

STATIN ASSOCIATED MYOPATHY

Statins are the most effective antilipemic agents for reducing LDL cholesterol and have been proven, in numerous studies involving diverse patient populations, to prevent both primary and secondary sequelae of cardiovascular disease.

Statins lower cholesterol production by competitively inhibiting 3-hydroxy-3-methylglutoyl co-enzyme A (HMGCoA) and the synthesis of Mevalonate, a precursor of both cholesterol and co-enzyme Q10 (CoQ10).^{Fig 1} A reduction in cholesterol synthesis increases the synthesis of hepatic low density lipoprotein (LDL) receptors on cell surfaces which increases plasma clearing of LDL and lowers serum cholesterol. Co-enzyme Q10 (CoQ10) is also a naturally occurring fat soluble quinone localized in hydrophilic portions of cellular membranes. While roughly half of the body's CoQ10 is ingested through dietary fat, the rest is endogenously synthesized. CoQ10 is an essential component of the mitochondrial electron transport system, protects against free radical induced oxidative stress and regenerates active forms of the antioxidants tocopherol (vitamin E) and ascorbic acid (vitamin C). The importance of CoQ10 in mitochondrial muscle function has led to the hypothesis that co-enzyme Q10 deficiency from statin therapy may participate in statin associated myopathy.¹⁻³ Statins are generally well tolerated. The most serious side effects are associated with liver and skeletal muscle abnormalities. Elevation of hepatic serum transaminases is dose dependent and occurs in a frequency of approximately 1%. Myopathic complaints range from mild myalgias to rhabdomyolysis. While mild myalgias with normal serum creatinine kinase (CPK) is probably not uncommon with statin therapy, the incidence of fatal rhabdomyolysis is reported as only 1.5 deaths per 10 million prescriptions.²

While the mechanism of statin therapy is not well understood, reduced intramuscular CoQ10 has received attention as a possible etiologic factor for the reasons discussed above. Clinical data, however, strongly linking this association is inconsistent. While statin therapy has been associated with a reduction in serum CoQ10 levels, data is lacking regarding consistent intramuscular CoQ10 levels in symptomatic patients with myopathy. In addition, clinical responses with CoQ10 supplementation have also been inconsistent. Other factors may also contribute to symptoms of myalgias including neuromuscular/inflammatory conditions and hypothyroidism. Hypothyroidism has been hypothesized as possibly potentiating the myotoxic effects of statins. Conceivably, higher doses of statins may also increase the possibility of statin induced myopathy.

What options are available in patients with putative statin induced or suspected myalgias, especially in high risk patients where stopping statin medication may not be the preferred option?

Consider these thoughts:

1. While myalgias and cramps with statins are not uncommon, true myopathy (associated with increasing CPK levels) is very rare (less than 0.1%); patient education and reassurance sometimes do much to allow patients to continue with this therapy.
2. Evaluate patients for hypothyroidism and other drugs that may increase the potential for myotoxicity (i.e., felodipine, verapamil, erythromycin, azole anti-fungals, cyclosporine A,

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fibric acid derivatives, Niacin). Consider using fenofibrate rather than gemfibrozil when adding this class to statins for mixed dyslipidemia – especially if using higher dose statins; the combination of gemfibrozil and cerivastatin was particularly myotoxic before the latter was removed from the market.

3. Consider using the variable pharmacological differences of statins in choosing options. For example, the hydrophilic statins – pravastatin, Rosuvastatin and Fluvastatin might be tried instead of atorvastatin, lovastatin and simvastatin which are lipophilic. Current evidence suggests that muscle damage is precipitated through CYP3A4 inhibition. Fluvastatin is metabolized by CYP2C9 and alternate pathways, and not by the CYP3A4 system which metabolizes atorvastatin, lovastatin, and simvastatin. Also consider using a lower dose of a hydrophilic statin with Ezetimibe. Doubling a statin dose only results in approximately a 6% reduction in LDL while adding Ezetimibe to the existing dose of a statin is associated with a 20-25% LDL reduction.
4. Finally, although the pathogenesis of statin induced myalgias is not definitively understood, and patient response to CoQ10 supplementation inconsistent, there are no known risks to this supplement and a trial of CoQ10 50 to 100 mg bid for two to three months is not unreasonable in selected patients, and may help alleviate myopathic symptoms.

REFERENCES

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