REVIEW ARTICLE

The Instability of the Lipid-Soluble Antioxidant Ubiquinol: Part 3–Misleading Marketing Claims

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Abstract

Background: A lack of understanding of the processes involved in the absorption and transfer of the ubiquinol form of Coenzyme Q10 has led to a situation in which incorrect marketing claims are being made for the absorption of ubiquinol supplements, possibly misleading physicians and patients in the selection of a Coenzyme Q10 supplement for heart health benefits.

In clinical trials, the ubiquinone form of Coenzyme Q10 has been associated with significantly improved symptoms and survival in patients with heart failure and significantly improved heart function and reduced cardiovascular mortality in community-living senior citizens. The ubiquinone form is the more stable and more extensively researched form. The ubiquinol form is unstable by virtue of being an electron donor that is easily oxidized to the ubiquinone form. Nevertheless, insufficiently documented marketing claims are being made for ubiquinol supplements.

Methods: To investigate whether or not oral ubiquinol from supplements is absorbed in the ubiquinol form or ubiquinone form, our labs conducted 2 studies of the instability of ubiquinol supplements: a lab study of 13 ubiquinol products sold in the United States and an *in vivo* study of ubiquinol absorption in large dogs.

Results: In the lab study, 76% to 84% of the oral ubiquinol in the nutritional supplements was oxidized to ubiquinone at body temperature in an 8.2 pH solution simulating small intestinal juice. That is to say, much of the oral ubiquinol had been converted to ubiquinone in the sort of pH environment that it would encounter prior to absorption. In a similar fashion, the percentage of ubiquinol converted to ubiquinone increased as the capsule contents passed through the stomach and small intestines of the study dogs.

Conclusions: Based on the data from the lab study and the large dog study, we concluded that ubiquinol in commercial nutritional supplements will most likely be oxidized to ubiquinone before it reaches the absorption cells and that the Coenzyme Q10 in the ubiquinol supplements will be absorbed predominantly in the ubiquinone state, transfer into the lymph nodes predominantly in the ubiquinone state and be reduced back to ubiquinol in the lymphatic system.

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Introduction

Coenzyme Q10 – A Redox Molecule

Coenzyme Q10 molecules are redox molecules with 2 bioactive states: the oxidized state known as **ubiquinone** and the reduced state known as **ubiquinol**. In addition, there is a transient intermediate state known as ubisemiquinone, which has uncharacterized biological functions. The oxidized form of Coenzyme Q10 is an electron acceptor; the reduced form of Coenzyme Q10 is an electron donor and is, accordingly, the much less stable form.[1]

Biological Functions of Coenzyme Q10

The late Dr. Karl Folkers, the chemist who determined the structure of the Coenzyme Q10 molecule, once called Coenzyme Q10 an "essential bio-nutrient."[1]

The oxidized form of Coenzyme Q10 has a recognized role in mitochondrial bioenergetics; it is essential for the production of adenosine triphosphate (ATP) energy in the electron transfer chain. The reduced form of Coenzyme Q10 is known for important lipid-soluble antioxidant activity, protecting lipoproteins from lipid peroxidation; ubiquinol is also capable of regenerating the active form of vitamin E. Research has shown that Coenzyme Q10 helps to counteract endothelial dysfunction and has anti-inflammatory effects.[2]

Heart Health Benefits of Coenzyme Q10 Supplementation

In the Q-Symbio Study, thrice daily adjunctive treatment of patients with chronic heart failure with

100 mg of Coenzyme Q10 in the ubiquinone form for 2 years was associated with significantly improved symptoms, quality of life and survival compared with the placebo treatment.[3]

In the KiSel-10 Study, daily supplementation of senior citizens (average age: 78 years) with a combination of twice daily 100 mg ubiquinone and 200 mcg of organic selenium for 4 years was associated with significantly improved heart function as shown on echocardiograms and significantly reduced cardiovascular mortality compared with supplementation with matching placebo medications.[4]

Follow-up analysis of the KiSel-10 study data has shown that combined Coenzyme Q10 and selenium supplementation was significantly associated with reductions in biomarkers of oxidative stress, systemic inflammation and fibrosis compared with placebo supplementation.[5]

A total of 3 meta-analyses of randomized controlled trials conducted with the ubiquinone form of Coenzyme Q10 showed that adjunctive treatment with Coenzyme Q10 significantly reduced mortality, increased exercise capacity[6] and improved ejection fraction.[7,8]

Ubiquinone Easily Converted to Ubiquinol

The ubiquinone form, not the ubiquinol form, is the form of Coenzyme Q10 that is synthesized in the human cells.[1] Moreover, optimal dietary and supplemental intakes of Coenzyme Q10 in the ubiquinone form will result in a statistically significant increase in the concentration of ubiquinol in the blood circulation.[9]

In a 2020 review article, Mantle and Dybring reported that 5 known enzyme systems exist to catalyze the reduction of the ubiquinone form of Coenzyme Q10 to the ubiquinol form. These enzyme systems include the cytochrome b5 reductase, lipoamide dehydrogenase, glutathione reductase, thioredoxin reductase and NAD(P)H dehydrogenase quinone 1 (NQO1) enzyme systems.[10]

Mohr, et al conducted a human study that showed that supplementation with ubiquinone increased the concentration of ubiquinol both in plasma and in all the lipoproteins in the plasma. In the study, a single oral dose of 100 mg or 200 mg of Coenzyme Q10 in the ubiquinone form increased the total plasma Coenzyme Q10 content by 80% or 150%, respectively, within 6 hours. Long-term supplementation in a thrice daily dose of 100 mg of ubiquinone daily resulted in a 4-fold enrichment of ubiquinol in plasma and low-density lipoproteins.[9]

Biosynthesis of Coenzyme Q10

Coenzyme Q10 biosynthesis peaks in humans in early adulthood, typically in the early 20s. The endogenous production of Coenzyme Q10 declines with increasing age in the adult years. There is considerable variation from individual to individual, but senior citizens will synthesize much less Coenzyme Q10 than they did previously.[11]

In particular, the ageing process and taking some prescription drugs, eg, bisphosphonates then fires two parts have stimulated the interest in the stability of ubiquinol in the acid profile between the stomach and the small intestines, absorption and and statins, is associated with the lessening of Coenzyme Q10 biosynthesis.[12] It is not possible in any practical sense to compensate for the drop in Coenzyme Q10 biosynthesis by changing dietary intake. Consequently, taking a daily Coenzyme Q10 supplement is desirable, and in many cases, necessary.[1]

It should be noted that cholesterol and Coenzyme Q10 are produced in the same biological pathway, the mevalonate pathway. Any use of a statin to inhibit the endogenous production of cholesterol will necessarily inhibit the endogenous production of Coenzyme Q10. Okuyama, et al postulated that statins may stimulate atherosclerosis and heart failure by causing coronary artery calcification. In their view, statins may do more harm than good by depleting the supply of Coenzyme Q10 and heme A, inhibiting the synthesis of vitamin K2 and inhibiting the biosynthesis of selenium-containing selenoproteins, among them glutathione peroxidase.[13]

Not All Coenzyme Q10 Supplements Are Equally Well Absorbed

There is significant variation in the absorption and bioavailability of commercially-available Coenzyme Q10 supplements depending on the formulation, ie, the variation in the solubilization of the Coenzyme Q10 active ingredient itself, the choice of the carrier oils for the Coenzyme Q10 and the heating and cooling process used during the manufacture of the Coenzyme Q10 capsules. Coenzyme Q10 supplements are not equally potent, not even if they are manufactured using the same CoQ10 raw material.[14]

The Cleveland Clinic indicates that the population reference values for plasma or serum Coenzyme Q10 concentrations range from 0.36 to 1.59 mcg/mL.[1] Unsupplemented normal healthy individuals who are not elderly should have a plasma CoQ10 concentration of approximately 0.8 mcg/mL.[15] The current consensus among CoQ10 researchers is that a plasma CoQ10 concentration of at least 2.5 mcg/mL is required for significant benefit from Coenzyme Q10 in the adjuvant treatment of patients with heart failure. In patients with neurodegenerative diseases, plasma CoQ10 concentrations higher than 3.5 mcg/mL are required for therapeutic effect.[15]

It is important to select a pharmaceutical-grade Coenzyme Q10 supplement with documented absorption and bioavailability.

Misleading Marketing Claims for Ubiquinol Supplements

The companies selling ubiquinol supplements in the United States make various marketing claims for the ubiquinol form of Coenzyme Q10 that cannot be

substantiated by searching the biomedical literature indexed in PubMed.[1]

These marketing claims for ubiquinol are, at best, only partially documented but are presented as absolute statements, eg, that ubiquinol is the more bioactive form, is the better absorbed form, is the form needed by people over a certain age and is the more water-soluble form.[16]

The health claims that are made for ubiquinol products seem to be based primarily on the reports of clinical trials that have been conducted with ubiquinone Coenzyme Q10. For example, the health claims for good heart health are based on the Q-Symbio study and the KiSel-10 study, both done with a well-documented ubiquinone preparation.[14]

Claims of Superior Ubiquinol Absorption

The first claims of the superiority of the ubiquinol form of Coenzyme Q10 were based on a study done on senescence in SAMP1 mice[17] and on an absorption study done in elderly Japanese men who were devoid of any clinical conditions.[18]

The human study was a 21-day plasma bioavailability study.[18] The ubiquinol dosages tested were 90 to 600 mg/day. The control Coenzyme Q10 was dry powder ubiquinone given at 90 mg/day. The 600 mg/day dose of ubiquinol raised the plasma CoQ10 concentration to higher than 6.0 ug/ml.

The dose response curve between 90 and 600 mg/day was not linear. The non-linear changes in plasma ubiquinol concentrations were thought to be related to ubiquinol's relatively large molecular weight and poor water solubility, which result in a long half-life of elimination.[18] The investigators claimed that the ubiquinol product was stable and safe at the doses studied.

The researchers in the mouse study claimed that ubiquinol increased the life span and health of the mice supplemented with ubiquinol compared with the mice treated with ubiquinone.[17]

Claims That Ubiquinol Supplements Always Have Superior Absorption

The origin of the mistaken idea that the Coenzyme Q10 in ubiquinol supplements is at all times better absorbed than the Coenzyme Q10 in ubiquinone supplements seems to have been the misapplication of the results from the study conducted by Dr. Hosoe and colleagues[18] to the results from a study of the ubiquinone supplementation of patients with Parkinson's disease conducted by Shults, et al.[19] The Parkinson's disease study was completed 8 years prior to the completion of the Hosoe study. The researchers in the Parkinson's disease study used a dry crystalline powder form of ubiquinone, which is poorly absorbed; however, that was the formulation that was commonly available in 1998.

The comparison of the absorption data in the Hosoe study with the absorption data in the Shults study showed superior absorption of the Coenzyme Q10 in the ubiquinol supplements. This comparison cannot be regarded as good science. It was a comparison based on results from different study patients instead of on results from the same study patients in a cross-over study design. It was a comparison based on results from different research laboratories, different researchers and different study protocols.[20] Using this comparison in current marketing claims for ubiquinol supplements is misleading because it is not a comparison of present-day ubiquinone supplement formulations with present-day ubiquinol supplement formulations.

Head-to-Head Comparison of Ubiquinone and Ubiquinol Absorption

In 2019, Professors G. López-Lluch and P. Navas at the Pablo de Olavide University in Sevilla, Spain, published the results of a double-blind cross-over study of a single dose absorption of Coenzyme Q10 both ubiquinol and ubiquinone supplements.[14] They used 4-week washout periods between the administrations of the various Coenzyme Q10 formulation. Their study showed that the bioavailability of Coenzyme Q10 supplements depends more on the formulation of the supplements—on the solubilization of the raw material crystalline powder Coenzyme Q10, on the heating and cooling processes used in the manufacture of Coenzyme Q10 capsules and on the choice of the carrier oils in the formulation—than it depends on the form of the Coenzyme Q10 supplements: ubiquinone or ubiquinol.[14]

The López-Lluch study showed that a patented ubiquinone formulation was associated with the best bioavailability, measured as area under the curve from hour 0 to hour 48 after ingestion of a single 100-mg capsule. The ubiquinone preparation's bioavailability was approximately double the bioavailability associated with a patented ubiquinol supplement formulated with medium-chain triglyceride oils and 12 mg of vitamin C added as a stabilizer for the ubiquinol content. The ubiquinol supplement, in turn, was associated with a bioavailability significantly greater than the bioavailability associated with a ubiquinone product that had a composition identical to the composition of the first ubiquinone preparation but had been manufactured without the same heating and cooling process.[14]

Given the outcome of the López-Lluch Coenzyme Q10 supplement study, it seems fair to conclude that the bioavailability of Coenzyme Q10 is influenced more by the formulation of the Coenzyme Q10 supplement than by the form. Ubiquinol is not always the form that yields the better Coenzyme Q10 absorption and bioavailability.[14]

It should be mentioned that there was considerable individual variation in the study participants' response to the various forms and formulations used in the López-Lluch Coenzyme Q10 bioavailability study. Professor López-Lluch concluded that individually adapted selection of the best Coenzyme Q10 formulation is important to enhanced Coenzyme Q10 bioavailability.[14]

Claims That Ubiquinol Supplements Are Necessary to Increase Plasma Ubiquinol Concentrations

The results of the Mohr, et al[9] and Zhang[21] studies show that administration of a ubiquinone supplement is associated with a significant increase in plasma ubiquinol concentrations. In other words, it is not necessary to take a ubiquinol supplement in order to get adequate ubiquinol concentrations in the blood. A well-formulated ubiquinone supplement will do the job.

Claim That People Older Than Age 40 Years Need Coenzyme Q10 in the Form of Ubiquinol

A PubMed search shows that the marketing claim that people older than age 40 years need to take the ubiquinol form of Coenzyme Q10 is not documented; neither the claim itself nor the choice of age 40 years and older. The claim seems to be based on the fact that the gene that codes for the NQO1 oxidoreductase enzyme is polymorphic in humans. Perhaps 1 in 20 whites and blacks, 3 in 20 Mexican Americans, and 5 in 20 Asian Americans may have the NQO1 polymorphism, meaning that they could not convert ubiquinone to ubiquinol using the NQO1 enzyme.[20] However, there are other multi-functional enzyme systems in the body—cytochrome b5 reductase, lipoamide dehydrogenase, glutathione reductase and thioredoxin reductase—that convert ubiquinone to ubiquinol.[10]

The evidence from the best ubiquinone clinical trials belies the contention that people older than age 40 years need a ubiquinol supplement. In the Q-Symbio study of Coenzyme Q10 adjuvant treatment in patients with chronic heart failure,[3] the KiSel-10 study of supplementation in senior citizens,[4] and the Morisco study of adjuvant treatment in patients with congestive heart failure,[22] the average age of the study patients was 63 years, 78 years and 67 years, respectively.

The elderly study patients benefited significantly from daily supplementation with the ubiquinone form of Coenzyme Q10. A sub-analysis of the European segment of the Q-Symbio study showed that raising serum Coenzyme Q10 concentrations to 3.55 mcg/mL is associated with significantly improved ejection fractions compared with raising the serum Coenzyme Q10 to 2.01 mcg/mL.[23]

The Vitetta study of plasma bioavailability of Coenzyme Q10 absorbed from the gut showed no significant difference in the intestinal absorption and bioavailability of Coenzyme Q10 in a comparison of 150 mg doses of ubiquinol and ubiquinone administered to men (average age: 37.7 years) and women (average age: 35 years). The researchers did find that the intestinal absorption and bioavailability of Coenzyme Q10 in the plasma varied significantly between patients, regardless of whether the ubiquinol form or the ubiquinone form had been administered.[24]

Claims that Ubiquinol is the More Bioactive Form

Both forms of Coenzyme Q10 are bioactive. Ubiquinone and ubiquinol are a redox pair; in the body, the 2 forms of Coenzyme Q10 are converted easily back and forth from one form to the other. Ubiquinone from supplements and ubiquinone from the oxidized ubiquinol in ubiquinol supplements is absorbed in the enterocytes as ubiquinone and then converted to ubiquinol in the lymph nodes.[1] This makes good sense, because Coenzyme Q10 in the ubiquinol form hinders the peroxidation of lipoprotein lipids in the blood circulation.[2]

However, the ubiquinone form of Coenzyme Q10 is in great demand in the inner membrane of the mitochondria, which is where ATP energy is produced. Consequently, the ubiquinol form is converted rapidly to the ubiquinone form.[1,10]

Claims That Ubiquinol Is the Water-Soluble Form of Coenzyme Q10

There are 2 hydroxyl groups on the ubiquinol molecule that make it possible to claim that ubiquinol is slightly—very slightly—more water soluble than ubiquinone; however, because of the hydrophobic isoprene tail, both the ubiquinol and ubiquinone molecules are lipophilic and are absorbed as lipids.[1,16]

In any case, the ubiquinone and ubiquinol molecules are relatively large: 864 and 866 Daltons, respectively. Even if they were water-soluble, which they are not, they would not be easily absorbed because of their size. Furthermore, water-soluble does not necessarily mean highly absorbed.[1,16]

Conclusions

The lab study and the large dog study, discussed in Part 1 and Part 2 of this report, respectively, have shown that it is very likely that oral ubiquinol will be oxidized to the ubiquinone form of Coenzyme Q10 before it (the ubiquinol) reaches the intestinal absorption cells. Although ingested as ubiquinol, it will be absorbed as ubiquinone and then reduced back to its ubiquinol form.

A review of the relevant literature leads to the conclusions that (1) both forms of Coenzyme Q10 are bioactive, (2) absorption and bio-availability is more dependent upon the formulation of the Coenzyme Q10 supplement than on the form of Coenzyme Q10 used (whether ubiquinol or ubiquinone), (3) a well-formulated ubiquinone supplement will significantly increase the concentration of ubiquinol in the plasma and in lipoproteins, (4) there is no evidence that individuals older than age 40 years must take a ubiquinol supplement and (5) it is misleading to suggest that ubiquinol is the water-soluble form of Coenzyme Q10.

Conflicts of Interest
The author declares no conflicts of interest.

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