**ABSTRACT**

Heart disease (HD) is the number one killer in the United States. In 2006, the direct and indirect costs associated with cardiovascular disease in the United States were estimated at 400 billion dollars. Statin therapy for cholesterol reduction is a mainstay intervention for cardiovascular disease (CVD) as reflected in atorvastatin’s status as the number one prescribed medication in the United States. Statin therapy, however, is also associated with side effects that signal mitochondrial distress. A commonly reported statin-induced symptom is myalgia, which is defined as muscle pain without an associated elevation of serum creatine kinase (CK). In clinical trials, the reports of myalgia vary from less than 1% to 25% of patients. Myopathy is a general term defined as an abnormal condition or disease of muscle tissue. Myopathy includes myalgia, myositis (inflammation of muscle tissue associated with elevated CK) and the very serious condition rhabdomyolysis (extreme myositis). Histological findings in statin-induced myopathy demonstrate electron chain dysfunction making “mitochondrial myopathy” the more precise term. Mitochondrial myopathy has been associated with statin-induced CoQ10 depletions. Given the density of mitochondria in cardiomyocytes, and CoQ10’s role in mitochondrial energy production, depletions have long been associated with increased risk for heart disease. In the case below, mitochondrial-specific organic acids, serum CoQ10, vitamin D and clinical history all suggest statin-induced mitochondrial myopathy, despite normal serum CK.

**SINOPSIS**

Las enfermedades coronarias (EC) constituyen la causa número uno de muerte en los Estados Unidos. En el 2006, los costes directos e indirectos relacionados con las enfermedades cardiovasculares en los Estados Unidos se estimaron en unos 400 millones de dólares. La terapia con estatinas para reducir el colesterol es una intervención principal para las enfermedades cardiovasculares (ECV), como se refleja en el estatus de la atorvastatina como el principal medicamento recetado en los Estados Unidos. El tratamiento con estatinas, sin embargo, está asociado a efectos secundarios que indican insuficiencia mitocondrial.

Un síntoma inducido por las estatinas que se notifica con frecuencia es la mialgia, definida como un dolor muscular sin un incremento asociado de creatina quinasa (CK) sérica. En los ensayos clínicos, las comunicaciones de mialgia varían desde menos del 1% hasta el 25% de los pacientes. La miopatía es un término general, definido como una condición anormal o enfermedad del tejido muscular. La miopatía incluye mialgia, miositis (inflamación del tejido muscular asociada a niveles elevados de CK) y la condición extremadamente grave de rhabdomiólisis (miositis extrema).

Los resultados histológicos en la miopatía inducida por estatinas demuestran una disfunción de la cadena de electrones, por lo que “miopatía mitocondrial” es un término más preciso. La miopatía mitocondrial se ha asociado a una reducción del CoQ10 inducida por estatinas. Dada la densidad de mitocondrias en los cardiomiocitos y el papel del CoQ10 en la producción de energía mitocondrial, esta reducción se ha asociado a un incremento del riesgo de enfermedades coronarias. En el caso que se indica más abajo, los ácidos orgánicos específicos mitocondriales, el CoQ10 sérico, la vitamina D y los antecedentes médicos sugieren una miopatía mitocondrial inducida por estatinas, a pesar de la CK sérica normal.
**Case Report**

**CASE HISTORY**

BT, a 57-year-old male, presented with fatigue, severe depression and myalgia. His fatigue and myalgia became worse with exercise. He was taking 40 mg of the cholesterol-lowering medication atorvastatin for many months. The onset of fatigue, myalgia and exercise intolerance occurred after the introduction of the statin.

**Initial Laboratory Results**

**Laboratory tests ordered and rationale:**
1. Urinary organic acids: Provides a functional assessment of mitochondrial activity
2. CoQ10: Deficiency may occur with statin therapy and may be associated with statin-induced side effects.
3. Vitamin D: Deficiency is associated with depression and statin-induced myalgia.
4. Serum creatine kinase: Elevation indicates muscle injury. In cases of elevation, isozymes may be obtained to determine involved organ system.

**Pertinent Negative Results:**
- Serum creatine kinase was within normal limits.

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**57-Year-Old Male with Statin-Induced Myopathy**

**Additional Symptoms and Conditions**
- Myalgia, hyperlipidemia, depression, fatigue

**Medication**
- Atorvastatin (Lipitor®)

**Tests Used**
- CoQ10, vitamin D; organic acids; serum creatine kinase

**Imbalances Identified**
- Low serum CoQ10 and vitamin D with elevated citric acid cycle intermediates

**Treatments**
- CoQ10, vitamin D3; reduce simple carbohydrates; consume a whole-foods based, high-fiber diet; exercise program; discontinue atorvastatin

**Outcome**
- Resolution of symptoms; maintenance of healthy cholesterol levels without medication

**Discussion/Significance**
- In this case, the side effects of fatigue, myalgia, exercise intolerance and depression required cessation of statin therapy. Laboratory evaluation of nutrients and mitochondrial function guided appropriate nutrient interventions. Assessment of mitochondrial health and the nutrients involved in mitochondrial function may be pivotal in determining who is most vulnerable to statin-induced side effects.

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**Carbohydrate Metabolism**

(B1, B3, Cr, Lipoic Acid, CoQ10)

- Pyruvate 2.1
- L-Lactate 23 H
- β-Hydroxybutyrate <DL*

**Energy Production (Citric Acid Cycle)**

(B comp., CoQ10, Amino acids, Mg)

- Citrate 610 H
- Cis-Aconitate 42
- Isocitrate 79
- a-Ketoglutarate 13.9
- Succinate 49.9 H
- Fumarate 0.55
- Malate 6.0 H
- Hydroxymethylglutarate 6.9 H

**Figure 1. Urinary organic acids.** Elevations in lactic acid and citric acid cycle intermediates suggested a functional need for Coq10. The cholesterol synthetic pathway was also inhibited, as shown by the elevation of hydroxymethylglutarate. (Units: μg/mg creatinine)
Case Report

Initial Assessment

Statin-induced mitochondrialopathy presenting with:

- Myalgia
- Depression
- Fatigue
- Exercise intolerance

Initial Plan

- Discontinue atorvastatin
- CoQ10 300 mg, 1 cap PO QD
- Vitamin D₃ 2000 IU, 1 cap PO QD
- Reduce simple carbohydrates; eat a whole-foods, high-fiber diet
- Cardiovascular exercise program

Treatment rationale: BT’s treatment was straightforward: Discontinue the most likely cause of the myalgia, which was atorvastatin; begin CoQ10 and vitamin D3 as laboratory findings demonstrated low normal levels; institute dietary changes and an exercise program for long-term cholesterol control.

Four-Month Follow-up

The patient responded well to the interventions. The myalgia, fatigue and depression resolved with the cessation of atorvastatin and the introduction of nutrients. Exercise tolerance improved and healthy cholesterol levels were maintained through diet and exercise.

DISCUSSION

Statin therapy has been associated with side effects that suggest mitochondrial distress, such as fatigue and myalgia, symptoms experienced by BT. When HMG-CoA reductase is chronically inhibited, the aforementioned compounds may become depleted. Depletion of CoQ10 in particular may result in a mitochondrialopathy, as evidenced in this case by imbalanced mitochondrial markers, including the elevated lactate and citric acid cycle intermediates (Figure 1). These data corroborated the findings in Figure 2, which showed low-normal serum CoQ10. HMG-CoA reductase inhibition may therefore have ultimately resulted in lowered energy (ATP) production via CoQ10 depletion (Figure 3). Since the mitochondria reside most densely in tissue with high energy demands, heart muscle is among the first to be affected. CoQ10 deficiency has been associated with mitochondrial myopathy, fatigue, heart disease and Parkinson disease.

While it has been understood for more than 20 years that statin drugs reduce CoQ10 levels and that CoQ10 depletion can induce mitochondrial myopathy, current standard guidelines don’t recommend routine use of CoQ10 in people taking statins. Atorvastatin in particular has been shown to significantly reduce CoQ10 very quickly—in as little as two weeks—and by more than 50% after 30 days of therapy. As discussed, it is speculated that the deficiency of CoQ10 is the cause of statin myopathy, exercise intolerance, and myoglobinuria. Research on the resolution of fatigue and myalgia with CoQ10 supplementation has been mixed when patients continue on statin therapy. However, significant improvement of symptoms such as myalgia, fatigue, dyspnea, memory loss, and peripheral neuropathy was demonstrated with 240 mg/day CoQ10 supplementation when the statin was discontinued.

Since myalgia could signal rhabdomyolysis, a serum creatine kinase (CK) level should be obtained in anyone reporting muscle pain while on statin therapy. BT’s vitamin D was shown to be low in Figure 2. While vitamin D depletion has not been directly associated with statin therapy, a recent study demonstrated that supplementation of high-dose vitamin D₃ led to a resolution of statin-induced myalgia in 92% of the study population. This finding suggests a link between statin-induced myalgia and vitamin D deficiency or insufficiency.

Depression—also experienced by BT—has been linked to statin therapy and may be associated with lower brain cholesterol levels. Vitamin D deficiency has been linked to depression. It may be that CoQ10 and vitamin D assessment should take place prior to

| 25-Hydroxyvitamin D | 15 L |
|---------------------|------|
| 16                  | 10 - 64 ng/mL |

| Coenzyme Q10 | 0.60 L |
|--------------|-------|
| 0.64         | 0.48 - 3.04 mg/L |

Figure 2. Serum vitamin D and CoQ10. Both levels were in the low range.
and during statin therapy, with treatment initiated as indicated. Cholesterol levels should also be periodically monitored and when warranted, prompt medication adjustment if found to be low or low-normal. Indeed, in one study, an increased incidence of death occurred after six years of 5 mg simvastatin therapy when LDL levels fell below 80 mg/dL.

In this case, BT responded very favorably to treatment that included cessation of atorvastatin, introduction of CoQ10, vitamin D, dietary changes and exercise. His program was successful in resolving his myalgia, fatigue, and depression. His exercise tolerance was improved, and he was able to maintain healthy cholesterol levels, thereby significantly reducing his risk for CVD.

CONCLUSION

Statin-related side effects, including fatigue, exercise intolerance and myalgia suggest mitochondrial vulnerability associated with CoQ10 depletion. Depression has also been associated with statin use. Vitamin D appears to be associated with statin myalgia, although the mechanism has yet to be elucidated. Mitochondrial vulnerability may be increased in persons with certain genetic variants in mitochondrial and P450 proteins and comorbid conditions such as diabetes. Functional assessment of mitochondrial health using organic acids, as well as direct assessment of nutrients including serum CoQ10 and vitamin D, may be key in determining who is at risk for statin-induced side effects. In this case, side effects required cessation of medication. However, identification and treatment of nutrient deficiencies, along with appropriate diet and exercise, successfully resolved side effects while keeping lipids at an acceptable level and significantly reducing risk for CVD. This type of program may be utilized in lieu of, or in conjunction with, statin therapy.

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