



Review

# Bioavailability of Coenzyme Q<sub>10</sub>: An Overview of the Absorption Process and Subsequent Metabolism

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**Abstract:** A lack of understanding of the processes determining the absorption and subsequent metabolism of coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) has resulted in some manufacturers' making incorrect claims regarding the bioavailability of their CoQ<sub>10</sub> supplements, with potential consequences for the use of such products in clinical trials. The purpose of the present review article is, therefore, to describe the various stages of exogenous CoQ<sub>10</sub> metabolism, from its first ingestion, stomach transit, absorption from the small intestine into the lymphatic system, transport in blood, and access into cells. In particular, the importance of CoQ<sub>10</sub> crystal dispersion in the initial formulation is emphasised, the absence of which reduces bioavailability by 75%. In addition, evidence comparing the relative bioavailability and efficacy of ubiquinone and ubiquinol forms of CoQ<sub>10</sub> has been reviewed.

**Keywords:** coenzyme Q<sub>10</sub>; bioavailability; ubiquinone; ubiquinol; absorption; transport; cellular metabolism

## 1. Introduction

Coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) is a substance similar to a vitamin in its biological functions, but by definition is not a vitamin because it can be synthesised by human cells. CoQ<sub>10</sub> has an essential role supplying all cells with energy [1]. Specifically, CoQ<sub>10</sub> shuttles electrons from complexes I and II to complex III of the mitochondrial respiratory chain. As such, it is an energy transfer molecule in the electron transport chain, which produces ATP chemical energy. CoQ<sub>10</sub> has an important role as an antioxidant that protects lipid-soluble cell membranes [1]. In addition to its role in oxidative phosphorylation above, CoQ<sub>10</sub> is a major lipid-soluble antioxidant, protecting cell membranes and circulating lipoproteins from oxidative damage by free radicals [1]. CoQ<sub>10</sub> is the only lipid-soluble antioxidant manufactured within the body; in addition to preventing lipid peroxidation, CoQ<sub>10</sub> is able to regenerate vitamins C and E back to their active fully reduced forms. The antioxidant function of CoQ<sub>10</sub> is attributed to its reduced ubiquinol form, which must be constantly regenerated from its ubiquinone oxidised form. Moreover, a gene expression profiling study demonstrated that CoQ<sub>10</sub> influences the expression of several hundred human genes [2]. In cell culture, CoQ<sub>10</sub> has been shown to reduce the activity of inflammatory markers, suggesting that CoQ<sub>10</sub> may have anti-inflammatory action via gene expression modification, most notably in elderly individuals [3,4].

Most of the body's daily requirement for CoQ<sub>10</sub> is produced within the body. Some CoQ<sub>10</sub> is ingested from food (typically 5 mg/day [5]). It is estimated that the daily requirement for CoQ<sub>10</sub>, from both endogenous bio-synthesis and food sources, is about 500 mg; this estimate is based on a total body quantity of about 2 mg of CoQ<sub>10</sub> and based on an average turnover time of 4 days in tissue [5]. This estimate serves as the justification for the size of the dosage (typically 300 mg/day) that is used in many clinical trial studies.

As people mature into adulthood and begin to increase in age, the ability of the body to synthesise its own CoQ<sub>10</sub> decreases; optimal human bio-synthesis occurs in the mid-twenties, with a continual gradual decline in tissue levels thereafter [6]. In addition to the normal aging process, CoQ<sub>10</sub> levels have also been shown to be depleted in a number of disorders, particularly heart disease [7]. The synthesis of CoQ<sub>10</sub> is a complex multistage process (governed by at least 13 genes), requiring a number of amino acids, vitamins, and trace element precursors and cofactors, deficiency of any of which can adversely affect normal CoQ<sub>10</sub> production [8]. Nutritional supplementation with CoQ<sub>10</sub> therefore provides a mechanism to maintain adequate levels within the body.

A lack of understanding of the processes determining the bioavailability of CoQ<sub>10</sub> has led some manufacturers to make incorrect claims relating to the bioavailability of their CoQ<sub>10</sub> supplements; this in turn is of potential relevance to the use of such supplements in clinical studies. The purpose of this review article is, therefore, to describe the bioavailability process of supplemental CoQ<sub>10</sub>, from its first ingestion all the way through to its uptake and utilisation within the cells, in order to clarify these misleading marketing claims.

## 2. Initial Formulation

Although CoQ<sub>10</sub> was originally purified from bovine heart tissue in the 1950s by Professor Frederick Crane [1], supplemental CoQ<sub>10</sub> is now manufactured via a yeast fermentation method. The Kaneka corporation of Japan is now a major supplier of CoQ<sub>10</sub> (produced via a fermentation process) to supplement manufacturers. The manufacturers then incorporate the CoQ<sub>10</sub> into their respective products. CoQ<sub>10</sub> produced via yeast fermentation produces the *trans*-form (as opposed to the *cis*-form) of CoQ<sub>10</sub>. This form is chemically identical to the form of CoQ<sub>10</sub> that is bio-synthesised within the body. The CoQ<sub>10</sub> raw material comes in the structural form of polymorphic crystals [9]. CoQ<sub>10</sub> in polymorphic crystalline forms will not be absorbed in the gastro-intestinal tract. CoQ<sub>10</sub> can be absorbed only as individual molecules, as described in Section 4 of this article below [10]. The CoQ<sub>10</sub> crystals must therefore be dissociated first into individual CoQ<sub>10</sub> molecules. These CoQ<sub>10</sub> molecules should remain fully dissociated throughout the shelf life of the CoQ<sub>10</sub> preparation. Not all CoQ<sub>10</sub> manufacturers have demonstrated an ability to achieve this dissociation of the crystals to single molecules [10].

CoQ<sub>10</sub> exists within the body in the oxidised form (ubiquinone) and the reduced form (ubiquinol); these two redox forms are continually inter-converted within cells as part of the normal function of CoQ<sub>10</sub>. In the blood, CoQ<sub>10</sub> is transported in ubiquinol form (bound to low-density lipoprotein- and very low-density lipoprotein- cholesterol), irrespective of the initial dietary form (ubiquinone or ubiquinol) [11]. Because the initial absorption of CoQ<sub>10</sub> into intestinal absorption cells was thought to be enhanced by the reduction of ubiquinone to ubiquinol [12], some still assume that ingestion of supplemental CoQ<sub>10</sub> in the ubiquinol form will facilitate the absorption process. However, given that ubiquinol is, by its very nature, inherently unstable and will oxidise to ubiquinone, until relatively recently, CoQ<sub>10</sub> supplements could only be produced using the ubiquinone form. Recent technical improvements in encapsulation methods have made the production of CoQ<sub>10</sub> supplements in the ubiquinol form possible. On the basis of the above rationale, some manufacturers of reduced CoQ<sub>10</sub> supplements have claimed that the reduced form of CoQ<sub>10</sub> is more readily absorbed from the gastro-intestinal tract, even though recent absorption and bio-availability studies have brought the issue of ubiquinol's claimed superior absorption into question, as explained in the sections that follow.

Of particular note in this regard is the clinical study by Lopez-Lluch et al. [13]. The bioavailability of seven CoQ<sub>10</sub> supplements differing in formulation (CoQ<sub>10</sub> crystal dispersion status, type of carrier oil, composition of other excipients, and CoQ<sub>10</sub> oxidation state) were administered in a single 100 mg dose to the same series of 14 healthy individuals, using a crossover/washout protocol. Bioavailability of the different formulations was quantified as the area under the curve (AUC) at 48 h.

In CoQ<sub>10</sub> studies, the AUC of the plasma CoQ<sub>10</sub> concentration is used to report bioavailability because the AUC represents the proportion of the dose that has entered the blood circulation.

C<sub>max</sub> is the peak plasma CoQ<sub>10</sub> concentration following the initial administration of a dose and prior to any subsequent administration.

The first point of note is the difference in bioavailability between samples 01 and 02 of the study. Both samples contained 100 mg CoQ<sub>10</sub> in identical ubiquinone form, in a soy carrier oil with identical excipient content and capsule specification; sample 01 (Myoqinon, Pharma Nord, Vejle, Denmark) had been subject to a patented thermal crystal dispersion process whilst sample 02 (from the same manufacturer) had not undergone this procedure. The respective mean AUC and C<sub>max</sub> values in the Lopez-Lluch study were 28.0 mg/L/48 h and 1.07 mg/L for sample 01, and 6.89 mg/L/48 h and 0.33 mg/L for sample 2. Failure to subject crystalline CoQ<sub>10</sub> to crystal dispersion therefore reduced bioavailability by approximately 75%.

A second point relates to the relative bioavailability of the ubiquinone and ubiquinol forms of CoQ<sub>10</sub>. For the ubiquinol form of CoQ<sub>10</sub> (sample 05), the AUC and C<sub>max</sub> values were 14.8 mg/L/48 h and 0.49 mg/L, respectively. Thus, the AUC for CoQ<sub>10</sub> in ubiquinol form was approximately twice of that for ubiquinone, which had not been subjected to thermal crystal dispersion (sample 02), but was only 52% of that for ubiquinone that had been subjected to thermal crystal dispersion (sample 01). It should be noted that it is not possible to subject ubiquinol to the same crystal dispersion process as that described for sample 01; this is because of the differential stability of ubiquinone and ubiquinol. These data therefore demonstrate (i) the importance of CoQ<sub>10</sub> crystal dispersion, the absence of which reduces bioavailability by some 75%; (ii) the fact that the relative bioavailability of ubiquinone and ubiquinol forms of CoQ<sub>10</sub> depends on CoQ<sub>10</sub> crystal dispersion status and carrier oil/excipient composition.

Several previous clinical studies have reported no significant difference in the relative bioavailability of ubiquinone and ubiquinol supplements. Thus, a cross-over study by Vitetta et al. [14] in 11 healthy volunteers evaluated the bioavailability of 3 different CoQ<sub>10</sub> formulations over a 6-week period, ubiquinone (150 mg), ubiquinol (150 mg), and a liposome ubiquinone formulation. There was a significant inter-subject variation in the baseline plasma CoQ<sub>10</sub> levels, which persisted after administration of the test formulations. In addition, it was noted that the bioavailability of CoQ<sub>10</sub> varied significantly between individuals, irrespective of the CoQ<sub>10</sub> form (ubiquinone/ubiquinol) administered. There was no significant difference in plasma CoQ<sub>10</sub> levels following administration of ubiquinone or ubiquinol formulations. The study therefore concluded that intestinal absorption of CoQ<sub>10</sub> is highly variable among individuals, and is independent of the form of CoQ<sub>10</sub> (ubiquinone/ubiquinol) administered. This is because the body is limited in how much CoQ<sub>10</sub> it can absorb at a given time, and thus if an individual takes several 100 mg capsules together, some of the CoQ<sub>10</sub> tends to be wasted [15].

Similarly in a 2002 study by Miles et al. [16], nine healthy adults were given single 180 mg doses of ubiquinone (LiQ-10 TM) or ubiquinol (Q-Nol TM) supplements, with a 2 week wash-out period; the results showed no significant difference between the two supplement types in raising plasma CoQ<sub>10</sub> levels (determined as C<sub>max</sub> and AUC).

In contrast to the above, several studies have reported significantly improved bioavailability of ubiquinol versus ubiquinone supplements, particularly in older subjects. For example, a 2009 study by Evans et al. [17] supplemented 100 mg ubiquinone or ubiquinol as a single dose (with 2-week wash-out period) in 10 healthy adults aged over 60 years; the bioavailability (determined as C<sub>max</sub> and AUC) was significantly higher for the ubiquinol supplement. Similarly, a 2018 study by Zhang et al. [18] supplemented ubiquinone or ubiquinol (200 mg/day for 2 weeks, with 2-week wash-out period) in 10 older (>55 years) men; ubiquinol significantly increased plasma CoQ<sub>10</sub> levels compared to ubiquinone but did not significantly increase ubiquinol levels compared to ubiquinone. In a 2014 study by Langsjoen and Langsjoen [19], supplementation with ubiquinone or ubiquinol (200 mg/day for 4 weeks with 4 weeks wash-out period) in 12 healthy adults resulted in significantly higher plasma CoQ<sub>10</sub> levels with ubiquinol. Langsjoen did not report the increases in plasma ubiquinol levels. It should be noted that in all of these studies, the apparently superior bioavailability of ubiquinol was

determined against supplemental ubiquinone samples that had not been subject to thermal dispersion, as described above.

A number of studies have been carried out with the objective of improving CoQ<sub>10</sub> bioavailability using a variety of agents; examples include polyethylene glycol [20], phosphorylated tocopherols [21], polyoxamer/polyvinyl pyrrolidone [22], and hydrolysed proteins [23]. However, again the bioavailability of these formulations has not been compared directly with ubiquinone that has undergone crystal dispersion, the importance of which is demonstrated in the study by Lopez-Lluch et al. [13] above.

In summary, on the basis of the evidence reviewed above, the concept of the superior bioavailability of supplemental ubiquinol compared to ubiquinone would appear to be mistaken. This concept, widely disseminated on the Internet, seems in part to have originated from an inappropriate comparison between bioavailability data from studies by Shults et al. in 1998 [24] and Hosoe et al. in 2007 [25]. The older study involved the use of a dry powdered crystalline form of ubiquinone, which is poorly absorbed but was the only formulation available at the time. Thus, the comparison was not a head-to-head comparison in that it did not test the ubiquinol absorption results against a formulation of ubiquinone dissolved in appropriate carrier oils. The two studies being compared were conducted more than 10 years apart. They used different study subjects: healthy volunteers vs. patients with Parkinson's disease, different investigators, different analytical labs, and different protocols.

### 3. Stomach Transit

CoQ<sub>10</sub> is a lipid soluble substance; therefore, the highest quality CoQ<sub>10</sub> preparations have the CoQ<sub>10</sub> dissolved in a well-suited carrier lipid (e.g., soy oil or palm oil). Typically, they are encapsulated in bovine gelatine capsules. The capsule material does not seem to be an important factor for absorption. The gelatine capsules readily dissolve within minutes inside the stomach and release the oil-dissolved CoQ<sub>10</sub>. The stomach transit time varies among individuals and varies according to the type of food eaten. The complete transit of the CoQ<sub>10</sub> from the stomach through the small intestines, and the lymph to the blood typically takes between 5 and 8 h [26]. The transited CoQ<sub>10</sub> enters the duodenum as part of the chyme. Although the CoQ<sub>10</sub> is in transit from the stomach into the duodenum, any CoQ<sub>10</sub> in the reduced form, the ubiquinol form, will be oxidised to the ubiquinone form; in studies of CoQ<sub>10</sub> absorption under conditions that simulate gastric conditions, this process usually takes about 90 min (Figure 20 in [26]).

The lipid solubility of CoQ<sub>10</sub> is a consequence of its inherent chemical structure—technically, it is due to the presence of an isoprenoid chain within the CoQ<sub>10</sub> molecule. CoQ<sub>10</sub> is not at all water soluble, and, contrary to some manufacturers' claims, cannot be made water-soluble [26]. Thus, any alteration to the structure of the CoQ<sub>10</sub> molecule in an attempt to increase water solubility means that the molecule is no longer CoQ<sub>10</sub>. Similarly, the presence of two additional hydrogen atoms within the chemical structure of ubiquinol (compared to ubiquinone) has a negligible effect on potential water solubility [26].

### 4. Duodenal Micellisation

In the duodenum, CoQ<sub>10</sub> molecules are subject to the process of micellisation, the formation of mixed micelles, through which various lipid-soluble substances, such as monoglycerides, fatty acids, and fat-soluble vitamins, are prepared for intestinal absorption. Bile from the gall bladder is secreted into the duodenum. Substances present in the bile interact with CoQ<sub>10</sub> molecules to form characteristic micellar spherical structures with a diameter of up to 20 nanometers. Each individual micelle may contain as many as thousands of CoQ<sub>10</sub> molecules. Micelles are constantly breaking apart and then reforming. The micelles are small enough to diffuse between intestinal villi before they break apart. In this way, the micelles are transporting the CoQ<sub>10</sub> molecules to the surface of the intestinal absorption cells preliminary to absorption. It is important to note that the micelles themselves are not absorbed; only single CoQ<sub>10</sub> molecules that have been released from micelles can be absorbed by intestinal absorption cells [27].

## 5. Enterocyte Absorption of CoQ<sub>10</sub> Molecules

The enterocyte cells that form the lining of the small intestines' villi absorb CoQ<sub>10</sub> via a process of "passive facilitated diffusion". This process is described as passive because the process does not require energy. Carrier molecules facilitate the diffusion of the CoQ<sub>10</sub> molecules through the cell membranes and into the enterocyte cells. Researchers have not definitively identified the carrier molecules for the CoQ<sub>10</sub>; however, some researchers have suggested the cholesterol transporter NPC1L1 (Niemann-Pick C1 Like 1) as a possible candidate [28,29].

In an attempt to understand CoQ<sub>10</sub> absorption, Singh et al. [30] investigated the efficacy of various dosing strategies on serum CoQ<sub>10</sub> levels in a group of 60 healthy adults. In the Singh study, a 200 mg CoQ<sub>10</sub> dose yielded a larger increase in serum levels than a 100 mg dose. However, divided dosages of 2 × 100mg of CoQ<sub>10</sub> yielded a larger increase in serum levels than a single 200 mg dose. The Singh data show that the human digestive system has a finite capacity to absorb CoQ<sub>10</sub> in a single dose. This discovery of a limited capacity to absorb CoQ<sub>10</sub> follows logically from the concept of the requirement for a CoQ<sub>10</sub> transporter for access into enterocytes as outlined above.

Once inside the enterocytes, the CoQ<sub>10</sub> molecules are incorporated into chylomicrons. Chylomicrons are lipoprotein-based particles that carry lipid-soluble substances and CoQ<sub>10</sub> in the lymph and the blood circulation. From the basal surface of the enterocytes, chylomicrons are released by the active process of exocytosis. Chylomicrons are substances that are too large to enter the blood circulation via the process of capillary absorption within villi. For this reason, the chylomicrons transit into the lymph circulation within villi. The chylomicrons enter the distal abdominal lymph duct. The chylomicrons with their CoQ<sub>10</sub> content then eventually enter the subclavian vein through the proximal abdominal and thoracic lymph ducts and continue in the blood circulation.

## 6. Redox Conversion of CoQ<sub>10</sub> Forms During Absorption

The CoQ<sub>10</sub> molecules in the blood circulation are found predominantly in the reduced form. Accordingly, at some point, dietary CoQ<sub>10</sub> in the oxidized ubiquinone form must therefore be reduced to the ubiquinol form; this occurs most probably in the lymph. Some CoQ<sub>10</sub> supplement manufacturers are selling supplemental CoQ<sub>10</sub> in the ubiquinol form because of the supposed superior bioavailability of the ubiquinol form of CoQ<sub>10</sub>. They are doing so because the absorption of CoQ<sub>10</sub> into the enterocytes has been thought to require the reduction of ubiquinone to ubiquinol, an assumption that is based in part on work in which ubiquinone was reduced to ubiquinol during uptake by cultured Caco-2 human epithelial intestinal absorption cells [12]. Thus, the production of supplemental CoQ<sub>10</sub> in the ubiquinol form was thought to facilitate the process of CoQ<sub>10</sub> absorption, especially in patients with malabsorption disorders for whom the process of CoQ<sub>10</sub> reduction process may be compromised, as well as in elderly individuals.

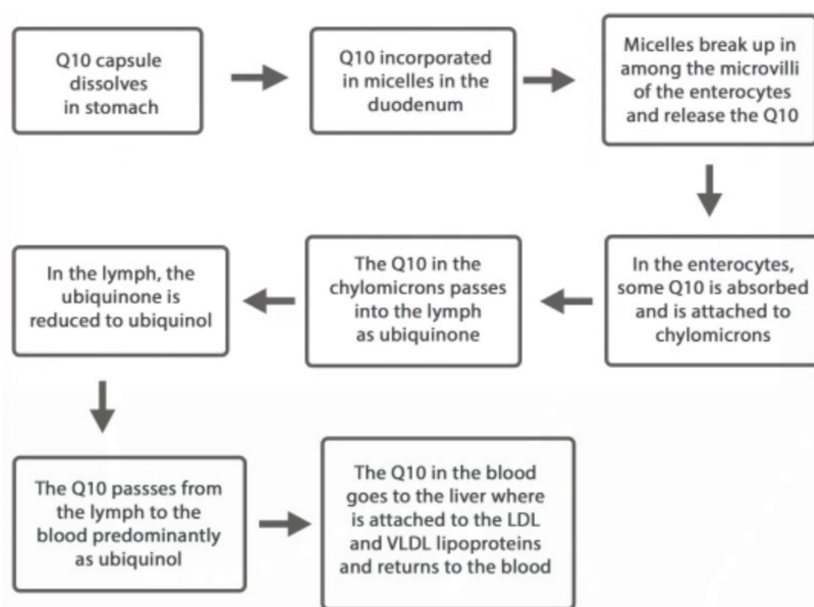
## 7. CoQ<sub>10</sub> Transport in the Blood

There is very little if any circulation of unbound CoQ<sub>10</sub>. The chylomicrons in the blood carry the CoQ<sub>10</sub> to the liver, where it is primarily loaded into LDL and VLDL lipoprotein particles. A much smaller quantity of CoQ<sub>10</sub> is packaged into high-density lipoprotein cholesterol. Moreover, the platelets and leucocytes in the blood contain CoQ<sub>10</sub>. The erythrocytes contain a quite small amount of CoQ<sub>10</sub> (Figure 1).

The highest plasma concentration (C<sub>max</sub>) of the ingested CoQ<sub>10</sub> is typically reached after about 6 hours. The half-life of the absorbed CoQ<sub>10</sub> is about 33 h. Accordingly, the amount of time it takes for CoQ<sub>10</sub> to reach a pharmacological steady state is rather prolonged (1-2 weeks). Normal plasma CoQ<sub>10</sub> levels vary from person to person and are typically in the range 0.5 to 1.5 µg/mL [7]. Twice daily supplementation with 100 mg of CoQ<sub>10</sub> has been reported to raise plasma CoQ<sub>10</sub> levels from 0.90 to 3.25 mcg/mL, that is, to the level required for therapeutic efficacy in cardiovascular disease [7,31].



By inhibiting the oxidation of LDL cholesterol, CoQ<sub>10</sub> seems to protect against atherosclerosis. There is a relatively low concentration of CoQ<sub>10</sub> (0.5–0.8 mol/LDL particle) in LDL cholesterol compared to the content of *alpha* tocopherol (8–15 mol/LDL particle) in LDL cholesterol. Even so, CoQ<sub>10</sub> has been shown to protect human low-density lipoprotein against lipid peroxidation better than alpha tocopherol [32]. The ratio of CoQ<sub>10</sub> to LDL cholesterol has not been widely used as a bio-marker; however, there is evidence that the ratio of CoQ<sub>10</sub> to LDL cholesterol may be more important in the prevention of atherosclerosis than is the HDL/LDL cholesterol ratio [33].



**Figure 1.** The transit of the ingested CoQ<sub>10</sub> from the stomach to the blood circulation.

## 8. CoQ<sub>10</sub> Utilisation Within Cells

CoQ<sub>10</sub> is found in all cells. The relative tissue levels reflect the extent of metabolic activity and energy demand in various tissues and organs; accordingly, the highest CoQ<sub>10</sub> levels are found in heart muscle tissue. Given its lipid nature, CoQ<sub>10</sub> is assumed to enter the cell membranes by diffusion from the lipoprotein carriers in the blood; to date, there has been no known transporter of CoQ<sub>10</sub> from blood into cells identified. Diffusion relies upon the movement of the CoQ<sub>10</sub> molecules from areas of high CoQ<sub>10</sub> concentration to areas of CoQ<sub>10</sub> lower concentration; this need for a higher CoQ<sub>10</sub> concentration in the blood than in the tissue cells is the rationale in clinical studies of heart failure patients for the use of CoQ<sub>10</sub> dosages of 300 mg/day (and for plasma CoQ<sub>10</sub> levels of at least 3 µg/mL). In this way, the movement of CoQ<sub>10</sub> from the blood into tissues such as cardiac muscle will be facilitated [7].

There is some evidence that increased blood CoQ<sub>10</sub> levels following supplementation is manifest as increased CoQ<sub>10</sub> levels within tissues. Thus, a 2002 study by Rosenfeldt et al. in 24 older adults supplemented with 300 mg/day of CoQ<sub>10</sub> or placebo for at least 7 days prior to cardiac surgery found that the CoQ<sub>10</sub> level of atrial tissue was significantly increased in those taking CoQ<sub>10</sub>, especially in patients greater than 70 years of age [34]. In a 2008 study by Keith et al., patients with left ventricular dysfunction, supplementation with 150 mg/day of CoQ<sub>10</sub> for 4 weeks before cardiac surgery increased CoQ<sub>10</sub> concentrations in the heart but not in skeletal muscle [35]. In 2015, Okuyama et al. summarized the evidence that statin medications cause heart failure by depleting the heart muscle cells of Coenzyme Q<sub>10</sub>, heme A, and selenoproteins, thereby impairing mitochondrial ATP production [36].

Once within cells, several enzyme systems capable of maintaining CoQ<sub>10</sub> in ubiquinol form have been identified. For example, cytochrome b5 reductase maintains CoQ<sub>10</sub> in its reduced form [37]. Moreover, lipoamide dehydrogenase, glutathione reductase, and the seleno-enzyme thioredoxin reductase act in a multifunctional regeneration system to reduce ubiquinone to ubiquinol,

thereby protecting cells from oxidative stress [38]. In addition, there is evidence that the enzyme NAD(P)H dehydrogenase quinone 1 (NQO1) acts as a component of the plasma membrane redox system. NQO1 enzymes act as a direct superoxide reductase to generate antioxidant forms of ubiquinone and vitamin E [39].

Recent studies by Bersuker et al. [40] and Doll et al. [41] have identified a membrane-associated oxidoreductase (FSP1) capable of reducing ubiquinone to ubiquinol during its passage through the membrane. Similarly, a study using human liver cancer cell line Hep G2 cells showed that intact cells could reduce the ubiquinone in low-density lipoproteins to ubiquinol, suggesting that a ubiquinone-reducing mechanism may exist in the plasma membrane, probably the outer surface, of Hep G2 cells. This mechanism may reduce extracellular ubiquinone to ubiquinol [42].

In animal models with Gram-magnitude dosages, CoQ<sub>10</sub> has been shown to cross the blood–brain barrier; however, researchers have not been able to definitively show its ability to cross the blood–brain barrier in humans. The difficulty of getting supplemental CoQ<sub>10</sub> into the brain with physiological dosages may explain the disappointing outcomes of some randomized controlled clinical trials supplementing CoQ<sub>10</sub> in patients diagnosed with neurodegenerative disorders [24].

All cells except red blood cells have the capacity to manufacture CoQ<sub>10</sub>. CoQ<sub>10</sub> researchers do not fully understand the relative contribution of cellular bio-synthesis of CoQ<sub>10</sub> and dietary derived CoQ<sub>10</sub> to cellular requirements. CoQ<sub>10</sub> molecules are found primarily within the mitochondria (approximately 50% of total cellular CoQ<sub>10</sub>) but are also found in many other types of sub-cellular organelles such as the endoplasmic reticulum, the Golgi apparatus, lysosomes, and peroxisomes [43]. Regardless of the origin of CoQ<sub>10</sub>, whether endogenous or exogenous, a means of transport is required between these various sub-cellular organelles. This means of transport between and among organelles inside the cells is thought to involve a vesicle-mediated process that involves the Golgi apparatus. Although this transport process is not completely understood at present, it may involve saposin B as a presumptive binding and transfer protein for CoQ<sub>10</sub> [44]. It should be noted that the important role of CoQ<sub>10</sub> elsewhere within the cell also needs to be taken into account.

## 9. Comparative Efficacy of supplemental Ubiquinone and Ubiquinol

Contrary to some manufacturers' claims, ubiquinol is not the active form of CoQ<sub>10</sub> compared to ubiquinone. Because ubiquinol and ubiquinone are continually inter-converted within the body, the concept that ubiquinol supplements may somehow be more efficacious than supplemental ubiquinone is incorrect, particularly in view of evidence reviewed above regarding relative bioavailability. However, it is correct that most randomised controlled clinical trials to date have been carried out using supplemental CoQ<sub>10</sub> in ubiquinone form. This is particularly the case in relation to cardiovascular disease, where supplemental ubiquinone has been shown to be especially effective in two studies, Q-SYMBIO and KISEL-10.

The Q-SYMBIO multi-national (nine country) study was carried out in 420 patients with chronic heart failure (NYHA class III and IV). The effect of CoQ<sub>10</sub> supplementation (3 × 100 mg/day for 2 years) on symptoms and biomarker status (hence the trial acronym Q-SYMBIO) was assessed, as an adjuvant to conventional medication (angiotensin-converting enzyme (ACE) inhibitors, beta blockers). Assessment included clinical examination, echocardiography, and NT-pro-brain natriuretic peptide (NT-proBNP) status. The primary long-term endpoint was the time to first major adverse cardiovascular event (MACE), which included unplanned hospitalisation due to worsening heart failure and cardiovascular death. supplementation with CoQ<sub>10</sub> significantly reduced the relative risk of MACE by 42%, with a reduction in both cardiac related deaths (43%) and all-cause mortality (42%). There was no significant difference in adverse events between the CoQ<sub>10</sub>-treated and placebo groups over the duration of the study [45]. Sub-group analysis of the effect of CoQ<sub>10</sub> supplementation in the European cohort (231 of 420 patients) of the Q-SYMBIO study has since been undertaken [46]. In these patients, the relative risk of MACE was reduced by 67%, cardiac related mortality by 53%, and all-cause mortality by 55%; in addition, left ventricular ejection fraction was significantly improved by 6%, which was not

observed in the original study. The improved outcome in the European cohort probably resulted from better patient compliance with supplementing CoQ<sub>10</sub>, resulting in a consistently higher plasma CoQ<sub>10</sub> level for the duration of the study: 3.4 µg/mL at 3 months and 3.6 µg/mL at 2 years, compared to 3.0 µg/mL at 3 months and 2.1 µg/mL at 2 years in the full cohort.

The KISEL-10 study was a clinical trial that enrolled 443 senior citizens living in south-eastern Sweden. The study was designed as a randomized, double-blind, placebo-controlled clinical trial. The elderly study participants—average age of 78 years—took either 200 milligrams of coenzyme Q<sub>10</sub> together with 200 µg of an organic high-selenium yeast preparation or matching placebos daily for 4 years [47].

Professor Urban Alehagen and the team of researchers from Linköping University and Karolinska Institute reported significantly reduced risk of death from heart disease in the active treatment group. The relative risk reduction was 53%. The researchers also reported significantly improved heart function as shown on echocardiograms and significantly reduced levels of the N-terminal-proBNP bio-marker for heart muscle dysfunction in the active treatment group compared to the placebo group [47].

Moreover, the researchers quantified health-related quality of life outcomes. They used the Short Form-36, Cardiac Health Profile, and Overall Quality of Life survey questionnaires. The active treatment with a combination of CoQ<sub>10</sub> and selenium was associated with a significant decrease in the number of days in the hospital and with significantly moderated deterioration in the senior citizens' health-related quality of life [48].

Sub-study analysis of the data from the KiSel-10 study showed significant reductions in the blood levels of known bio-markers for inflammation—C-reactive protein and sP-selectin—and in known bio-markers for oxidative stress—copeptin and adrenomedullin [49,50].

The cardio-protective effect of the combined daily supplementation with CoQ<sub>10</sub> and selenium endure for several years beyond the period of intervention. A follow-up analysis showed that the significantly reduced risk of death from heart disease still held 12 years after the intervention [51]. Professor Alehagen has identified the reductions in systemic inflammation, in oxidative stress, and in fibrosis of heart muscle tissue as possible mechanisms to explain the beneficial effect of combined coenzyme Q<sub>10</sub> and selenium supplementation on the risk of heart disease in community living senior citizens [51,52].

There are unsubstantiated manufacturers' claims circulating on the internet that individuals over 40 years of age may be progressively less able to absorb supplemental ubiquinone. However, the two studies above provide evidence that older individuals (Q-SYMBIO average age 63 years; KISEL-10 average age 78 years) are able to absorb and subsequently benefit from a properly formulated ubiquinone supplement (Table 1).

**Table 1.** Clinical studies conducted with CoQ<sub>10</sub> in the form of ubiquinone in individuals well over the age of 40 years.

Clinical Trial	Participants' mean age	Outcome
Q-Symbio Study (2014)	62 years	Improved symptoms and survival in chronic heart failure patients
Kisel-10 Study (2013)	78 years	Improved heart function and reduced cardiovascular mortality in senior citizens
Italian Multi-Center Study (1993)	67 years	Fewer hospitalizations and fewer complications in chronic heart failure patients

## 10. Conclusions

As detailed above, the process of CoQ<sub>10</sub> absorption is complex. It is not surprising that the absorption and bioavailability of CoQ<sub>10</sub> supplements can vary widely and does indeed do so. This variability depends primarily on the formulation of the preparation. As there is considerable inter-individual variability in the uptake of CoQ<sub>10</sub>, the absorption and bioavailability of CoQ<sub>10</sub> also depends on the capacity of a person to absorb a preparation with a given formulation. Thus, studies



by both Wahlqvist et al. [53] and Lopez-Lluch et al. [13] demonstrate the ability of some individuals to absorb a particular formulation better than other formulation. The inter-individual variations in the absorption of CoQ<sub>10</sub> were demonstrated as large inter-individual variations in the 36 h AUC and 48 h AUC, respectively, following the CoQ<sub>10</sub> administration.

With regard to the relative importance of ubiquinone and ubiquinol supplemental forms of CoQ<sub>10</sub>, there now seems to be evidence that there are multi-functional systems in place to convert ubiquinone to ubiquinol, involving as many as five different enzymes. Studies by Nordman et al. [38], Ross and Siegel [39], Bersuker et al. [40], Doll et al. [41], and Takahashi et al. [42] are of relevance. Takahashi et al. [42] established that isolated liver cancer cells are able to convert ubiquinone, either in the external medium or associated with LDL cholesterol, to ubiquinol, and that this conversion occurs due to the action of an outward-facing membrane-associated entity that was not further identified. The authors further consider that many other cell types may have the capacity to reduce ubiquinone to ubiquinol in the external cellular environment; if this is found to be the case, then presumably any of the various cell types lining the gastrointestinal tract would be able to facilitate this conversion, and the requirement for supplemental CoQ<sub>10</sub> in reduced form to maximise absorption would be negated.

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