COENZYME Q10 IN HEALTH AND DISEASE

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Presentation Outline

• Background on CoQ
• Measuring CoQ
• Normal values and variation
• CoQ in disease states
  – Statin therapy
  – Statin induced myalgia
  – Heart Failure
  – Endothelial function
  – Diabetes
  – Hypertension
CoQ10 and vitamin K

Coenzyme Q is a hydrophobic quinone (ubiquinone) involved in electron transport. In the body it occurs mainly as the hydroquinone (ubiquinol).

It is chemically related to the K vitamins, and similar analytical principles can be applied to both groups of compounds.
CoQ

- Synthesised endogenously
- Present in the body in reduced and oxidised form, 96% is in reduced form in healthy subjects
- Reduced to oxidised ratio may indicate oxidative stress
- Reduced form can act as an antioxidant
- Circulates in blood bound to lipoproteins
CoQ - role in health

The diagram illustrates the role of CoQ in the mitochondrial electron transport chain. CoQ acts as a shuttle between the cytochrome C1 (Fe-S) and cytochrome b (Fe-S). It also interacts with succinate and FAD, facilitating the transfer of electrons to NADH and generating ATP through the formation of ADP. The process involves the reduction of O₂ to H₂O, with the intermediate 1/2O₂ forming water. The diagram highlights the importance of CoQ in energy production and cellular health.
CoQ - role in health

- Antioxidant
  - reduced form only
  - regenerates \( \alpha \)-tocopherol

- Mitochondrial function
  – generation of ATP

- Synthesis by the mevalonate pathway

- Also obtained from the diet - especially meats
Why measure Coenzyme Q?

- Coenzyme Q (CoQ) biosynthesis is inhibited by statin drugs and this may contribute to muscular complications of cholesterol lowering therapy.
- Individual variation within the reference range
- Variable bioavailability of supplements
- Low levels may be associated with a worse prognosis in vascular disease.
- Clinical research into the significance of CoQ in vascular disease.
Measuring plasma CoQ

- HPLC with electrochemical detection
- CV < 5%
- Lithium heparin plasma
- Sample protected from light
- Storage at -80°C
CoQ is more soluble in lipids than in lower alcohols such as ethanol.

Ethanol and methanol are not miscible with triacylglycerols.

Two-phase extraction, evaporation, and redissolution in ethanol gives low yields, much of the CoQ remaining with the undissolved plasma lipid.

Good recoveries can be obtained by extraction into 1-propanol with about 7 vol propanol to 1 vol sample.
CoQ is not strongly absorbed by normal phase silica, so practical mobile phases (for normal phase chromatography) contain very little polar modifier. As a result it is difficult to extract CoQ into an injection solvent that does not have a lot more eluting power than the mobile phase. Most methods use reverse phase columns with highly non-polar mobile phases.
Reduced coenzyme Q$_{10}$ (ubiquinol) is more hydrophilic than the quinone and elutes earlier from a reversed phase column.

Clean separations are easily achieved.
Detection of plasma CoQ

UV detection (275 nm)

Electrochemical detection

Fluorescence detection
Analysis of plasma CoQ

- Coenzyme Q₉ was found in all human plasma samples studied.
- Illustration of separation on a C30 column.
- Separation (and co-chromatography with added standard) was confirmed on three different columns.
CoQ₉ has been widely used as an internal standard. But it is present in normal human plasma.

The ethyl analogue of coenzyme Q₁₀ has been used: this needs to be synthesized.

However, with propanol extraction the efficiency is close to 100% so internal standards are not really necessary.
<table>
<thead>
<tr>
<th></th>
<th>Between-Run %CV</th>
<th>Within-Run %CV</th>
<th>Recovery (%)</th>
<th>Concentration Range (µmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultraviolet detection</td>
<td>3.2</td>
<td>2.4</td>
<td>93 - 103</td>
<td>0.24 - 0.98</td>
</tr>
<tr>
<td>detection assay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrochemical</td>
<td>3.3</td>
<td>3.2</td>
<td>98 - 102</td>
<td>0.15 - 2.76</td>
</tr>
<tr>
<td>detection assay</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

No effect of anticoagulants on ultraviolet assay, CoQ in EDTA plasma samples on average 4.4 ± 2.9% lower than in lithium heparin and serum samples (c.f. total cholesterol)
### Ninety five percent reference intervals

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>95% interfractile reference interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CoQ&lt;sub&gt;10&lt;/sub&gt;</td>
<td>205</td>
<td>0.46 – 1.78 µmol/L</td>
</tr>
<tr>
<td>Total CoQ&lt;sub&gt;10&lt;/sub&gt; – Males</td>
<td>90</td>
<td>0.45 – 2.05 µmol/L&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total CoQ&lt;sub&gt;10&lt;/sub&gt; - Females</td>
<td>115</td>
<td>0.46 – 1.71 µmol/L&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total CoQ&lt;sub&gt;10&lt;/sub&gt; – Age 18 – 44 years</td>
<td>105</td>
<td>0.43 – 1.61 µmol/L</td>
</tr>
<tr>
<td>Total CoQ&lt;sub&gt;10&lt;/sub&gt; – Age 45 – 83 years</td>
<td>100</td>
<td>0.57 – 1.95 µmol/L</td>
</tr>
</tbody>
</table>

<sup>a</sup> stratification not required according to Harris and Boyde criteria

No significant difference between fasted (N = 115) and non-fasted (N = 90)

Measured CoQ, total cholesterol, and direct LDL cholesterol.
Significant correlation between CoQ and total (r = +0.651) and LDL-Cholesterol (r = +0.600). Both p < 0.001
Biological variation

- Healthy young male volunteers (N = 10)
- 7 fasting baseline measurements at least a week apart, over 2 month period
- Measured CoQ, LDL-Cholesterol, total cholesterol, and HDL-Cholesterol, all had healthy lipid levels
## Inter- and Intra-individual variation

<table>
<thead>
<tr>
<th></th>
<th>Intra-individual %CV</th>
<th>Inter-individual %CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CoQ</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>CoQ to LDL-C ratio</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>CoQ to TC ratio</td>
<td>14</td>
<td>18</td>
</tr>
</tbody>
</table>

- CoQ is tightly distributed around a homeostatic set point
Inter- and Intra-individual variation

- Index of individuality (II)
- Low index (<0.6) - values for an individual span a small part of the reference interval
- High index (>1.4) - values for an individual cover most of the reference interval
- For total CoQ10, II = 0.42

- Reference change value (RCV)
  \[ \text{RCV} = 2^{1/2} \times Z \times (CV_a^2 + CV_i^2)^{1/2} \]
- For total plasma CoQ_{10}, RCV = 35\% (for a 95\% significant change)
- Example: Total CoQ_{10} concentration = 1 \mu mol/L
  \[ \Rightarrow \text{95\% significant change is below or over 0.65, or 1.35} \mu mol/L \]
Bioavailability of CoQ supplements

- Seven different CoQ supplement brands
  - Blackmores - CoQ dissolved in oil + surfactant
  - Solgar - dry powder
  - Q-Gel - CoQ dissolved in oil + surfactant
  - Thompsons - CoQ dissolved in oil
  - Good Health - dry powder, chewable tablets
  - Radiance - CoQ dissolved in oil + surfactants
  - Kordels - CoQ in dissolved in oils
### Bioavailability of CoQ supplements

#### Supplement adherence

<table>
<thead>
<tr>
<th>Brand</th>
<th>Claimed</th>
<th>Measured (mean ±SD)</th>
<th>Yield Recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q-Gel</td>
<td>30</td>
<td>41 ± 1.3</td>
<td>137</td>
</tr>
<tr>
<td>Radiance</td>
<td>50</td>
<td>63 ± 2.1</td>
<td>125</td>
</tr>
<tr>
<td>Blackmores</td>
<td>50</td>
<td>60 ± 4.1</td>
<td>121</td>
</tr>
<tr>
<td>Solgar</td>
<td>30</td>
<td>39 ± 4.4</td>
<td>130</td>
</tr>
<tr>
<td>Kordel’s</td>
<td>75</td>
<td>95 ± 5.5</td>
<td>127</td>
</tr>
<tr>
<td>Thompson’s</td>
<td>30</td>
<td>36 ± 1.9</td>
<td>121</td>
</tr>
<tr>
<td>Good Health</td>
<td>30</td>
<td>30 ± 2.0</td>
<td>100</td>
</tr>
</tbody>
</table>

(n = 6 tablets or capsules)
Bioavailability of CoQ supplements

- Healthy young males (N = 10)
- Given single nominal 150 mg dose of each supplement brand, at least a week apart
- Blood samples taken at baseline, and six hours after ingestion of supplement
- Standardised breakfast and lunch provided (total CoQ content of diet approximately 315 µg)
Bioavailability of CoQ supplements

**Median values and 25th and 75th quartiles for change in CoQ10 for each supplement**

<table>
<thead>
<tr>
<th>CoQ10 Supplement Brand</th>
<th>Change in CoQ10 (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kordels</td>
<td>0.2</td>
</tr>
<tr>
<td>Blackmore’s</td>
<td>0.4</td>
</tr>
<tr>
<td>Thompson’s</td>
<td>0.6</td>
</tr>
<tr>
<td>Radiance</td>
<td>1.0</td>
</tr>
<tr>
<td>Good Health</td>
<td>1.2</td>
</tr>
<tr>
<td>Solgar</td>
<td>1.4</td>
</tr>
<tr>
<td>Q-Gel</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Bioavailability of CoQ$_{10}$ supplements

Percentage adsorption for individual participants, all supplements

Percentage CoQ increase

Participant
Primary CoQ deficiency

- A rare, apparently autosomal recessive disorder with a clinical spectrum that encompasses three major phenotypes:
  - A myopathic form, characterised by exercise intolerance, mitochondrial myopathy, myoglobinuria, epilepsy, and ataxia
  - A generalised infantile variant with severe encephalopathy and renal disease
  - An ataxic form, dominated by ataxia, seizures, and cerebellar atrophy
CoQ and disease

Deficiency is relevant in

- Statin-induced myalgia
- Congestive Heart Failure
- Hypertension
- Parkinsons disease
- Alzheimers disease
- Chronic fatigue
- Infertility
- Cancer
- Diabetes
Statins Inhibit HMG-CoA Reductase

The mevalonate pathway links cholesterol and CoQ synthesis

Acetyl-CoA → HMG-CoA → Mevalonate → Farnesyl-pyrophosphate

STATINS (HMG-CoA reductase inhibitors)

- Coenzyme Q₁₀
- Cholesterol
Statin-induced CoQ deficiency

- 24 CHF patients
- Randomised placebo-controlled study
- 40 mg Atorvastatin for six weeks
- 33% CoQ reduction (p < 0.001)
Statin-Induced Myopathy

• Most frequently reported side effect of statin therapy

• Local data → 13% myalgia on statins

• Often necessitates reduction in statin dose or cessation of treatment
Effect of CoQ Supplementation on Simvastatin-Induced Myalgia

Patients with Prior Statin-Myalgia (n=44)

Two-Week Washout of Lipid Lowering Therapies

Randomisation

Coenzyme Q10 (200 mg/day) (n=22)

Placebo (n=22)

In combination with open label simvastatin 10mg/day with upward dose titration every 4 weeks if tolerated to a maximum of 40mg/day

Data collection at baseline and 4 weekly for up to 12 weeks

Young et al. Am J Cardiol (accepted 2007)
Changes in Plasma CoQ Levels

Plasma CoQ\textsubscript{10} Levels (\textmu mol/L)

* p<0.001 for comparison between regimes

* p<0.001 for within group changes from baseline
## Statin Dose Tolerated at 12 Weeks

<table>
<thead>
<tr>
<th>Dose tolerated</th>
<th>Simvastatin Alone (n=22)</th>
<th>CoQ&lt;sub&gt;10&lt;/sub&gt; &amp; Simvastatin (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40mg/day</td>
<td>13 (59%)</td>
<td>16 (73%)</td>
</tr>
<tr>
<td>20mg/day</td>
<td>3 (14%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>10mg/day</td>
<td>2 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>0</td>
<td>4 (18%)</td>
<td>6 (27%)</td>
</tr>
</tbody>
</table>

Values are counts (percentages). $\chi^2$ test – no significant differences
Changes in Pain Severity Scores

Coenzyme Q$_{10}$ (n=18)  
- 40% reduction in pain score (p<0.001)

Vitamin E (n=14)  
- No change in pain score (NS)

Caso et al. Am J Cardiol 2007; 99: 1409-12
CHF Background: CoQ$_{10}$ and CHF

- Reduced levels of CoQ$_{10}$ have been reported in plasma and myocardium of patients with chronic heart failure [1]

- Q-SYMBIO (Coenzyme Q$_{10}$ as adjunctive treatment of chronic heart failure. A randomised double-blind multicenter trial with focus on Symptoms, Biomarker status (BNP) and long-term Outcome) [2]
  
  - An International study, expected completion late 2010
  - 550 patients in NYHA classes III-IV in randomised parallel groups to receive 300 mg CoQ10 daily vs placebo on the top of stable, current treatment
  - 6-minute walk tests and NTproBNP status assessment
  - Long-term follow-up to evaluate the effects on morbidity (unplanned cardiovascular hospitalisations) and mortality as a composite endpoint in patients with severe heart failure receiving optimal medical therapy


5.2 mmol/L was the best predictor of mortality by ROC-curve analysis.

Log-rank p=0.0011 for the difference between groups.

- n=303
  - n=126 below 5.2 mmol/L
  - n=177 above 5.2 mmol/L

- 36-month survival 59% in below 5.2 mmol/L and 75% in above 5.2 mmol/L group.

CHF Background: CoQ$_{10}$ therapy

- ATP generation is critical for cardiac function
- In Japan, adjunctive therapy with CoQ$_{10}$ has been an accepted medication for CHF since the 1970’s
- Also in parts of Europe and Russia CoQ$_{10}$ is considered a part of standard therapy for congestive heart failure patients
- Plasma CoQ$_{10}$ correlates with plasma lipids

n=205
(Healthy New Zealand Reference Range)
Study Objective and Methods

• To investigate the association of plasma CoQ$_{10}$ concentrations and mortality in a chronic heart failure population

• Randomised, controlled and blinded study

• Patients recruited 2-4 weeks post-discharge from index hospital admission with CHF

• N=236

• Median (range) follow-up was 2.69 (0.12 - 5.75) years
ROC curve – Total Cholesterol

- AUC (± SE) = 0.486 ± 0.041
- P* = 0.740
- Optimal cut-off cannot be determined due to non-significant ROC-curve

(* p-value is for difference from a random effect)
ROC curve – CoQ\textsubscript{10}

- \( P^* = 0.041 \)
- \( \text{AUC (± SE)} = 0.582 ± 0.040 \)
- Optimal cut-off = 0.73 \( \mu \text{mol/L} \)

(* p-value is for difference from a random effect)
- Survival with CoQ<sub>10</sub> above and below the ROC-curve determined best predictive value of mortality.
- Log-rank p<0.001 for the difference between groups
CoQ10 and endothelial function: Study Design

- Double-blind, placebo controlled cross over 6-wk study.
- 24 patients with CHF [NYHA II or III, LVEF < 40%].
Statin therapy improved endothelial function in CHF

AUC = Area under the curve, ACh = Acetylcholine (7.5 - 30 µg/min), * p<0.05, ** p<0.01
Plasma Coenzyme Q$_{10}$ Reduction vs Improvement in Endothelial Function Post Statin Therapy

Absolute change in AUC

Absolute reduction in coenzyme Q10 levels [µmol/L]

$r = 0.55, p = 0.011$

* during ACh infusion at 30 ug/min
CoQ and Diabetes

- Plasma CoQ reduced in diabetes.
- CoQ shown to improve HBA1c, glucose levels, reduce insulin levels.
- CoQ also reduced blood pressure.
- CoQ improved vascular function (FMD), but not microcirculation.
- Combination CoQ and Fibrate treatment improved microcirculatory function.
CoQ and Hypertension

- Recent meta-analyses – 12 trials
- Decrease in systolic blood pressure: 11-17mmHg
- Decrease in diastolic blood pressure: 8-10mmHg
- Antioxidant mechanism
- CoQ maybe useful adjunct in resistant hypertension and patients with side effects.
Conclusions

• CoQ is clinically relevant to a number of diseases
• Supplementation may be indicated in heart failure, statin induced myalgia, diabetes and hypertension
• Monitoring is appropriate during supplementation
LIPID AND DIABETES RESEARCH GROUP

Collaborators:anko

CANTERBURY HEALTH LABORATORIES