

CME CREDIT EDUCATIONAL OBJECTIVE: Readers will assess the current evidence for using coenzyme Q10 supplements

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Coenzyme Q10: A therapy for hypertension and statin-induced myalgia?

ABSTRACT

Some small clinical trials seem to show that coenzyme Q10 supplements can be used to lower blood pressure and to treat or prevent myalgia caused by hydroxymethylglutaryl coenzyme A reductase inhibitors (statins). However, larger trials are needed to determine if they are truly effective for these purposes. The authors examine the evidence and also discuss issues such as bioavailability, elimination, safety, and cost.

KEY POINTS

In some clinical trials, coenzyme Q10 supplements significantly lowered diastolic and systolic blood pressure.

Statins may lower coenzyme Q10 serum levels, and some investigators have evaluated the relationship between coenzyme Q10 deficiency and statin-related myalgia, but more evidence is needed to support the use of coenzyme Q10 supplements to prevent or treat myalgia.

Coenzyme Q10 supplementation appears to be relatively safe. Most clinical trials have not reported significant side effects that necessitated stopping therapy. Gastrointestinal effects include abdominal discomfort, nausea, vomiting, diarrhea, and anorexia. Allergic rash and headache have also been reported.

COENZYME Q10 SUPPLEMENTS have been purported to be effective for treating a variety of disorders,^{1,2} in particular hypertension and statin-induced myalgia.

Several studies³⁻⁷ found that coenzyme Q10 supplementation significantly lowered blood pressure in hypertensive patients. Moreover, some trials have demonstrated that statin therapy reduces serum or muscle levels of coenzyme Q10,⁸⁻¹⁴ prompting investigations to determine whether coenzyme Q10 deficiency is related to statin-induced muscle pain.¹⁵⁻¹⁷

In this review, we discuss the efficacy and safety of coenzyme Q10 supplementation in patients with hypertension and those taking statins, and some of the caveats about using supplements that are not approved by the US Food and Drug Administration (FDA), as well as the bioavailability and quality of available formulations.

WHAT IS COENZYME Q10?

Coenzyme Q10, also known as coenzyme Q, ubiquinone, and ubiquinol, is found in all human cells, with the highest concentrations in the heart, liver, kidney, and pancreas.^{1,2} It is a potent antioxidant, a membrane stabilizer, and an integral cofactor in the mitochondrial respiratory chain, helping to generate adenosine triphosphate, the major cellular energy source.^{1,2,18} It may also regulate genes associated with cell metabolism.¹⁹

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■ RATIONALE FOR SUPPLEMENTATION

Coenzyme Q10 supplementation has been used, recommended, or studied in heart failure, hypertension, parkinsonism, mitochondrial encephalomyopathies, and other ailments.

In hypertension

Depending on the class, various antihypertensive drugs can have adverse effects such as depression, cough, and cardiac and renal dysfunction.^{20,21} Furthermore, many patients need to take more than one drug to control their blood pressure, increasing their risk of side effects. Some researchers believe coenzyme Q10 supplementation may reduce the need to take multiple antihypertensive drugs.⁵

Coenzyme Q10 appears to lower blood pressure. The exact mechanism is not known, but one theory is that it reduces peripheral resistance by preserving nitric oxide.²¹ Nitric oxide relaxes peripheral arteries, lowering blood pressure. In some forms of hypertension, superoxide radicals that inactivate nitric oxide are overproduced; coenzyme Q10, with its antioxidant effects, may prevent the inactivation of nitric oxide by these free radicals. Alternatively, coenzyme Q10 may boost the production of the prostaglandin prostacyclin (PGI₂) a potent vasodilator and inhibitor of platelet aggregation, or it may enhance the sensitivity of arterial smooth muscle to PGI₂, or both.^{1,22}

In patients taking statins

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), first-line agents for lowering cholesterol levels to prevent cardiovascular disease, are some of the most commonly prescribed medications.^{23,24} However, statin therapy carries a risk of myopathy, which can range from muscle aches to rhabdomyolysis.^{23,24}

In a clinical advisory,²⁵ the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute recommend that patients on statin therapy who experience muscle soreness, tenderness, or pain with serum creatine kinase levels 3 to 10 times the upper limit of normal should have their creatine kinase level checked weekly. If the level is 3 to 10 times

the upper limit of normal, statin therapy may be continued, but if it exceeds 10 times the upper limit, then statins and other potential offending agents (eg, niacin, fibrate) need to be discontinued.

Statins inhibit the synthesis of cholesterol by reducing the production of mevalonate, a precursor of both cholesterol and coenzyme Q10. Since both cholesterol and coenzyme Q10 are produced by the same pathway, it is not surprising that statins have been reported to reduce serum and muscle coenzyme Q10 levels.⁹⁻¹⁴ However, one study did not report a significant reduction of coenzyme Q10 levels in muscle tissue in patients treated with simvastatin 20 mg for 6 months.²⁶

Nonetheless, researchers have hypothesized that a reduction in coenzyme Q10 levels in muscle tissue causes mitochondrial dysfunction, which could increase the risk of statin-induced myopathy,¹³⁻¹⁷ and some believe that treatment with coenzyme Q10 may reduce myalgic symptoms and allow patients to remain on statin therapy.^{13,24}

Researchers have investigated the potential of coenzyme Q10 supplementation to reduce or prevent statin-induced myopathy.¹⁵⁻¹⁷ (More on this below.)

Interestingly, a randomized, placebo-controlled trial²⁷ found that 6 months of daily therapy with simvastatin (Zocor) 20 mg or pravastatin (Pravachol) 40 mg lowered systolic and diastolic blood pressure significantly in patients with no documented history of cardiovascular disease or diabetes. A possible mechanism of statin-induced blood pressure reduction is the up-regulation of endothelial nitric oxide synthetase, a potent vasodilator. Coenzyme Q10 levels were not assessed during this study. Whether coenzyme Q10 supplementation used to treat statin-induced myalgia enhances or inhibits the antihypertensive effects of statins is not yet known.

■ EVIDENCE OF EFFECTIVENESS IN HYPERTENSION

A number of trials provide clinical evidence that some patients with high blood pressure may benefit from coenzyme Q10 supplementation (TABLE 1).^{3-7,28-31}

Rosenfeldt et al²⁸ performed a meta-

In the body, cholesterol and coenzyme Q10 are produced by the same pathway

TABLE 1

Effect of coenzyme Q10 supplements on blood pressure

INVESTIGATORS	NO. OF PATIENTS	BLOOD PRESSURE (MM HG)			
		BASELINE PLACEBO GROUP	COENZYME Q10 GROUP	FOLLOW-UP PLACEBO GROUP	COENZYME Q10 GROUP
Yamagami et al ³	20	168/96	167/97	164/93	148/91 ^a
Digiesi et al ³¹	18	167/103	167/103	166/103	156/95 ^b
Langsjoen et al ⁵	109	—	159/94	—	147/85 ^c
Singh et al ⁶	64	166/105	168/106	164/103	152/97 ^d
Burke et al ⁷	85	164/82	165/81	163/82	147/78 ^e

^a Statistically significant difference in systolic pressure vs baseline, $P < .01$

^b Crossover study; statistically significant differences in systolic and diastolic pressures vs baseline and vs placebo, $P < .001$

^c Cohort study; statistically significant differences in systolic and diastolic pressures vs baseline, $P < .001$

^d Statistically significant differences in systolic and diastolic pressures vs placebo, $P < .05$

^e Statistically significant difference in systolic pressure vs baseline and vs placebo, $P < .01$

analysis and found that some trials documented statistically significant reductions in diastolic or systolic blood pressure or both, while others reported negligible effects.^{3,29} In one small trial,³⁰ blood pressures actually went up in patients taking coenzyme Q10. Coenzyme Q10 dosages and length of therapy varied from study to study in the meta-analysis. Only minor adverse effects such as gastrointestinal upset and headache were reported.

Yamagami et al³ randomly assigned 20 patients with hypertension and a low coenzyme Q10 level to receive 100 mg of coenzyme Q10 or placebo daily for 12 weeks. Patients continued their usual antihypertensive regimen during the study period. Blood pressures, coenzyme Q10 levels, and antihypertensive drugs used were comparable between the study groups.

After 12 weeks of therapy, the mean coenzyme Q10 level in the active-treatment group had more than doubled, from 0.704 to 1.597 $\mu\text{g/mL}$. This group also experienced a statistically significant drop in systolic blood pressure, from 167 mm Hg at baseline to 148 mm Hg at 12 weeks. In the placebo group, the systolic blood pressure was 168 mm Hg at baseline and 164 mm Hg at 12 weeks; the change was not statistically significant. Diastolic pressure was not significantly lower at 12 weeks than at baseline in either group.

The authors concluded that coenzyme

Q10 supplementation brought a mild reduction in high blood pressure in patients who had low coenzyme Q10 serum levels.

Digiesi et al³¹ randomized 18 patients with essential hypertension to receive either coenzyme Q10 100 mg or placebo daily for 10 weeks. All antihypertensive therapy was discontinued at baseline. After the first 10 weeks, patients went through a 2-week washout period and then were switched to the opposite therapy for an additional 10 weeks. Mean baseline blood pressure values were 167 mm Hg systolic and 103 mm Hg diastolic.

Those taking the supplement had a statistically significant decrease in systolic and diastolic pressures ($P < .001$). The antihypertensive effect was noted in the 3rd or 4th week of active treatment and persisted for the duration of therapy. The effects dissipated 7 to 10 days after coenzyme Q10 was stopped.

Langsjoen et al⁵ evaluated the effects of adding coenzyme Q10 to the antihypertensive drug regimen of 109 patients who had a primary diagnosis of essential hypertension in a prospective observational study. Patients with hypertension as a secondary diagnosis and other cardiovascular diseases were excluded. Variable doses of coenzyme Q10 were given, adjusted according to clinical response and to achieve serum levels greater than 2.0 $\mu\text{g/mL}$. The average dose was 225 mg/day; the mean serum level attained was 3.02 $\mu\text{g/mL}$.

Some clinicians believe taking coenzyme Q10 may reduce myalgia and allow patients to stay on statin therapy

Over several months, patients taking the supplement had a reduction in mean systolic pressure from 159 mm Hg at baseline to 147 mm Hg ($P < .001$), and a reduction in mean diastolic pressure from 94 to 85 mm Hg ($P < .001$). Thirty-seven percent of patients were able to discontinue one antihypertensive drug, 11% discontinued two drugs, and 4% were able to stop taking three drugs. However, 46% remained on the same antihypertensive regimen, and 3% needed an additional drug.

Singh et al⁶ randomized 64 patients who had coronary artery disease and who had been on antihypertensive drugs for more than 1 year to receive either B-complex vitamins or coenzyme Q10 (hydrosoluble Q-Gel) 60 mg orally once daily for 8 weeks. Five patients were not available for follow-up; therefore, only 59 patients were evaluated. Fifty-five (93%) of the 59 patients were taking only one antihypertensive drug. Initial antihypertensive drug use was similar between study groups and was continued throughout the trial.

After 8 weeks of therapy, the coenzyme Q10 group had significantly lower systolic and diastolic blood pressure than the placebo group ($P < .05$ for both). There was also a statistically significant decrease in the dosage of antihypertensive drugs in the coenzyme Q10 group but not in the placebo group ($P < .05$), reflecting coenzyme Q10's additive antihypertensive effect.

Burke et al⁷ randomized 41 men and 35 women with isolated systolic hypertension (systolic pressure 150–170 mm Hg, diastolic pressure < 90 mm Hg) to receive a twice-daily dose of 60 mg of emulsified coenzyme Q10 (hydrosoluble Q-Gel) with 150 IU of vitamin E or placebo containing vitamin E alone for 12 weeks. The study also included 5 men and 4 women with normal blood pressure, all of whom received coenzyme Q10. A total of 80 patients completed treatment. The primary goal of the study was to determine the efficacy of coenzyme Q10 in the treatment of isolated systolic hypertension in patients without comorbid conditions. Blood pressures were monitored twice a week during the trial, by the same nurse.

After 12 weeks of treatment, the mean reduction in systolic pressure in hypertensive patients on coenzyme Q10 was 17.8 ± 7.3 mm

Hg. There were no significant changes in diastolic pressure in any study group with treatment. Patients with isolated systolic hypertension who were taking coenzyme Q10 had a statistically significant reduction in systolic pressure compared with baseline and placebo ($P < .01$ for both). Approximately 55% of patients on coenzyme Q10 achieved a reduction in systolic pressure of 4 mm Hg or greater, while 45% did not respond to therapy. The mean plasma coenzyme Q10 level of the treatment group increased from 0.47 ± 0.19 $\mu\text{g/mL}$ to 2.69 ± 0.54 $\mu\text{g/mL}$ after 12 weeks; however, the study did not have the statistical power to demonstrate a relationship between coenzyme Q10 levels and changes in blood pressure. Twenty-seven (34%) of the 80 patients were taking a statin while on coenzyme Q10 therapy.

■ STUDIES IN STATIN-INDUCED MYOPATHY

Thibault et al³² and Kim et al³³ reported that patients taking lovastatin (Mevacor) at dosages as high as 35 mg/kg/day to inhibit tumor growth achieved symptomatic relief of statin-induced musculoskeletal toxicity after coenzyme Q10 supplementation.

Caso et al¹⁵ performed a small pilot study in 32 patients to determine if coenzyme Q10 supplementation would improve myalgic symptoms in patients treated with statins. In this double-blind, randomized trial, patients received either coenzyme Q10 100 mg/day or vitamin E 400 IU/day for 30 days. The extent of muscle pain and its interference with daily activities were determined before and after therapy using the Brief Pain Inventory Questionnaire. The statins were atorvastatin (Lipitor) 10 mg or 20 mg, lovastatin 40 mg, pravastatin 40 mg, and simvastatin 10, 20, 40, and 80 mg. Five patients in the coenzyme Q10 group and four patients in the vitamin E group were taking nonsteroidal anti-inflammatory drugs before and during the trial. The intensity of muscle pain and its interference with daily activities were similar between study groups before the start of therapy.

After 30 days of treatment with coenzyme Q10, the pain intensity had decreased significantly from baseline ($P < .001$). In contrast, no change in pain intensity from baseline was

In Singh et al, after 8 weeks, the coenzyme Q10 group had significantly lower systolic and diastolic pressures than the placebo group

noted in patients receiving vitamin E. The Pain Severity Score was significantly different between study groups, favoring the coenzyme Q10 group ($P < .001$). Sixteen of 18 patients on coenzyme Q10 reported a reduction in pain, while only 3 of 14 patients on vitamin E reported a similar response. Also, the interference of pain with daily activities significantly improved with coenzyme Q10 ($P < .02$), whereas vitamin E did not have a significant impact on this.

Young et al¹⁷ randomized 44 patients with prior statin-induced myalgia to receive increasing doses of simvastatin (10–40 mg/day) in combination with either coenzyme Q10 (Q-Gel) 200 mg/day or placebo. The primary goal was to determine if coenzyme Q10 supplementation would help improve statin tolerance in patients with a history of statin-induced myalgia. Plasma coenzyme Q10 and lipid levels were measured at baseline and at the end of the study. The intensity of myalgia was assessed with a visual analogue scale.

At 12 weeks, the coenzyme Q10 plasma level was significantly higher in the treatment group than in the placebo group ($P < .001$). However, no differences were noted between groups in the number of patients who tolerated the 40-mg/day simvastatin dose ($P = .34$) or in the number of patients who remained on any simvastatin dose ($P = .47$). Additionally, myalgia scores did not differ between groups ($P = .63$). The authors acknowledged that there were only small increases in the myalgia pain scores reported in either group. Therefore, patients in the treatment group may not have experienced sufficiently severe muscle pain to have benefited from coenzyme Q10 supplementation.

■ IS COENZYME Q10 SAFE?

Studies have indicated that these supplements are well tolerated, with relatively few adverse effects or potential drug interactions.^{1,2,34}

The FDA does not routinely assess the purity or quality of over-the-counter coenzyme Q10 products.³⁵ However, the United States Pharmacopeia (USP) does test dietary supplements to make sure that they are not mislabeled and that they do not contain contaminants.³⁶

A USP-verified dietary supplement should:

- Contain the exact ingredients listed on the label in the listed potency and amounts
- Not include harmful levels of certain contaminants such as lead, mercury, pesticides, or bacteria
- Appropriately disintegrate and release its contents into the body within a specified period of time
- Be produced using the FDA's current Good Manufacturing Practices.³⁶

Side effects, contraindications, warnings

Coenzyme Q10 is a relatively safe dietary supplement. It is contraindicated in patients who are allergic to it or to any of its components.² Most clinical trials have not reported significant adverse effects that necessitated stopping therapy.³⁴ However, gastrointestinal effects such as abdominal discomfort, nausea, vomiting, diarrhea, and anorexia have occurred.^{1,2,34} Allergic rash and headache have also been reported.^{1,2,34} In addition, coenzyme Q10's antiplatelet effect may increase the risk of bleeding.^{37,38} It undergoes biotransformation in the liver and is eliminated primarily via the biliary tract,³⁹ so it can accumulate in patients with hepatic impairment or biliary obstruction.

Interactions with drugs

Coenzyme Q10's effects on platelet function may increase the risk of bleeding in patients taking antiplatelet drugs such as aspirin or clopidogrel (Plavix).^{37,38} On the other hand, since it acts like vitamin K, it may counteract the anticoagulant effects of warfarin (Coumadin).^{1,2,40}

Coenzyme Q10 may have an additive antihypertensive effect when given with antihypertensive drugs.⁴¹

Coenzyme Q10 may improve beta-cell function and enhance insulin sensitivity, which may reduce insulin requirements for diabetic patients.^{42,43}

■ SLOWLY ABSORBED

Coenzyme Q10 is absorbed slowly from the gastrointestinal tract, possibly because it has a high molecular weight and is not very water-soluble.³⁹

One pharmacokinetic study found that af-

Mitochondrial dysfunction associated with low levels of endogenous coenzyme Q10 in muscle could lead to statin-induced myopathy

Coenzyme Q10 supplements may increase bleeding in patients on antiplatelet drugs but may counteract warfarin

ter a single 100-mg oral dose of coenzyme Q10, the mean peak plasma levels of about 1 µg/mL occurred between 5 and 10 hours (mean 6.5 hours).⁴⁴ Coenzyme Q10 100 mg given orally three times daily produced a mean steady-state plasma level of 5.4 µg/mL; about 90% of this steady-state concentration was achieved after 4 days.³⁹

Some formulations have significantly better oral bioavailability and therefore produce higher plasma levels. Soft-gel capsules, especially those with vegetable oil or vitamin E, may have better absorption.⁴³

A pharmacokinetic study showed that the area under the curve of the plasma coenzyme Q10 concentration was more than twice as high with Q-Gel soft-gel capsules, a completely solubilized formulation, than with soft-gel capsules with an oil suspension, powder-filled hard-shell capsules, or regular tablets.⁴⁵ Another study reported that colloidal-Q10, a formulation contained in VESIsorb (a novel drug delivery system sold as CoQsource) had greater bioavailability than solubilized and oil-based preparations.⁴⁶ Commercially available solubilized preparations containing ubiquinol, a metabolized form of coenzyme Q10, have been shown to produce higher serum levels than solubilized products.⁴⁷

Of note: unless the manufacturer claims that its product is water-soluble, the USP does not evaluate its dissolution rate.⁴⁸ Therefore, USP-verified coenzyme Q10 products that are not water-soluble may have lower bioavailability than their solubilized counterparts.

Dry dosage forms of coenzyme Q10 (eg, tablets, capsules) may be more readily absorbed if taken with a fatty meal.⁴³

■ SLOWLY ELIMINATED

Taken orally, coenzyme Q10 has a low clearance rate, with an elimination half-life of about 34 hours.³⁹

After absorption, exogenous coenzyme Q10 is taken up by chylomicrons that transport it to the liver, where it is incorporated into very-low-density lipoproteins. It is then distributed to various organs, including the adrenal glands, spleen, kidneys, lungs, and heart. Coenzyme Q10 is eliminated primarily via the biliary tract. About 60% of an oral dose is eliminated in the

feces during chronic oral administration.³⁹

■ TWICE-DAILY DOSING

A typical daily dose of coenzyme Q10 for treating hypertension is 120 to 200 mg, usually given orally in two divided doses.¹ For statin-induced myopathy, 100 to 200 mg orally daily has been used.¹

Coenzyme Q10 is given in divided doses to enhance its absorption and to minimize gastrointestinal effects.^{1,43} Taking it with a fatty meal may also increase its absorption.⁴³

Since solubilized forms of coenzyme Q10 and ubiquinol have significantly greater bioavailability than nonsolubilized forms, the therapeutic dose of these formulations may be lower.⁴⁷

■ MONITORING DURING TREATMENT

Without supplementation, the mean serum level of endogenous coenzyme Q10 has been reported to be 0.99 ± 0.30 mg/L (range 0.55–1.87).¹⁸ Serum levels above 2 µg/mL have been associated with significant reductions in blood pressure.^{5,7,28}

The possible effects of coenzyme Q10 on blood pressure, blood glucose levels, serum creatine kinase levels, and myopathic symptoms should be kept in mind when monitoring patients who have hypertension,⁴¹ diabetes,^{41,42} or statin-induced myalgia.^{15,17} Coenzyme Q10's possible potentiating effects on antiplatelet drugs and its inhibitory effect on warfarin should be kept in mind as well.

■ COST VARIES

Coenzyme Q10 is available in different dosage forms (eg, regular and rapid-release soft-gel capsules, regular and chewable tablets, chewable wafers, and liquid) from a variety of manufacturers. Products come in different strengths, typically ranging from 30 to 400 mg. USP-verified formulations are listed at www.usp.org/USPVerified/dietarySupplements/ under "Verified Supplements." Only USP-verified products that claim to be water-soluble meet USP dissolution requirements.

The cost varies, depending on the vendor.

In general, dosage forms with greater bioavailability, such as Q-Gel and ubiquinol supplements, are more expensive. For example, a regimen of 60 mg twice daily of regular-release coenzyme Q capsules may cost approximately \$20 per month, compared with \$60 per month for the same supply of Q-Gel Ultra capsules. However, in some cases, supplements that produce higher serum levels may be more cost-effective.

■ CURRENT ROLE IN THERAPY

As an antihypertensive adjunct

Several small clinical trials have shown that coenzyme Q10 supplementation can lower blood pressure. The supplements were reported to be safe and well tolerated. Moreover, some patients with essential hypertension who were taking coenzyme Q10 were able to discontinue one or more antihypertensive drugs. A significant reduction in blood pressure with use of coenzyme Q10 would be expected to reduce the adverse consequences of hypertension in the same manner as conventional antihypertensive agents.

However, no large, double-blind, randomized study has evaluated the impact of coenzyme Q10 when taken with other antihypertensive drugs (eg, angiotensin-converting enzyme inhibitors, beta-blockers, diuretics) on specific clinical end points such as the in-

cidence of stroke or death from a major cardiac event. Furthermore, its effects on cardiac function, exercise tolerance, and quality of life have not been determined.

The bottom line. In some cases, it seems reasonable to recommend this product as an adjunct to conventional antihypertensive therapy. Larger, well-designed clinical trials of coenzyme Q10's antihypertensive effects on specific clinical end points such as the risk of stroke or myocardial infarction are needed to define its true therapeutic value.

As a treatment for statin-induced myalgia

Clinical evidence supporting coenzyme Q10's use in the treatment of statin-induced myopathy is limited. Whether coenzyme Q10 is depleted from muscle tissue during statin therapy has not been confirmed. Supplementation helped reduce the severity of musculoskeletal effects of megadoses of lovastatin. However, clinical trials of coenzyme Q10 in the treatment of myalgia associated with antilipidemic statin doses did not consistently report significant improvement. Nevertheless, coenzyme Q10 has been shown to be relatively safe, with few adverse effects.

The bottom line. In some cases, coenzyme Q could be considered as a possible treatment for statin-induced myalgia, pending large-scale studies to determine if it is truly effective for this purpose. ■

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