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Comparison Study of Plasma Coenzyme Q_{10} Levels in Healthy Subjects Supplemented With Ubiquinol Versus Ubiquinone

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Abstract

The bioavailability of the reduced form of coenzyme Q_{10} (ubiquinol) was compared to oxidized coenzyme Q_{10} (ubiquinone) with identical soft gel capsule excipients by measuring steady state plasma coenzyme Q_{10} (CoQ_{10}) levels in 12 healthy volunteers. After baseline levels of ubiquinol, ubiquinone, total CoQ_{10}, α-tocopherol, and total cholesterol were obtained, follow-up lab work was performed after 4 weeks of 200 mg/day of ubiquinone, after 4 weeks washout, and after 4 weeks of 200 mg/day of ubiquinol. Plasma total CoQ_{10} increased from 0.9 to 2.5 μg/mL ($P < 0.001$) after 4 weeks of ubiquinone and increased from 0.9 to 4.3 μg/mL ($P < 0.001$) after 4 weeks of ubiquinol. Total CoQ_{10}/cholesterol ratio increased from 0.2 to 0.7 μmol/mmol after 4 weeks of ubiquinone and increased from 0.2 to 1.2 μmol/mmol after 4 weeks of ubiquinol. Both the increase in plasma CoQ_{10} and the increase in CoQ_{10}/cholesterol ratio were significantly better after ubiquinol ($P < 0.005$ and $P < 0.001$, respectively) than after ubiquinone indicating superior bioavailability. Plasma ubiquinol/total CoQ_{10} ratio increased from baseline during ubiquinol supplementation ($P < 0.005$) and remained unchanged after ubiquinone supplementation. No side effects were noted in this study.

Keywords

coenzyme Q_{10}, ubiquinone, ubiquinol, plasma level, supplementation

Coenzyme Q_{10} (CoQ_{10}) is recognized as an essential cofactor for the function of mitochondrial complexes I, II, and III and is thereby critical for the production of approximately 95% of cellular adenosine triphosphate (ATP).[1–4] CoQ_{10} is also a clinically relevant antioxidant located in the inner mitochondrial membrane, which is a major site of free radical production,[5–8] it is also present in plasma membranes and is carried in blood by lipoproteins. Human CoQ_{10} comes from two sources, cellular biosynthesis that peaks in a person's early to mid 20s and gradually declines with age[9,10] and from dietary sources. After the age of about 30, we become more dependent upon dietary sources of CoQ_{10} such as heart, liver, and kidney. Because CoQ_{10} is highly concentrated in heart muscle[9] and CoQ_{10} levels are low in heart failure,[11,12] many early studies involved the treatment of heart failure with supplemental CoQ_{10}.[13,14]

Until recently all supplemental CoQ_{10} has been in its oxidized ubiquinone state (Figure 1), which in its pure form is a bright orange, fat-soluble, crystalline powder. Shortly after absorption, ubiquinone is reduced to its ubiquinol state, $CoQ_{10}H_2$. Pure ubiquinol is a white, crystalline powder that may have higher polarity than ubiquinone due to the two hydroxyl groups. The most recent advance in supplemental CoQ_{10} is stabilized ubiquinol which is available as an over-the-counter supplement. Supplemental ubiquinol has been evaluated in healthy volunteers who reached a plateau total plasma CoQ_{10} concentration of 2.8 μg/mL on 90 mg of ubiquinol per day, 3.8 μg/mL on 150 mg per day, and 7.3 μg/mL on 300 mg per day after 4 weeks of treatment.[15] In 10 children with Down syndrome, 3-month treatment with ubiquinol at 10 mg/kg/day showed significant improvement in the ubiquinol/total CoQ_{10} ratio representing an improvement in oxidative stress.[16] No adverse effects were noted in either of these studies. The primary purpose of this study is to evaluate plasma CoQ_{10} and $CoQ_{10}H_2$,

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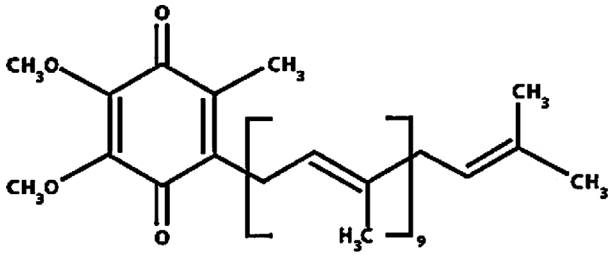
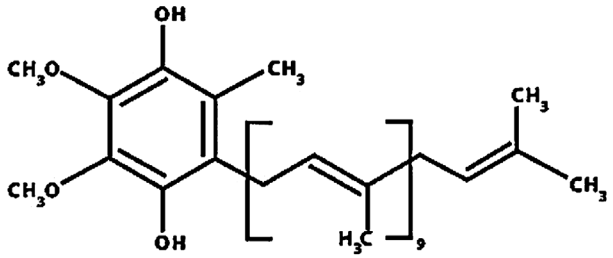


Ubiquinone



Ubiquinol

Figure 1. Molecular structures of ubiquinone (CoQ10) and of ubiquinol (CoQ10H2).

α-tocopherol and total cholesterol in healthy middle aged volunteers on supplemental ubiquinone versus ubiquinol using identical excipients.

Materials and Methods

Subjects

After approval by the Human Subjects Ethics Committee at East Texas Medical Center Hospital, Tyler, Texas, in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, 18 healthy volunteers between the ages of 29 and 50 years old were enrolled and all signed an informed consent prior to their enrolment. Healthy volunteers were defined as men or women with no chronic disease, on no regular prescription medication who have not taken CoQ_{10} supplement within the preceding 3 months. Although supplemental CoQ_{10} has no known toxicity in pregnancy and has recently been shown to be safe and effective at decreasing pre-eclamsia in pregnancy,[17] volunteers who were pregnant or were planning to become pregnant were excluded.

Subjects had baseline fasting plasma analysis for CoQ_{10} levels (both ubiquinol and ubiquinone), along with simultaneous analysis of α-tocopherol and total cholesterol. Plasma CoQ_{10} was measured as reduced, oxidized and total CoQ_{10} levels in μg/mL, as the ratio of reduced CoQ_{10} to total CoQ_{10} (% reduced CoQ_{10}) and as the molar ratio of total CoQ_{10} to total cholesterol (μmol/mmol). Supplemental CoQ_{10} is not known to influence cholesterol status but, since CoQ_{10} is carried along with cholesterol in lipoproteins, the purpose of measuring total cholesterol is to normalize the total CoQ_{10} level to the total cholesterol level.[18–21]

Six of the 18 volunteers were excluded due to noncompliance, which was determined by pill count: any volunteer with more than 12 extra 50 mg CoQ_{10} capsules after pill count in either the ubiquinone or the ubiquinol phase was excluded. Twelve volunteers completed the study with good compliance. Eleven volunteers were Caucasian and one was African American with six males and six females. No volunteers were on any supplemental α-tocopherol, nor were they taking any regular prescription medicines. No volunteers suffered from any known chronic illness, none were smokers and none were obese.

Intervention

All subjects were asked to make no major change in their routine diet or activity and also to avoid α-tocopherol supplementation for the duration of the study because supplemental α-tocopherol in amounts greater than 300 IU competes with CoQ_{10} for absorption and may confound results.[19] After baseline measurements all subjects started 200 mg of ubiquinone supplement (four 50 mg KanekaQ10™ soft gel capsules), taken once daily with their evening meal. After 4 weeks, a repeat fasting plasma analysis was performed. Pills were counted to assess compliance. After the first 4 weeks on supplemental ubiquinone, the ubiquinone was stopped for a 4-week washout period followed by fasting plasma analysis. For the third 4 weeks phase of the study, subjects were given ubiquinol 200 mg per day with their evening meal (four 50 mg KanekaQH™ soft gel capsules). Both the ubiquinone and ubiquinol soft gels contained identical inactive ingredients: diglyceryl monooleate, bee wax, soy lecithin, and canola oil. At the end of this 4-week period, remaining pills were counted to document compliance and a final fasting plasma analysis was obtained.

Statistics and Coenzyme Q_{10} Analysis Method

Analysis of plasma data was performed with a standard two-tailed *t*-test for paired data using EXCEL software. A P value <0.01 was considered significant. The HPLC analysis of reduced and oxidized forms of CoQ_{10}, α-tocopherol and total cholesterol are based on previously published method[22,23] and has been described in detail.[24] The intraday coefficient of variation (CV) for repeatability in measurements of plasma total CoQ_{10} was 1.5% and interday CV was 2.8%. The limit of detection for CoQ_{10} was found to be 1 ng/mL (signal to noise ratio = 3). All plasma samples were immediately frozen at −80°C and

the HPLC analysis was performed within 8 days of specimen collection in all but three samples to minimize oxidation during storage.

Results

Baseline and follow up plasma levels of CoQ_{10}, % reduced CoQ_{10}, total cholesterol and α-tocopherol are shown in Table 1. Plasma CoQ_{10} increased significantly after 4 weeks of ubiquinone and returned to baseline after the 4-week washout. After the 4 weeks of ubiquinol supplementation both total CoQ_{10} ($P < 0.005$) and CoQ_{10}/Chol ratio ($P < 0.001$) were significantly higher than with ubiquinone. The ubiquinol/total CoQ_{10} ratio, expressed as % reduced CoQ_{10} of total CoQ_{10}, increased significantly from baseline only in ubiquinol supplementation period ($P < 0.005$). There was tendency of higher ubiquinol/total CoQ_{10} ratio in ubiquinol supplementation period as compared to ubiquinone supplementation period ($P = 0.074$). There was no change in either α-tocopherol or total cholesterol levels and there were no side effects.

Discussion

Out of an initial 18 healthy volunteers between the ages of 29 and 50, we attained excellent compliance in 12 volunteers with a total of four fasting plasma samples for each volunteer. There are few studies whose primary purpose is to compare the bioavailability of ubiquinol with ubiquinone. Evans et al.[25] reported the comparison of bioavailability of ubiquinol and ubiquinone. Miles et al.[26] also reported the comparison of bioavailability of ubiquinol and ubiquinone. Although these reports show the superior bioavailability of ubiquinol, these studies used only a single dose and the excipients of the supplements were not identical. Since it is reported that excipients' composition affects the bioavailability of CoQ_{10},[27,28] interpretation of these studies is difficult. In general, oil-based preparations of CoQ_{10} are better absorbed than dry formulations.[26] In the current study, the excipients for the two CoQ_{10} formulations were selected to be identical to eliminate the effect of the excipients' composition. Therefore, this is the first repeated dose study to formally compare the bioavailability of ubiquinol and ubiquinone without being affected by the excipients. Every effort was made to ensure good compliance.

Almost all previous clinical trials with CoQ_{10} demonstrate considerable variability in the absorption of CoQ_{10} among individuals. The reasons for this degree of individual variability are not established but may be related to CoQ_{10}'s low bioavailability due to its poor water solubility and its relatively large molecular weight of 863 g/mol.[27,29] Table 2 demonstrates a threefold variability with one volunteer (case #7) attaining a CoQ_{10} level of 9.8 μg/mL on 200 mg ubiquinol/day as compared to another (case #9) attaining only 2.6 μg/mL on the same dose of ubiquinol. Some people clearly absorb ubiquinone very well as evidenced by cases #5 and #6. Conversely, cases #4 and #9 absorb ubiquinone relatively poorly. Given the importance of plasma CoQ_{10} for therapeutic effect,[24,30] a better understanding of this variability would be most helpful.

All supplemental CoQ_{10} products are better absorbed when taken with a meal.[31] It has also become clear that health benefits from supplemental CoQ_{10} correlate with attained plasma levels.[24,30] Normal plasma CoQ_{10} levels are 0.8 ± 0.2 μg/mL and because CoQ_{10} is carried along with cholesterol in lipoproteins, it is more accurate to simultaneously measure total cholesterol and report

Table 1. Mean Plasma Levels in 12 Volunteers, Comparing Baseline, 200 mg/day of Ubiquinone, Washout, and 200 mg/day of Ubiquinol

		4 Weeks		
Subjects, N = 12	Baseline	Ubiquinone	Washout	Ubiquinol
Total CoQ_{10} (μg/mL)	0.88 ± 0.30	2.50 ± 1.23[a]	0.86 ± 0.29	4.34 ± 1.97[a,b]
Total CoQ_{10} (μmol/L)	1.014 ± 0.345	2.895 ± 1.425[a]	0.998 ± 0.337	5.012 ± 2.275[a,b]
% Reduced CoQ_{10}[c]	$98.9 \pm 0.7\%$	$99.0 \pm 0.8\%$	$98.7 \pm 1.5\%$	$99.5 \pm 0.2\%$[d]
Total cholesterol (mg/dL)	167 ± 25	155 ± 26	159 ± 24	167 ± 24
Total cholesterol (mmol/L)	4.3 ± 0.7	4.0 ± 0.7	4.1 ± 0.6	4.3 ± 0.6
CoQ_{10}/cholesterol (μmol/mmol)	0.23 ± 0.06	0.71 ± 0.33[a]	0.24 ± 0.07	1.15 ± 0.41[a,e]
α-Tocopherol (μg/mL)	12.5 ± 4.7	11.4 ± 3.1	11.5 ± 3.1	12.1 ± 3.0

Values are means ± SD.
[a] $P < 0.001$, compared against baseline.
[b] $P < 0.005$, 4 weeks ubiquinol compared against 4 weeks ubiquinone supplementation.
[c] % Reduced $CoQ_{10} = CoQ_{10}H_2/(CoQ_{10}H_2 + CoQ_{10}) \times 100$.
[d] $P < 0.005$, compared against baseline.
[e] $P < 0.001$, compared against 4 weeks ubiquinone supplementation.

Table 2. Plasma CoQ_{10} in 12 Volunteers Comparing Baseline, 200 mg/day of Ubiquinone, Washout, and 200 mg/day of Ubiquinol

Case #	Total CoQ_{10} Baseline (μg/mL)	After 4 Weeks Ubiquinone (μg/mL)	After 4 Weeks Washout (μg/mL)	After 4 Weeks Ubiquinol (μg/mL)
1	0.73	2.45	0.78	3.39
2	0.93	2.36	0.96	3.26
3	0.99	2.34	0.78	3.62
4	0.38	0.70	0.47	2.95
5	0.87	4.37	0.83	5.50
6	0.87	5.12	0.99	5.32
7	1.65	3.31	1.52	9.85
8	0.92	2.32	1.03	3.31
9	0.99	1.56	1.16	2.63
10	0.68	2.11	0.51	3.16
11	0.81	1.80	0.65	4.45
12	0.70	1.60	0.68	4.58
Mean ± SD	0.88 ± 0.30	2.50 ± 1.23[a]	0.86 ± 0.29	4.34 ± 1.97[a,b]

[a] $P < 0.001$, compared against baseline.
[b] $P < 0.005$, 4 weeks ubiquinol compared against 4 weeks ubiquinone.

plasma CoQ_{10} as a ratio to total cholesterol.[18–21] Plasma total CoQ_{10}/cholesterol molar ratios in healthy people on no supplemental CoQ_{10} are >0.2 μmol/mmol. Significant benefit in heart failure requires plasma CoQ_{10} level >2.5 μg/mL.[24] In neurodegenerative disease plasma CoQ_{10} levels >3.5 μg/mL are believed to be required for therapeutic effect.[30]

In our current study we found that ubiquinol was significantly better absorbed than ubiquinone, which can be attributed to the reduced versus oxidized form of CoQ_{10} alone, as the formulations were otherwise identical in the two oil-based soft gels. This may in part be due to the higher polarity of ubiquinol as compared to ubiquinone, and should be investigated further. This study also showed a significant increase in plasma ubiquinol/total CoQ_{10} ratio during ubiquinol supplementation but not during ubiquinone supplementation, suggesting lower oxidative stress. This could be due to the higher CoQ_{10} plasma levels achieved with the ubiquinol compared to ubiquinone supplementation. The plasma ubiquinol/total CoQ_{10} ratio is reported to decrease with aging[32] and in high oxidative stress associated health conditions such as amyotrophic lateral sclerosis[33] and diabetes.[34,35] This decrease of plasma ubiquinol/total CoQ_{10} ratio may be the result of higher oxidation of ubiquinol in the body.[36]

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Declaration of Conflicting Interests

The authors received funding and were supplied the ubiquinone and ubiquinol soft gels for the performance of this specific study by Kaneka Corporation of Japan and Kaneka Nutrients, L.P. of Texas, USA.

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