Coenzyme Q10: Who needs it?

Geneva Clark Briggs, PharmD, BCPS
Coenzyme Q10

- Available in more than 100 single-ingredient and combination-ingredient products
- Greater than $200 million in sales/year
Coenzyme Q10

- Other names: ubiquinone, ubidecarenone, coenzyme Q
- A fat soluble benzoquinone produced in mitochondria (heart, liver, kidney and pancreas)

Coenzyme Q10

- Component of the mitochondrial electron transport chain

NADH, nicotinamide adenine dinucleotide; Q, CoQ10; C, cytochrome C; Fe-S, iron-sulfur clusters; ADP, adenosine diphosphate; ATP, adenosine triphosphate.
Coenzyme Q10

- Two forms - ubiquinone and ubiquinol
- Reduced form, ubiquinol, inhibits protein and DNA oxidation and lipid peroxidation
- Only lipid soluble antioxidant synthesized endogenously
Some Purported Indications for CoQ10

- Familial CoQ10 deficiencies
- Statin induced myopathy
- Heart failure
- Hypertension
- Parkinson’s disease
Clinical Syndromes of CoQ10 Deficiency

- Inherited metabolic muscle and mitochondrial diseases
  - Myopathy with recurrent myoglobinuria and CNS involvement
  - Cerebellar ataxia with variable CNS involvement
  - Isolated myopathy
  - Mitochondrial encephalomyopathy
Clinical Syndromes of CoQ10 Deficiency

- Supplementation may reduce symptoms
- May require high doses and 6 months or more of therapy to improve symptoms
- UbiQGel - FDA orphan drug status for treating mitochondrial encephalomyopathies
Prevention/Treatment of Statin Induced Myalgia
Biosynthetic Pathway

Tyrosine or Phenylalanine

\[ \text{4OH-Benzoate} \]

\[ \text{Decaprenyl-PP} \]

Ubiquinone

Acetyl-CoA

HMG-CoA

HMG CoA reductase

Mevalonate

\[ \text{Farnesyl-PP} \]

\[ \text{Squalene} \]

\[ \text{Cholesterol} \]
AHA/ACC/NHLBI Definitions

- myopathy - any disease of muscle
- myalgia - focal or diffuse muscle aches or weakness with no elevation of creatine kinase
- myositis - muscle pain with a systemic inflammatory response and elevated creatine kinase more than 3× ULN
- rhabdomyolysis - severe muscle damage with damage to another organ, notably the kidneys, myoglobinuria and creatine kinase more than 10× ULN
Familial CoQ10 deficiency
- severe causes mitochondrial myopathic changes with exercise intolerance and recurrent myoglobinuria.
- Less severe is associated cerebellar ataxia, muscle weakness.

Do statins decrease CoQ10?

- Some small studies do show ↓ plasma levels with treatment
- Other studies show no change in CoQ10 levels

*Clin Pharmacol Ther 2008;8:731-9.*
*Atherosclerosis 2007;195:e182-9.*
*Int J Cardiol 2007;118:173-7.*
Lipid Corrected CoQ10 Levels

- CoQ10 is carried in blood by lipoproteins
- When plasma levels are corrected for lipid values on statins - no change in CoQ10 levels

### Studies of CoQ10 in Myalgia

<table>
<thead>
<tr>
<th>Study population</th>
<th>Study Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 patients with statin induced myopathy, elevated CK levels</td>
<td><strong>Prospective</strong>, 25 control muscle biopsy samples</td>
<td>Muscle structure was normal in 14, showed evidence of mitochondrial dysfunction and nonspecific myopathic changes in 2 patients.</td>
</tr>
</tbody>
</table>

Muscle CoQ10 concentration not statistically different between patients and control subjects.

Muscle CoQ10 was normal in 4, < normal in 10, > normal in 4.

*Arch Neurol 2005;62:1709-12.*
## Studies of CoQ10 in Myalgia

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<th>Study population</th>
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<tr>
<td>44 patients with myalgia on statins, CoQ10 200 mg/day or placebo, 12 weeks, simvastatin titrated to 40 mg/day, reduced dose or stopped therapy if myalgia developed</td>
<td>Randomized, placebo-controlled</td>
<td>16 of 22 [73%] CoQ10 tolerated 40 mg/day vs 13 of 22 [59%] with placebo, p = 0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 of 22 [73%] CoQ10 stayed on therapy vs 18 of 22 [82%] with placebo, p = 0.47</td>
</tr>
</tbody>
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*Am J Cardiol 2007;100:1400-3.*
### Studies of CoQ10 in Myopathy

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<th>Study population</th>
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<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Patients with myopathic symptoms secondary to statin, CoQ10 (100 mg/day, n = 18) or vitamin E (400 IU/day, n = 14) for 30 days</td>
<td>Randomized, double-blind</td>
<td>Pain severity ↓ 40% (p &lt; 0.001) and pain interference with daily activities ↓ 38% (p &lt; 0.02) in CoQ10 group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No changes in pain severity (+9%, p = NS) or pain interference with daily activities (-11%, p = NS) in vitamin E group</td>
</tr>
</tbody>
</table>

Am J Cardiol 2007;99:1409-12.
What we don’t know for sure ...

- Do plasma levels of CoQ10 need to be corrected for lipid levels?
- Do lower circulating CoQ10 levels reflect low mitochondrial levels?
- Do lower plasma levels have long term impact?
## Genetic Risk Factors Associated with Statin Induced Myalgia

<table>
<thead>
<tr>
<th>Gene (statin)</th>
<th>Polymorphism/mutation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statin pharmacokinetics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C8 (cerivastatin)</td>
<td>475delA</td>
<td>Rhabdomyolysis observed in homozygote</td>
</tr>
<tr>
<td>CYP2D6 (fluvastatin)</td>
<td>CYP2D6*3, *5</td>
<td>Higher incidence of drug intolerance in homozygotes</td>
</tr>
<tr>
<td>CYP2D6 (simvastatin)</td>
<td>CYP2D6*4</td>
<td>Atorvastatin and simvastatin-induced myopathy</td>
</tr>
<tr>
<td>CYP3A5 (lovastatin, pravastatin, simvastatin, and atorvastatin)</td>
<td>CYP3A5*1, *3, *5</td>
<td>Elevated plasma simvastatin; homozygotes for CYP3A5*3 at greater risk for muscle damage</td>
</tr>
<tr>
<td>SLCO1B1(OATP1B1) (simvastatin)</td>
<td>SNP in intron 11</td>
<td>Mild myopathy with elevated serum creatine kinase</td>
</tr>
<tr>
<td>SLCO1B1(OATP1B1) (simvastatin, pravastatin, atorvastatin, rosuvastatin, and pitavastatin)</td>
<td>T521C, V174A</td>
<td>Myopathy; increased plasma statin levels, except fluvastatin</td>
</tr>
<tr>
<td>ABCB1 (atorvastatin, simvastatin)</td>
<td>Various</td>
<td>Elevated plasma statin levels</td>
</tr>
<tr>
<td><strong>Metabolic muscle disease genes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COQ2 (multiple)</td>
<td>CoQ2 polymorphisms</td>
<td>Associated with statin intolerance [34*]</td>
</tr>
<tr>
<td>CPT2 (multiple)</td>
<td>S113L</td>
<td>Rhabdomyolysis in heterozygotes and homozygotes [25]</td>
</tr>
<tr>
<td>PYGM (multiple)</td>
<td>R50X</td>
<td>Rhabdomyolysis in heterozygotes [25]</td>
</tr>
<tr>
<td>AMPD1 (multiple)</td>
<td>Q12X + P48L</td>
<td>Rhabdomyolysis in homozygotes only [25]</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGTR1 (multiple)</td>
<td>SNP in intron 3</td>
<td>Variations in serum creatine kinase during therapy [35]</td>
</tr>
<tr>
<td>NOS3, exon 8 (multiple)</td>
<td>D298E</td>
<td>Variations in serum creatine kinase during therapy [35]</td>
</tr>
<tr>
<td>HTR3B and HTR7 (multiple)</td>
<td>One SNP/gene</td>
<td>Individual variations in pain perception [36]</td>
</tr>
<tr>
<td>APOE (multiple)</td>
<td>E4</td>
<td>Reduced compliance in E4 carriers</td>
</tr>
<tr>
<td>SLC16A4</td>
<td>Lactic acid transporter</td>
<td>Downregulated by statin therapy leading to myopathy</td>
</tr>
</tbody>
</table>

Reviews of the Issue

- American College of Cardiology - “The value of coenzyme Q10 with statin use has not been clearly established.” J Am Coll Cardiol 2005;46:184-221.
Other Medications That May Lower CoQ10

- Glyburide, phenformin, and tolazamide
- Propranolol, metoprolol, and alprenolol
- Phenothiaxine antipsychotic
- Tricyclic antidepressants
- Methyldopa
- Hydrochlorothiazide
- Clonidine
- Hyrdralazine

BUT no evidence of AE from lowering or benefit of supplementation
CoQ10 and Heart Failure
COQ10 Mechanism of Action in Heart Failure

- Enhance cardiac contractility
  - essential cofactor for mitochondrial electron transport and myocardial energy supply
- Reduce endothelial dysfunction
Studies of CoQ10 in Heart Failure

- Approved for this use in Japan since 1974
- 5 double blind studies (~900 subjects) found ↓ symptoms
  - 1 found ↓ hospitalizations
- 2 found no benefits (~85 subjects)

Eur Heart J. 2006;27:2675-81.

Studies of CoQ10 in Heart Failure

- Low plasma levels have been shown to be an independent predictor of HF mortality
- 3.7% (95% CI 1.59-5.77) net improvement in the ejection fraction
- 0.28 L/minute (95% CI 0.03-0.53) average increase in cardiac output

*J Am Coll Cardiol* 2008;52:1435-41.
Reviews of the Issue

- ACC - “The value of coenzyme Q10 in cardiovascular disease treatment has not been clearly established.”

Severe Heart Failure

- Case where ubiquinol should be used instead of ubiquinone
  - ubiquinone has very low bioavailability in severe heart failure (moderate gut edema)
  - small study found improved serum levels

CoQ10 and Hypertension
COQ10 Mechanism of Action in Hypertension

- CoQ10 decreases cytoplasmic NADH levels and thereby diminishes the reductive power that drives superoxide synthesis in endothelium and vascular smooth muscle.
Hypertension

- Meta-analysis of 12 clinical trials (362 patients) concluded CoQ10 has the potential to lower systolic and diastolic blood pressure, without significant side effects

Hypertension

- Systolic decrease - \(\sim 16\) mm Hg
- Diastolic - \(\sim 10\) mm Hg
- Reduction occurs gradually over months
- Effective dose varies widely
  - 100-200 mg/day

CoQ10 and Parkinson’s Disease
Possible Mechanism of Action in Parkinson’s Disease

- Patients with PD have reduced activity of complex I and II/III in the mitochondrial electron transport chain in mitochondria isolated from platelets and substantia nigra
- Coenzyme Q10 is the electron acceptor for complexes I and II
Parkinson’s Disease

- 2 positive/3 negative trials (n=140)
- 1,200 mg/day of CoQ10 slowed progressive deterioration of function [total Unified Parkinson Disease Rating Scale]
  - did not postpone the onset of symptomatic therapy or affect UPDRS motor score

Neurosci Lett. 2003;341:201-204.
Arch Neurol. 2007;64:938-44.
Possible Indications Lacking Data or Still Under Study

- Duchenne’s muscular dystrophy
- AIDS
- Periodontal disease
- Alzheimer’s disease

- Down’s syndrome
- Male infertility
- Migraine
- Diabetes
- Amyotrophic lateral sclerosis
General Issues with CoQ10

- No absolute contraindications
  - Little info on use during pregnancy and in kids

- DI:
  - Case reports of ↑INR in combo with warfarin, study found no interaction
  - Possible mild decrease in BP and glucose

- AE
  - GI upset, diarrhea
General Issues with CoQ10

Bioavailability
- Varies significantly between individuals and products
- Softgel capsule in oil and nanoparticular appear to be best
- Measure plasma levels to ensure absorption
- Divided doses also appear better than one large dose
<table>
<thead>
<tr>
<th>Condition</th>
<th>Most Common Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial cytopathies</td>
<td>150 mg/day or 2 mg per kg/day with titration, up to 3,000 mg/day in some patients</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>1,200 mg/day in four divided doses</td>
</tr>
<tr>
<td>Heart failure</td>
<td>50-300 mg/day</td>
</tr>
<tr>
<td>Hypertension</td>
<td>100-200 mg/day</td>
</tr>
<tr>
<td>With statins</td>
<td>? 60-300 mg/day</td>
</tr>
</tbody>
</table>
Consumer Lab Testing

Example “passed” products

- Nature Made® CoQ10 200 mg (200 mg per softgel, in oil)
- Nature’s Bounty® Extra Strength Q-Sorb™ Co Q-10 (200 mg per softgel, in oil)
- BioSolv® Advanced Formula Quinogel® 100 mg (100 mg per softsule, solubilized and in oil)
- Vitamin World® Ubiquinol 100 mg (100 mg per rapid release softgel, in oil)

Failed product

- Healthy America CoQ10 (150 mg per softgel)
### Dietary Sources of CoQ10

<table>
<thead>
<tr>
<th>Food Source</th>
<th>mcg/g</th>
<th>Food Source</th>
<th>mcg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pork heart</td>
<td>126.8-203</td>
<td>Sesame oil</td>
<td>32.0</td>
</tr>
<tr>
<td>Reindeer</td>
<td>157.9</td>
<td>Soybeans</td>
<td>19 - 30.1</td>
</tr>
<tr>
<td>Beef heart</td>
<td>113.3</td>
<td>Peanuts, roasted</td>
<td>26.7</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>92.3</td>
<td>Sesame seeds</td>
<td>23.0</td>
</tr>
<tr>
<td>Canola oil</td>
<td>63.5 - 73.4</td>
<td>Pork liver</td>
<td>22.7</td>
</tr>
<tr>
<td>Sardine</td>
<td>64.3</td>
<td>Chicken</td>
<td>14.0 - 21.0</td>
</tr>
<tr>
<td>Mackerel</td>
<td>43.3</td>
<td>Pistachios, roasted</td>
<td>20.1</td>
</tr>
<tr>
<td>Pork</td>
<td>24.3-41.1</td>
<td>Ham</td>
<td>20.0</td>
</tr>
<tr>
<td>Beef liver</td>
<td>39.2</td>
<td>Walnuts, raw</td>
<td>19.0</td>
</tr>
</tbody>
</table>
Also Found in Many Other Products
CoQ10 Bottom Line

- Although touted for many indications, little consistent evidence for effectiveness.
- May be of benefit in:
  - Familial CoQ10 deficiencies
  - Hypertension
  - Parkinson’s disease
  - Heart failure
- Appears to be safe