Is Coenzyme Q10 Effective in Reducing Statin-Induced Myalgias

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Citation

Abstract
Hyperlipidemia is a major risk factor for cardiovascular events such as acute myocardial infarction, coronary artery disease, and stroke. High cholesterol is prevalent in 20-25% of the adult population (1). For some individuals, lifestyle changes such as diet and exercise are not enough to lower cholesterol to acceptable levels. For these individuals pharmacological treatment, such as statin therapy, is necessary. According to the American Heart Association, 106.7 million Americans over the age of 20 have high cholesterol and of those, it is estimated that 11 to 25 million are on statin therapy (1). Myalgias, or muscle aches, are a relatively common symptom of statin therapy and can be significant enough to cause cessation of treatment. Post-marketing studies show a 13.6% incidence of statin-induced myalgias (2). Research is being done to find ways to reduce the myalgias so individuals can remain on statins and therefore reduce their risk of cardiovascular events. On promising treatment option for statin-induced myalgias is the use of coenzyme q10. The question this paper asks is whether coenzyme q10 is effective in reducing statin-induced myalgias. This question is relevant because proper treatment would decrease the number of patients stopping statin therapy, therefore decreasing the risk of cardiovascular events in a large portion of the American population. This paper will critically examine two randomized studies, each with different outcomes, to help determine if the use of coenzyme q10 is effective in reducing statin-induced myalgias.

BACKGROUND
According to the Center for Disease Control and Prevention about 17% of Americans have high total cholesterol (3). This affects at least 42 million Americans with 63 million Americans having borderline high cholesterol (3). Cholesterol is a fatty substance made of lipoproteins used by the body for maintaining and building cell membranes, and producing hormones and bile acids. Cholesterol is attained through our diet and synthesized in our bodies; 20–25% of our daily cholesterol synthesis occurs in the liver. There are three different types of cholesterol; low density lipoproteins (LDL), high density lipoproteins (HDL), very low density lipoproteins (VLDL) and triglycerides.

Excess LDL cholesterol is deposited in the blood vessels causing plaque formation on arterial walls that subsequently narrow the lumen. This is known as atherosclerosis. These plaques are also subject to instability, leading to thrombus formation and subsequent embolic events such as acute myocardial infarction, cerebral vascular accident and pulmonary embolisms.

Triglycerides are a different type of lipid which is used by the body for energy. Excess amounts of triglycerides, will circulate through the blood and be stored as fat in adipose tissue. Though the mechanism is not fully known, excess triglycerides may lead to atherosclerosis and subsequent risk of heart disease and stroke.

HDL is synthesized in the liver. It is a high density lipoprotein that is able to transport LDL cholesterol from within the arteries back to the liver for excretion or re-utilization. Therefore, higher levels of HDL seem to protect against cardiovascular diseases by removing excess LDL cholesterol from the arterial system.

High cholesterol or hyperlipidemia is usually asymptomatic. Some signs of high cholesterol include eruptive xanthomas, tendinous xanthomas, and lipemia retinalis. Often hyperlipidemia goes undiagnosed until routine testing is done or an embolic event, such as the ones previously described, occur.

The diagnosis of hyperlipidemia is made by performing a fasting lipid panel. A fasting lipid panel will show the total cholesterol, LDL, HDL and triglyceride levels in a fasting state. The American Heart Association states that total
cholesterol should be below 200 mg/dl, triglycerides less then 150 mg/dl, HDL greater then 40 mg/dl for men and 50 mg/dl for women, and LDL should be below 100 mg/dl. Diabetics with a history of heart attack should aim for an LDL of less then 70 mg/dl (1).

Treatments include diet modifications, physical activity, bile acid-binding resins, fibric acid derivatives, niacin, ezetimibe and HMG-CoA reductase inhibitors or statins. Diet modification can lower LDL levels by 5-10 % (3). Patients should follow a low cholesterol diet which is low in total fat, especially saturated fats, and high in fruits, vegetables and insoluble fiber. Aerobic exercise has been shown to increase HDL levels and decrease levels of LDL and triglycerides. The American Heart Association recommends at least 30 minutes of aerobic activity daily. Other life style changes which reduce the risk of cardiovascular disease include smoking cessation, and control of hypertension.

Bile acid-binding resins, cholestyramine and colestipol work by binding bile acids in the terminal ileum causing increased bile acid synthesis, therefore increasing LDL receptor activity in the liver (4). They are indicated for individuals with elevated LDL levels. They can reduce LDL cholesterol by 10-15% (4). Side effects include gastrointestinal symptoms like nausea, vomiting and abdominal discomfort, and rarely myalgias.

Fibric acid derivatives such as gemfibrozil, Tricor and clofibrate inhibit VLDL production and stimulate the lipoprotein lipase enzyme to clear excess VLDL. They also increase HDLs and lower triglycerides by up to 40% (4). There main indication is for use in patients with hypertriglyceridemia. Side effects include gastrointestinal symptoms, myalgias, cholelithiasis, and myositis.

Niacin inhibits the release of free fatty acids in peripheral tissue, thereby reducing hepatic triglyceride synthesis. It is mainly used to increase levels of HDL in patients with low HDL levels. Side effects include flushing, itching, elevated liver function tests, elevated uric acid levels, impaired glucose tolerance and gastrointestinal symptoms.

Zetia or ezetimibe inhibits dietary absorption of cholesterol from the small intestine. No side effects greater than placebo were noted in trials. Zetia decreases total cholesterol and LDL levels and is used in combination with statins in the form of Vytorin.

Currently statin therapy is used when diet and exercise alone are not sufficient at lowering LDL levels. Statin therapy reduces the incidence of myocardial infarction and overall mortality in individuals with hyperlipidemia (4). It is able to reduce LDL cholesterol as much as 35% (4). Statin drugs work by inhibiting 3-hydroxy-3-methilglutaryl coenzyme A (HMG-CoA) which is a rate limiting step in the production of cholesterol. Side effects include headache, nausea, vomiting, rash and muscle pain or myalgias.

Myalgias are defined as a muscle ache or weakness without increased serum CK levels. The actual cause of myalgias is uncertain but it is believed to be caused by disruption in the mevalonate pathway and alterations in several metabolic pathways. By inhibiting HmG-CoA, statin drugs also inhibit isoprenylated proteins, Co-Q10 and glycosylation. These products are responsible for mitochondrial function and muscle function such as myogenesis and myoregeneration. Without these products, skeletal muscle experiences apoptosis, degradation and mitochondrial dysfunction.

Myalgias experienced with statin use can lead to discontinuation of therapy. By discontinuing the medication, the patient is at risk for recurrence of hyperlipidemia and subsequent cardiovascular events. Since hyperlipidemia affects so many individuals and myalgia symptoms are very common, it is important to find a way for patients to reduce symptoms in order to continue therapy, thereby reducing the risk for myocardial infarction, stroke and overall mortality.

Co-Q10 is made by the body along the same pathway as cholesterol; therefore, statin therapy also limits the production of Co-Q10. Co-Q10 is important for mitochondrial function and decreases oxidative stress. It is hypothesised that decreased levels of Co-Q10 cause impaired metabolism and affect muscle function. By administering oral Co-Q10 it is believed this will prevent and treat statin-induced myalgias. If this hypothesis is true, it will allow patients to remain on statin therapy, thereby reducing their overall cardiovascular risk.

**METHODS**

Journal articles were acquired using online Academic Search Premiere with the key words “statin* AND Coenzyme Q10". The search was limited to only full text articles from the year 2000 to the present. The total number of results was 48. Another search was conducted online through Google Scholar with the key words, “statin* AND Coenzyme Q10.” The search could not be limited to full text articles, however, it was limited from the year 2000 to the present and included only articles related to medicine and pharmacology. There were 2,810 results attained.
Two randomized controlled double-blind study (level 1) were chosen, since this type of study is the best at answering questions of treatment. These two articles were chosen because they directly examined whether coenzyme Q10 decreased myalgias induced by statin therapy. The trails were preformed on humans and all were written in English.

**DISCUSSION**

**ARTICLE #1**

The first article entitled, “Effect of Coenzyme Q10 on Myopathic Symptoms in Patients Treated with Statins” was conducted by Dr. Caso, et al (1). The article was peer-reviewed and published in The American Journal of Cardiology. The purpose of the randomized double blind study was to determine whether Coenzyme Q10 reduced muscle pain and decreased interference in daily activities. Thirty two patients, 15 women and 17 men, were enrolled in the trial based on their medical records. The patients were all located at cardiology clinics, being treated with statin therapy and experiencing symptoms defined as, “presence of muscle pain alone or accompanied by other symptoms such as muscle weakness and fatigue” with no other evident cause. Exclusion criteria included individuals with hepatic, vascular, renal or endocrine disease, coagulopathy or other serious medical conditions. The demographics of the patients were not listed in the article.

Patients were given the Brief Pain Inventory questionnaire, which provides information on the intensity of pain and degree to which pain interferes with function. The questionnaire is a numeric scale from 0 to 10 and rates pain at its worse, least, average, during the prior week and currently. It also asks about the relief of pain, quality of pain and perception of pain. The study does not mention how or who administered these questionnaires during their initial visit. A CK and fasting lipid profile were also obtained. The patients were randomly assigned to one of two groups though the study does not specify how the patients were assigned to these groups. The first group was given 100 mg of Co-Q10 while the second group was given 400 IU of vitamin E as a control. Dispensing of the medications was carried out by the pharmacist at the General Clinical Research Center without direct contact with the patients. Both the physicians performing the study and the subjects were blinded. The study does not give details as to the appearance of the two medications, or who the individuals administering the questionnaire and collecting the data. They also do not mention if the individuals administering the questionnaire and collecting the data were blinded. Patients continued their statin therapy along with either the Co-Q10 or vitamin E for 30 days. All patients were accounted for at the end of the study and remained 100% compliant with the treatments. The researchers measured compliance by counting the number of pills remaining at the end of the trial. Patients returned to the clinic on the 30th day to complete the Brief Pain Inventory questionnaire once again and had a CK and fasting lipid profile repeated. The results of the study showed a decrease in perceived muscle ache by 40% and improved daily life activities by 38% in the Co-q10 group; both of which were statistically significant.

This article was a peer-reviewed, current study which directly tested the question asked. The design for the study was appropriate and addressed the issue in a clear, articulate manner. The groups were similar at the beginning of the trial, did not have any significant difference in selection or underlying variables and each were treated equally during the study. However, the demographics for each group were not stated in the article. This could impact the study since other medical illnesses such as diabetes, prior heart disease and age can have an impact on fasting lipid testing, perception of pain (as in diabetic neuropathy), and risk factors for cardiovascular disease. The trial was truly a double blind study. The population and sample size for the study was not appropriate. There were only 32 patients enrolled, 16 patient per group, which was not a significant number compared to the overall number of individuals with statin-induced myalgias. Appropriate inclusion and excision criteria were followed. Methods for the trial were sound. The analysis was appropriate and supported the conclusion. No obvious bias was noted in the study. The article did not address any problems with the study.

Some problems with the study were that all participates were on different dosages and types of statins. This difference in treatment was not accounted for in the study. This could have had an effect since there is a linear correlation with the dosage of statin and myalgia symptoms. The dosage could also have an affect on the fasting lipid test as higher doses may show greater control of cholesterol levels. Also, the use of vitamin E causes another variable in the study. A placebo or sugar pill should have been used to decrease the number of overall variables between the two groups. By choosing vitamin E versus a placebo, it is impossible to say if vitamin E could have played a role in reduction or exacerbation of myalgia symptoms.
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ARTICLE #2

The second article entitled, “Effect of Coenzyme Q10 on Supplementation on Simvastatin-Induced Myalgia” was written by Dr. Young and associates (2). The article appeared in the American Journal of Cardiology. The purpose of this randomized controlled study was to determine if coenzyme Q10 affected simvastatin tolerability and myalgia symptoms. Forty-four patients were enrolled in this double blind study. Inclusion criteria included patients using simvastatin with myalgia symptoms severe enough to stop adequate statin therapy. Exclusion criteria included patients with a myocardial infarction or CVA three months prior to the study, those with alanine aminotransferase or aspartate aminotransferase over three times the normal level, heart failure, warfarin use, and antioxidant vitamin supplementation. Demographics for the patients were not listed in the article.

Before beginning the trial, patients discontinued coenzyme Q10 or cholesterol modifying therapies except for ezetimibe for two weeks. Patients were then classified as having severe or moderate myalgias while on statin therapy. Sever was defined as the inability to tolerate statin dose of 20 to 40 mg/day and moderate was defined as myalgia symptoms at doses less than 20 mg/day. The article did not mention who made these classifications. Patients were randomly placed into one of two groups though the article does not explain how this was done. The first group was treated with 200 mg of Coenzyme Q10 daily and the other group was given a placebo. The article does not mention what the placebo was. Each group received simvastatin titrated to 40 mg at weekly intervals. The trial lasted 12 weeks. Fasting blood work was obtained including a total plasma CoQ10, lipid panel, CK, electrolytes, renal and liver function and CBC. Symptoms were evaluated by patients using a visual analogue scale documenting the intensity of pain and number of sites affected. Patients with significant symptoms decreased or stopped their therapy. The primary outcome included patients who tolerated 40 mg/d at the end of 12 weeks.

The results of the study showed no significant difference in the number of patients who tolerated 40 mg/day of simvastatin. There was no significant difference in relief of myalgia symptoms as per the researchers though no questionnaire or data were given as support. The results also showed a decrease in plasma Co-Q10 levels in the placebo group and a significant increase in plasma CK in the placebo group. All other lab work showed no significant difference.

Lab data confirmed a decrease in plasma Co-Q10 levels with statin therapy and increase in plasma Co-Q10 levels when given Co-Q10 supplementation. Lab data also showed a significant increase in plasma CK levels in those undergoing statin therapy alone and no significant increase with Co-Q10 supplementation. This lab data proves that statin therapy does affect Co-Q10 and CK levels in the blood.

The article was a current, peer-reviewed study that tested the stated question. The design was appropriate and addressed the issue in a clear, articulate manner. According to the demographics listed, the groups were similar and did not have any significant difference in selection. The population and sample size for the study was appropriate. A criterion for selection was followed. Methods for the trial were sound. The analysis was appropriate for the conclusion. The study only examined patients who completed the 12 week program on 40mg/d of simvastatin and dismissed those who completed the study on lower doses. No obvious bias was noted in the study. The article did not list any flaws or issues regarding the study.

Some problems with this study was that the study relied on how many patients in each group were able to complete the study at 40 mg/d at the end of a 12-week period. They performed no formal questionnaire as to the patients’ perception of myalgia pain. They inferred their the patient relief of myalgia symptoms rather than directly analyzing the patients’ complaints. Other reasons for discontinuation of therapy or lowering doses of simvastatin were not addressed in the article. The study did not take into consideration the differences in perceived pain by the patients and whether 20 mg/d was a therapeutic dosage for certain patients. This could impact the study by disregarding those who had attained therapeutic levels and symptoms relief, thereby skewing the study. The article dismissed the blood work results showing changes between the two groups rather then explaining their significance. This could impact the study by not acknowledging possible differences and showing a possible significant affect of Co-Q10. This also showed a bias in the researcher’s conclusion. Also, the article did not analyze its own study with critiques or changes which means the researchers did not look into ways of improving their technique or acknowledging downfalls in their design. This could have an impact in the study since there were areas which could be improved and may have been improved had the researchers acknowledged them during the study.
CONCLUSION

After examining the two studies done on the treatment of statin-induced myalgias with coenzyme Q-10, no definitive conclusion can be made. Each study resulted in a different conclusion and also had significant flaws, which could have affected the end result. However, the use of Co-Q10 shows increases the plasma levels of Co-Q10 which shows the efficacy of Co-Q10 supplementation and may translate into increased intramuscular levels of Co-Q10. Co-Q10 also decreases the CK levels which shows a decreased amount of skeletal muscle damage as a result of statin therapy. The evidence does show a perceived decrease in muscle ache and increased ability to perform daily activities. No negative side effects were noted and patients experienced a benefit in activities of daily living. The affect of supplementation noted by the patients and the affect it had on their daily activities lends support for the use of Co-Q10 for statin induced myalgias. Future large-scale studies need to be performed to address issues encountered during the prior studies.

Until further studies are performed the use of Co-Q10 should be continued in patients experiencing statin-induced myalgias. The current studies show a correlation in reduction of perceived myalgia symptoms while using Co-Q10 with no negative side effects. Since there is no evidence of harm with Co-Q10 and research has shown some promising results, patient should use Co-Q10 for myalgia symptoms.

References

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