

The Instability of the Lipid-Soluble Antioxidant Ubiquinol: Part 2—Dog Studies

William V. Judy, PhD

Abstract

Background: Coenzyme Q10 is one of the most widely sold nutritional supplements in the United States. Coenzyme Q10 is available in both its oxidized form (ubiquinone) and its reduced form (ubiquinol). The predominant marketing of Coenzyme Q10 to physicians and patients asserts that the ubiquinol form of Coenzyme Q10 has superior absorption to the ubiquinone form. This study has been designed to compare and contrast the stability and absorption of ubiquinol supplements, as well as the claims made for ubiquinol compared with ubiquinone.

Ubiquinol, the reduced state of Coenzyme Q10, is commercially available as a nutritional supplement; however, ubiquinol, by its nature as an electron donor, is much less stable than ubiquinone, the oxidized state of Coenzyme Q10. The absorption, bioavailability and efficacy of ubiquinol products has been much less often tested in clinical trials. Consequently, insufficiently documented marketing claims are being made for ubiquinol supplements.

Methods: In Part 1 of this report on the instability of the lipid-soluble antioxidant ubiquinol, SIBR Research

presented data from lab studies showing that oral ubiquinol is likely to be oxidized to ubiquinone and absorbed as ubiquinone. In this Part 2, SIBR Research conducted a study of the transfer and absorption of orally ingested ubiquinol in large dogs.

Results: In the dog studies, the percentage of ubiquinol converted to ubiquinone increased as the capsule contents passed through the stomach and small intestines and into the lymph system.

Conclusions: The dog studies demonstrate that oral ubiquinol in commercial nutritional supplements is not stable in the gastrointestinal tract of large dogs. Based on these results, it seems likely that in humans also, most of the ubiquinol from capsules will be oxidized to ubiquinone in the acid profile between the stomach and the small intestines, where there is a wide range of acidity. The ubiquinol from the supplement will be absorbed in the ubiquinone state and will pass into the lymph system as ubiquinone, where it will be reduced back to ubiquinol. It will pass from the lymph system into the blood circulation as ubiquinol.

William V. Judy, PhD, Founder and President, SIBR Research.

Corresponding author: William V. Judy, PhD

E-mail address: sibrinc@cs.com

Introduction

Ubiquinone (fully oxidized state) and ubiquinol (fully reduced state) are the major states of the lipid-soluble vitamin-like bionutrient known as Coenzyme Q10 (CoQ10). There is also a transient intermediate state, ubisemiquinone (also known as semiquinone) that has multiple unexplained biologic functions.¹

In American usage, the terms CoQ10 and CoQH2 are commonly used for ubiquinone and ubiquinol, respectively. In European usage, the designations Q10 and QH2 are more commonly used.

Both the ubiquinone state and the ubiquinol state are bioactive redox forms of Coenzyme Q10. Ubiquinone plays an essential role in the production of cellular ATP energy. Ubiquinol plays an important role as a lipid-soluble antioxidant. As such, ubiquinol helps prevent the peroxidation of the LDL lipoproteins in the blood.²

It is misleading to claim that ubiquinol is more important than ubiquinone.² Both states of Coenzyme Q10 are important. That ubiquinol is the predominant form of Coenzyme Q10 in the blood makes sense in that there is relatively little need for the bioenergetics form (ubiquinone) in the circulation while there is a manifest need for the antioxidant form (ubiquinol).²

When Coenzyme Q10 in the blood passes into the tissues, there are numerous enzyme systems available to maintain adequate levels of ubiquinol. Mantle and Dybring list 5 enzyme systems that facilitate this conversion: NAD(P)H dehydrogenase quinone 1 (known as NQO1),

glutathione reductase, lipoamide dehydrogenase, cytochrome b5 reductase and thioredoxin reductase.³

Ubiquinol: The Inherently Unstable State of Coenzyme Q10

Because ubiquinol has the property of being an electron donor, it is useful as an antioxidant, and a lipid-soluble antioxidant at that. When it donates 2 electrons, it is oxidized to the ubiquinone form. It is this ability to act as an electron donor that makes the ubiquinol form inherently unstable.²

Biological Functions of Coenzyme Q10

As mentioned above, Coenzyme Q10 has vitamin-like effects and functions in the body, but it cannot be considered a vitamin as the cells are able to synthesize Coenzyme Q10 in the same mevalonate pathway that produces cholesterol. Among the vital biologic functions of Coenzyme Q10 are that it:⁴

- acts as a co-factor in the cellular process of mitochondrial oxidative phosphorylation and thus in the process of adenosine triphosphate (ATP) energy production
- functions as an antioxidant that protects the cells against damage from harmful free radicals
- improves endothelial function and thus protects against atherosclerosis
- promotes cell signaling through its effect on the expression of genes that code for the involved proteins
- has demonstrated anti-inflammatory effects

Ubiquinone: The Form of Coenzyme Q10 Synthesized in the Cells

The form of Coenzyme Q10 that is synthesized in the cells is ubiquinone. Ubiquinol is, then, the product of redox reactions involving ubiquinone.^{2,5} Ingested ubiquinone in rodents has been shown to increase the ubiquinol concentration in the lymph.⁶ It is not necessary to take a ubiquinol supplement in order to get enough ubiquinol in the blood circulation.^{5,6}

Studies have shown that cellular biosynthesis of CoQ10 peaks in early adulthood, typically in the 20s, and then, with considerable inter-individual variability, steadily decreases with increasing age.⁷ Both the ageing process and the use of various prescription medications, chief among them statins and bisphosphonates, contribute to the decline in the endogenous biosynthesis of Coenzyme Q10.⁸⁻¹⁰ It has been hypothesized that the use of statin medications can deplete the supply of Coenzyme Q10 and result in the calcification of coronary arteries and the impairment of heart muscle function.¹¹

It is not feasible to eat enough food or to change one's diet to make up for the loss of endogenously produced Coenzyme Q10. For example, it would be necessary to eat nearly 3 lb of steak or 2 lb of liver to meet the need for a daily intake of 3.5 mg of Coenzyme Q10.¹²

Consequently, daily Coenzyme Q10 supplementation is necessary. However, commercially available Coenzyme Q10 supplements vary considerably in their absorption and bioavailability and, thus, in their efficacy.

Differences in the manufacturer's method of solubilization of the active ingredient Coenzyme Q10, in the manufacturer's choices of the carrier oils for the Coenzyme Q10 and in the manufacturer's heating and cooling processes during the production of the Coenzyme Q10 capsules are decisive with respect to the absorption of the contents of the capsules. Even when they are produced with the same Coenzyme Q10 raw material, Coenzyme Q10 supplements are not equally well absorbed.¹³

Coenzyme Q10 Status Needed for Therapeutic Benefits

Reference values for plasma or serum Coenzyme Q10 status range widely from 0.36 to 1.59 mg/L.¹² A normal healthy individual who is not elderly and not taking a supplement is expected to have a plasma Coenzyme Q10 status of 0.8 mg/L.¹⁴

At the Ninth Conference of the International Coenzyme Q10 Association in New York in 2018, the assembled Coenzyme Q10 researchers generally agreed that a plasma Coenzyme Q10 status of 2.0 to 2.5 mg/L is needed for an individual to realize significant improvement in Coenzyme Q10 as an adjunctive treatment of heart failure.¹⁴

Misleading Marketing Claims for Ubiquinol Supplements

American companies marketing ubiquinol supplements make the following claims, for which more documentation from clinical trials is needed:

- better absorbed form
- more bioactive form
- form needed by people over age 40 years
- more water-soluble form¹⁰

At best, claims of this nature are only partially documented. These claims can be misleading for the consumer of Coenzyme Q10 supplements who is not familiar with the state of Coenzyme Q10 research. SIBR Research will address these marketing claims in Part 3 of this report.

For the moment, let it suffice to say that the formulation of Coenzyme Q10 supplements seems to be much more important for absorption and bio-availability than the form of the supplement, ie, whether the supplement uses ubiquinone or ubiquinol as the active ingredient.¹³

Ubiquinol Is Easily Oxidized Back to Ubiquinone

The production of Coenzyme Q10 capsules is difficult in and of itself, and the production of ubiquinol capsules is even more difficult. In order to prevent the oxidation of the ubiquinol to ubiquinone already in the process of filling the

capsule, conscientious ubiquinol supplement manufacturers need to encapsulate the ubiquinol under nitrogen.

Ubiquinol will be oxidized to ubiquinone if the ubiquinol is exposed to room air during the manufacturing process. The results of the lab studies reported in Part 1—studies of the capsule contents of 13 commercially available ubiquinol products—show that, for the most part, the ubiquinol in the capsule remains in the ubiquinol state.¹⁵

It is easy for the consumer to check the contents of a ubiquinol capsule. They should cut open the capsule and examine the fluid contents. If the fluid is orange in color or becomes orange within an hour after being exposed to air, the contents of the ubiquinol capsule have been oxidized to the ubiquinone state. If the capsule contents are white, resembling milk, then the ubiquinol from the capsule is still in its ubiquinol state.¹⁶

The lab studies reported in Part 1 of this article indicate that in many cases the ubiquinol from the capsule does not remain in its reduced form as it passes through 2.2 pH and 8.2 pH solutions simulating the conditions in the stomach and the small intestines.¹⁵

In 2 different studies, SIBR Research has investigated the question of the stability of ubiquinol sold in capsules:

Part 1. The Instability of the Lipid-Soluble Antioxidant Ubiquinol: Lab Studies

Part 2. The Instability of the Lipid-Soluble Antioxidant Ubiquinol: Dog Studies

The 2 studies represent SIBR Research's search for an answer to the question: is oral ubiquinol from supplements oxidized to the ubiquinone state prior to Coenzyme Q10 arriving at the intestinal absorption cells?

In other words, the 2 studies were conducted to learn whether the oral ubiquinol from supplement capsules is absorbed as ubiquinol or is converted to ubiquinone and absorbed as ubiquinone prior to arriving in the lymph vessels.

Materials and Methods

In-Vivo Study

In the *in vivo* studies, 6 dogs were trained to lie quietly on a lab table. The dogs were fed a high fat diet for 3 days to make the lymph vessels appear a milky white color. Catheters (Medical Supply House, 21-gauge) were inserted into the stomach, small intestines, distal lymph vessels from the absorption cells, proximal lymph vessels channeling the lymph to the systemic circulation and the brachial vein. Catheters were exteriorized to the back, flushed with a saline heparin mix and sealed in a protective cover. After 3 days, each dog was fed a vegetable diet and rested overnight.

On the study day, the dogs were given a cup of vegetable dog chow in water (Chewy Pet Foods) and 100 mg of Coenzyme Q10 (Product name available upon request). Control samples were collected from each

catheter. A total of 3 ml samples were collected from each site at hourly intervals, rapidly frozen at -82°C, and stored. With completion of all 6 dog studies, the samples were shipped overnight to the analytical lab for analysis of total Coenzyme Q10 content, ubiquinol content and ubiquinone content.

The analytical reports were sent to the statistical lab for analysis. Group means and standard deviations for total Coenzyme Q10 content, ubiquinol content, and ubiquinone content were calculated for each site on the dogs and are presented in this report. A *P* value of .05 was considered statistically significant.

Results

In Vitro Lab Studies

The results of the lab studies were reported in Part 1 of this article.¹⁵

In Vivo Study in Large Dogs

The data from the large dog study show that the administered ubiquinol was oxidized more and more as it passed through the stomach and the small intestines on its way to the enterocytes. This finding is consistent with the findings in the *in vitro* studies reported above.

The percentage of ingested ubiquinol that was converted to ubiquinone increased as the Coenzyme Q10 passed from the capsule and traversed the stomach and small intestines until it reached the enterocytes. The percentage of ubiquinol in the ubiquinol capsules administered to the dogs was 93%. After 5 minutes in the stomach, the group mean percentage of ubiquinol was 87% of the total Coenzyme Q10, and after 60 minutes, the group mean percentage of ubiquinol was 55% of the total Coenzyme Q10.

In the dogs' small intestines, the group mean percentage of ubiquinol fell to a low of 8% of the total Coenzyme Q10. Thereafter, in the lymph collecting duct adjacent to the absorption cells, the group mean percentage of ubiquinone decreased to 54% in the distal lymph nodes, 10% in the abdominal lymph nodes, and 4.9% in the thoracic lymph nodes before entering the blood.

After absorption predominantly in the ubiquinone state, the Coenzyme Q10 first appeared in the abdominal lymph nodes as ubiquinone but was rapidly converted back to ubiquinol, as it traversed the lymphatic system before entering the venous blood. In the venous blood, the ubiquinol was measured at 96% while the ubiquinone was measured as 4%.

Discussion

In Vitro Study

The data from the *in vitro* study show that the ubiquinol in ubiquinol supplements is generally stable while still in the capsule but is considerably less stable in 2.2 pH and 8.2 pH solutions simulating the stomach and the duodenum.

Figure 1. The ingested ubiquinol was oxidized to ubiquinone in the stomach and small intestines. It was reduced back to ubiquinol in the lymph nodes.

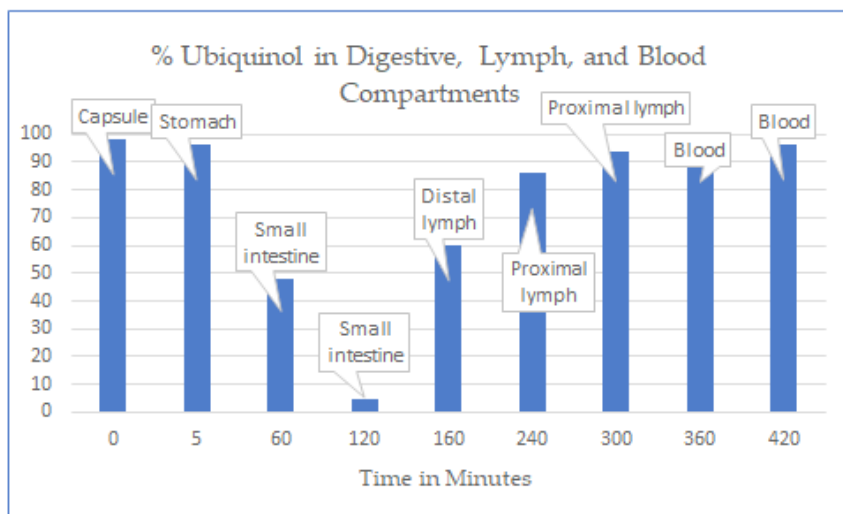
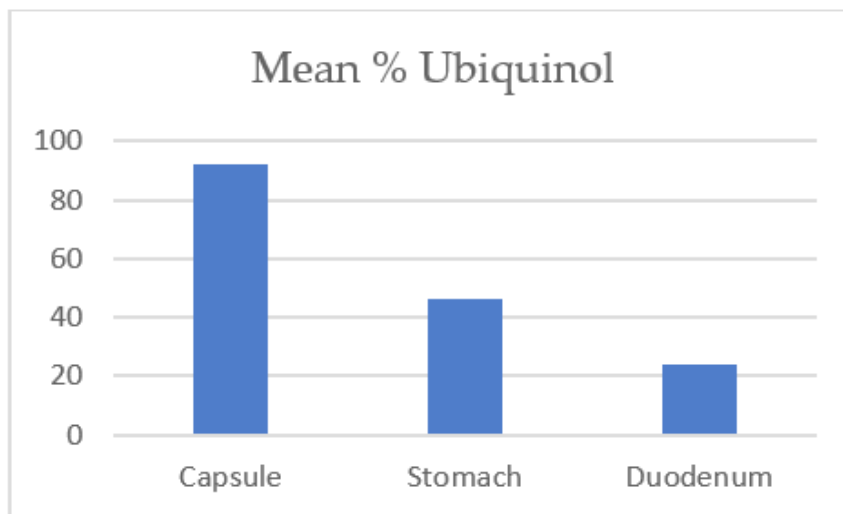


Figure 2. Ubiquinol as a percentage of total CoQ10 declines as the orally ingested ubiquinol passes through the gastrointestinal tract.



Given these results from an investigation of 13 commercially available ubiquinol supplements, the purchaser of a typical ubiquinol supplement can expect that three-fourths or more of the ubiquinol that they bought will be oxidized to the ubiquinone state of Coenzyme Q10 before the capsule contents reach the intestinal absorption cells.

In Vivo Study

The results of the dog study show that the ingested ubiquinol is mostly (92%) oxidized in the small intestines before it reaches the enterocytes. The results suggest that the fraction of ingested ubiquinol that does get absorbed is mostly absorbed in the ubiquinone form.

Then, entering the lymph nodes from the enterocytes, the ubiquinone (converted from the ingested ubiquinol) is fairly rapidly converted back to ubiquinol. It traverses the lymph system and enters the blood circulation predominantly in the ubiquinol state.¹²

That Coenzyme Q10 is primarily in the ubiquinol state in the blood can be explained by the need for the antioxidant form of Coenzyme Q10 to protect against the peroxidation of the lipoproteins in the blood. In the blood, there is relatively little need for the oxidized form of Coenzyme Q10, which is the essential form needed for the process of ATP energy generation.¹²

The lipid solubility and the large molecular size of the Coenzyme Q10 molecules make absorption a difficult process. The relatively long period (5 to 8 hours) after

absorption that it takes for ingested Coenzyme Q10 to reach a maximum concentration (C_{max}) in the blood plasma is caused primarily by the slow flow of the lymph. There is less pressure in the lymph vessels than in the blood vessels. A good estimate is that a sample of the lymph distal to the enterocytes will show the C_{max} of exogenous Coenzyme Q10 as soon as 2 hours after ingestion.¹²

Implications for Ubiquinol Marketing Claims

At this point, it is relevant to address the various marketing claims which assert that ubiquinol is the superior and/or necessary form for Coenzyme Q10; eg, the claims for ubiquinol on the website ubiquinol.org.

SIBR Research will address what it regards as misleading marketing claims for ubiquinol supplements in Part 3 of this article.

Conclusions

The *in vitro* studies reported in Part 1 of this article showed that between 76% and 84% of the ubiquinol in 13 commercially-available ubiquinol supplements is oxidized to ubiquinone in pH solutions, simulating the pH in the stomach and in the small intestines.

The low pH in the gastric juice is characterized by the presence of many free hydrogen ions, and the somewhat elevated pH in the small intestines is characterized by the presence of many free hydroxyl ions. Ubiquinol acts as an electron donor in the gastric and small intestine juices; accordingly, the ubiquinol from supplement capsules is converted to ubiquinone, the oxidized form of Coenzyme Q10.

In the dog study, the measurements of the relative percentages of ubiquinol and ubiquinone at various stages show that the ingested ubiquinol is largely oxidized to ubiquinone before it reaches the enterocytes. When it passes from the enterocytes into the lymph system, it is converted back to ubiquinol, and it is predominantly as ubiquinol that it enters the blood circulation.

As far as SIBR Research can ascertain, this is the first published report of the oxidation of orally ingested ubiquinol to ubiquinone prior to arrival at the intestinal absorption cells.

Ethical Approval

SIBR Research received ethical approval for the large dog study from the Institutional Review Board at the University of Texas in Austin.

Conflicts of Interest

The author declares no conflicts of interest.

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