2,5,10]

4. Epidemiology of Statin-Induced Rhabdomyolysis

In randomized clinical trials, rhabdomyolysis is very rare. However, real-world evidence and pharmacovigilance reports suggest a higher occurrence in routine practice, likely due to broader patient heterogeneity, comorbidities, and polypharmacy. Risk varies among statins and increases with higher doses and interacting drugs. The historical withdrawal of cerivastatin due to an excess of fatal rhabdomyolysis cases illustrates the importance of dose, pharmacokinetics, and interaction potential in determining safety. [1,3,6]

5. Risk Factors for Rhabdomyolysis in Statin Users

Risk is multifactorial. Key contributors include high-intensity dosing, older age, female sex, low body mass, renal or hepatic impairment, untreated hypothyroidism, diabetes, and genetic susceptibility (e.g., SLCO1B1 variants). Drug–drug interactions are among the most clinically actionable factors, particularly with CYP3A4 inhibitors and certain combination lipid-lowering regimens. Dehydration, heat stress, infections, and unaccustomed strenuous exercise may further lower the threshold for muscle injury. In many cases, rhabdomyolysis develops through the convergence of several risk factors rather than statin exposure alone. [2,4,7,8,11]

6. Physical Activity and Exercise-Related Risk

Exercise is a recognized trigger for rhabdomyolysis, especially when intense, prolonged, unaccustomed, or performed under adverse environmental conditions. In physically active individuals, exercise-induced muscle microtrauma may synergize with statin-related vulnerability, increasing susceptibility to severe muscle breakdown. Clinical interpretation is challenging because athletes frequently report muscle soreness and may have transient CK elevations after training. Therefore, clinicians should consider symptom pattern, severity, functional impairment, systemic features, and urine discoloration, and maintain a low threshold for laboratory evaluation when symptoms are atypical or disproportionate. [6,12]

7. Diagnostic Approach and Clinical Management

Evaluation should include CK, renal function (creatinine, urea), electrolytes (especially potassium and calcium), and urinalysis for myoglobinuria. When rhabdomyolysis is suspected, the statin should be discontinued promptly, strenuous activity stopped, and supportive management initiated—most importantly aggressive hydration and monitoring for complications. Severe cases may require hospitalization, treatment of hyperkalemia, and renal replacement therapy. After recovery, decisions regarding lipid-lowering therapy should be individualized; in confirmed severe statin intolerance or prior rhabdomyolysis, non-statin options (e.g., ezetimibe, PCSK9 inhibitors, bempedoic acid, inclisiran) may help achieve LDL-C targets while minimizing recurrence risk. [1,2,7]

8. Conclusions

Statin-induced rhabdomyolysis is rare but clinically significant. The risk is shaped by dose, statin properties, interactions, comorbidities, and individual susceptibility, and may be amplified by strenuous physical activity. In sports medicine settings, individualized risk assessment, patient education, careful monitoring of atypical muscle symptoms, and early diagnostic testing are essential to preserve cardiovascular benefit while minimizing the risk of severe muscle toxicity. [1,2,6]

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Conflicts of Interest

The authors declare no conflict of interest.

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