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Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics

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Abstract
Available data on the absorption, metabolism and pharmacokinetics of coenzyme Q10 (CoQ10) are reviewed in this paper. CoQ10 has a fundamental role in cellular bioenergetics. CoQ10 is also an important antioxidant. Because of its hydrophobicity and large molecular weight, absorption of dietary CoQ10 is slow and limited. In the case of dietary supplements, solubilized CoQ10 formulations show enhanced bioavailability. The T_{max} is around 6 h, with an elimination half-life of about 33 h. The reference intervals for plasma CoQ10 range from 0.40 to 1.91 μmol/l in healthy adults. With CoQ10 supplements there is reasonable correlation between increase in plasma CoQ10 and ingested dose up to a certain point. Animal data show that CoQ10 in large doses is taken up by all tissues including heart and brain mitochondria. This has implications for therapeutic applications in human diseases, and there is evidence for its beneficial effect in cardiovascular and neurodegenerative diseases. CoQ10 has an excellent safety record.

Keywords: *Coenzyme Q10, ubiquinone, absorption, tissue distribution, plasma concentration, pharmacokinetics*

Introduction

Coenzyme Q (CoQ) is a naturally occurring compound with properties similar to those of vitamins. Because of its ubiquitous distribution in nature CoQ is also known as ubiquinone. CoQ belongs to a homologous series of compounds that share a common benzoquinone ring structure but differ in the length of the isoprenoid side chain. In humans and a few other mammalian species, the side chain is comprised of 10 isoprene units, hence it is called coenzyme Q10 (CoQ10). CoQ10 is similar to vitamin K in its chemical structure but it is not considered a vitamin because it is synthesized in the body. The chemical nomenclature of CoQ10 is 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone that is in the *trans* configuration (natural). CoQ10 has a fundamental role in cellular bioenergetics as a cofactor in the mitochondrial electron transport chain (respiratory chain) and is therefore essential for the production of ATP [1]. CoQ10 functions as a mobile redox agent shuttling electrons and also protons in the electron transport chain. The redox functions of CoQ10 extend beyond its role in the mitochondria [1,2]. Furthermore, CoQ10 in its reduced form as the hydroquinone (called ubiquinol) is a potent lipophilic antioxidant and is capable of recycling and regenerating other antioxidants such as tocopherol and ascorbate [1,2]. Other important functions of CoQ10 such as cell signaling and gene expression have also been described [2].

CoQ10 is available over the counter as a dietary supplement in the US and elsewhere. Potential benefits of CoQ10 supplementation have been recognized with particular reference to cardiovascular

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and neurodegenerative diseases [3–5], and as such CoQ10 has become an increasingly popular dietary supplement in recent years. Because of interest in its use as a therapeutic agent in clinical medicine, this review is intended to provide some basic information on the absorption, tissue distribution, metabolism and pharmacokinetics of CoQ10 along with data on plasma CoQ10 response to oral ingestion of pharmacologic doses.

Absorption and transport of CoQ10

Being a lipophilic substance the absorption of CoQ10 follows the same process as that of lipids in the gastrointestinal tract. The uptake mechanism for CoQ10 appears to be similar to that of vitamin E, another lipid-soluble nutrient. The absorption of CoQ10 is enhanced in the presence of lipids. Likewise, the absorption of supplemental CoQ10 can be improved if ingested with a fatty meal. Digestion helps in the release of dietary CoQ10 from the food matrix but for supplemental CoQ10 products that are based on pure CoQ10, gastric digestion does not appear to an important factor. In the small intestine, secretions from the pancreas and bile facilitate emulsification and micelle formation that is required for the absorption fats. No specific site along the small intestine has been identified for the absorption of CoQ10. Similar to vitamin E and other lipophilic substances, CoQ10 is first incorporated into chylomicrons following absorption and transported via the lymphatics to the circulation [6]. Data from rat studies indicate that CoQ10 is reduced to ubiquinol either during or following absorption in the intestine. This has been confirmed in a recent cell culture study using human Caco-2 cells [7]. Following absorption, ubiquinol first appears as a part of mesenteric triacylglycerol-rich lipoproteins. These particles are converted to chylomicron remnants in circulation by lipoprotein lipase and then taken up rapidly by the liver where CoQ10 is repackaged mostly into VLDL/LDL particles and rereleased into circulation, analogous to the handling of alpha tocopherol [8,9]. HDL also contains a small amount of CoQ10. Plasma CoQ10 concentrations are highly dependent on plasma lipoproteins [10]. Circulating CoQ10 redistributes among lipoproteins possibly to protect them from oxidation. About 95% of CoQ10 in circulation exists in its reduced form as ubiquinol in human subjects [11,12].

The efficiency of absorption of orally administered CoQ10 is poor because of its insolubility in water, limited solubility in lipids, and relatively large molecular weight. In one study with rats it was reported that only about 2–3% of orally-administered CoQ10 was absorbed [13]. As a general rule, higher the ingested dose lower the percent dose absorbed. In the case of supplemental CoQ10 in the form of finished dosage forms, the absorption is also dependent on factors such as the nature of the formulation, and solubilized formulations of CoQ10 have been shown to have enhanced bioavailability [14–16].

Tissue distribution of CoQ10

In humans and animals, CoQ is present in all tissues in varying amounts. CoQ9 is the predominant form in relatively short-lived species such as rats and mice whereas in humans and other long-lived mammals the major homolog is CoQ10. The distribution and redox state of CoQ10 in various human tissues are shown in Table I [11,12].

The total body pool of CoQ10 is estimated to be approximately 0.5–1.5 g in a normal adult [17]. Rats contain both CoQ9 and CoQ10 and their distribution in various tissues is shown in Table II [18].

As a general rule, tissues with high-energy requirements or metabolic activity such as the heart, kidney, liver and muscle contain relatively high concentrations of CoQ10 [1]. Being a lipophilic molecule, the distribution of CoQ10 in tissues is related not only to its metabolic activity but also to its lipid content. Data on the subcellular distribution of CoQ10 show a large portion (40–50%) of CoQ10 localized in the mitochondrial inner membrane, with smaller amounts in the other organelles and also in the cytosol. The high concentration of CoQ10 in the mitochondria reflects its important role in mitochondrial function. A typical subcellular distribution pattern for CoQ9 and CoQ10 in rat liver is shown in Table III [18].

A major portion of CoQ10 in tissues is in the reduced form as the hydroquinone or ubiquinol, with the exception of brain and lungs. This appears to be a reflection of increased oxidative stress in these two tissues. In blood, about 95% of CoQ10 is in the reduced form [11,12]. CoQ10 is also present in the cerebrospinal fluid mostly as ubiquinol at a very low concentration (about 9 pmol/l) as compared with that in plasma [19]. Among blood cells, lymphocytes and platelets contain significant amounts of CoQ10 whereas red blood cells which lack mitochondria contain only a tiny amount that is likely to be

Table I. Distribution and redox state of CoQ10 in human tissues.

Tissue	CoQ10 (nmol/g)	Redox state (% reduced)
Heart	132.0	61.0
Kidney	77.0	75.0
Liver	63.6	95.0
Muscle	46.0	65.0
Brain	15.5	23.0
Intestine	13.3	95.0
Lungs	9.2	25.0
Plasma (μmol/l)	1.1	96.0*

Adapted from Aberg et al. [11].
* Miles et al. [12].

Table II. CoQ content of various tissues in rat.

Tissue	CoQ9 (pmole/mg protein)	CoQ10 (pmole/mg protein)	CoQ9+CoQ10 (% reduced)
Liver	1040	99	85.4
Kidney	1513	160	43.2
Heart	2201	173	21.1
Muscle	653	44	40.2
Brain	642	274	27.7
Plasma (nmol/l)	1030	72	54.0

Adapted from Zhang et al. [18].

associated with membranes. Lymphocyte CoQ10 content can be increased by CoQ10 supplementation with concomitant functional improvement as evidenced by enhanced reversal of oxidative DNA damage [20].

Tissue uptake of CoQ10

Since CoQ10 is synthesized de novo in all tissues, it is presumed that under normal circumstances they are not dependent on an exogenous supply of CoQ10. Furthermore, there is no evidence at present to show that dietary CoQ10 that is secreted into circulation in association with lipoproteins by the liver is taken up by other tissues under normal conditions. However, tissue CoQ10 content is subject to regulation by several physiologic factors including oxidative stress and also aging [1]. Furthermore, CoQ10 status may be compromised under many pathophysiologic conditions [1,3,4].

Intestinal absorption of dietary CoQ10 is very limited. In one study with rats, orally-administered CoQ10 was found to appear in circulation, liver and spleen but none in heart or kidney, and the uptake of CoQ10 by the liver tissue was found to be dose-dependent, up to 12 μmol/100 g body weight [13]. The uptake appeared to plateau at this dose. Repeated daily dosing also resulted in an increased uptake by the liver. On the other hand, intravenously administered CoQ10 as a lipid microsphere was taken up by heart and kidney in addition to the other tissues [21]. Furthermore, chronic ingestion of relatively large doses of CoQ10 in the diet has been shown to increase CoQ10 concentrations especially in the heart and brain mitochondrial fractions in rodent models [22–24]. This indicates that dosage and duration of CoQ10 administration are important factors regulating its uptake by heart and the brain.

Table III. Subcellular distribution of CoQ in rat liver.

Fraction	CoQ9 (pmol/mg protein)	CoQ10 (pmol/mg protein)
Homogenate	1040	99
Mitochondria	5919	535
Microsomes	249	57
Golgi vesicles	805	92
Lysosomes	1126	120
Plasma membranes	353	37
Nuclear fraction	188	27
Peroxisomes	121	13
Cytosol	106	11

Adapted from Zhang et al. [18].

Metabolism of CoQ10

Data on the metabolism of CoQ10 in animals and humans are very limited. In the few animal studies available, both rats and guinea pigs have been used to examine the in vivo metabolism of CoQ10. While CoQ9 is the major CoQ homolog in rats, CoQ10 is the primary form in guinea pigs and it would therefore appear that this species might be a more appropriate animal model for studying CoQ10 metabolism.

In one of the earlier studies, data on the metabolic fate of CoQ in rats was studied using CoQ7 as a model compound [25]. Radioactivity from an orally administered dose of ^{14}C-labeled CoQ7 in corn oil peaked at 6 h in blood. It was found to be absorbed intact via the lymphatics and concentrated mainly in the liver and also excreted via the bile. Part of the radioactivity in the bile was reabsorbed. The fecal excretion was found to be the main route of elimination of labeled CoQ7. In another rat study with ^{14}C-labeled CoQ10, Kishi et al. [26] found that plasma radioactivity peaked at 2 h following oral administration of CoQ10. Most of the radioactivity at the peak was in the liver. Administration of CoQ10 increased the endogenous levels of not only CoQ10 in plasma and liver but also of CoQ9. This indicates that interconversion of exogenous CoQ10 to CoQ9 is possible in rats. Furthermore, there is evidence to show that administration of exogenous CoQ10 does not depress the synthesis of endogenous CoQ9 in rats indicating that there is no down-regulation of CoQ9 synthesis by increased concentrations of CoQ9 and CoQ10 in the liver [13]. The finding that CoQ10 ingestion leads to an increase in tissue CoQ9 content has been confirmed in recent studies with both rats and mice [23,24,27]. Whether such a conversion occurs in humans is not clear at this time.

In one study with guinea pigs where ^{14}C-labeled CoQ10 was administered intravenously, 4.8% of radioactivity was recovered in the bile. The main

metabolite was presumed to be a glucuronide of Q acid I [2,3 dimethoxy-5-methyl-6-(3′-methyl-5′-carboxy-2-pentenyl)-1,4-benzohydroquinone] formed in the liver. The cumulative recovery of radioactivity in the urine over 48 h amounted to 8.3% consisting of a mixture of conjugated and unconjugated metabolites, tentatively identified as Q acid I and Q acid II [2,3 dimethoxy-5-methyl-6-(3′-carboxypropyl)-1,4-benzoquinone] in free and also the corresponding hydroquinone conjugated forms [28].

Bentinger et al. [29] have made a very interesting observation recently in the identification of phosphorylated metabolites of CoQ10. In this study, ^{3}H-labeled CoQ10 with the label in the first methylene group in the side chain was synthesized so that the metabolites with shorter side chains would retain their radioactivity and thus could be identified and quantitated. The labeled CoQ10 was administered to rats intraperitoneally which resulted in an efficient uptake into circulation (14,500 dpm/mg protein at 24 h following administration of 200 μCi intraperitoneally). High concentrations were found in spleen, liver, and white blood cells, and lower concentrations in adrenals, ovaries, thymus, and heart. In the liver homogenate, most of the labeled CoQ10 appeared in the organelles. Purified mitochondria had a low concentration that was mainly localized in the lysosomes. Surprisingly, high-concentrations of radioactivity was found in white blood cells indicating the importance of CoQ10 in their function. All organs that took up the labeled CoQ10 also contained water-soluble metabolites. The majority of metabolites (only a small fraction of the total radioactivity) were excreted through the kidney. Fecal excretory products consisted of, in addition to intact CoQ10, a small fraction of the metabolites. Mass spectrometric fragmentation analysis of major urinary metabolites showed that these compounds contained the ring structure with a short side chain and were phosphorylated. Thus, these results demonstrate that CoQ10 is metabolized in all tissues; the metabolites are phosphorylated in the cells, transported in the blood to the kidney, and excreted into the urine. Again, it should be noted that the urinary metabolites of CoQ10 accounted for only a small fraction of CoQ10 that was absorbed, and the major route of elimination of CoQ10 was by way biliary and fecal excretion. Since phosphorylation of metabolites is not a normal catabolic process, phosphorylated metabolites of CoQ10 may indeed have functional significance. Thus the identification of these novel metabolites should stimulate additional research in this area.

Assessment of CoQ10 status

Plasma or serum CoQ10 concentrations are usually employed for the assessment of CoQ10 status in humans primarily because of the ease of sample collection. There are several excellent methods based on HPLC for the analysis of CoQ10 in plasma or serum [30–36] and fasting samples are preferred. CoQ9 is frequently used as an internal standard for human samples, and CoQ11 is also used in some instances. Di-ethoxy CoQ10 was proposed in one study [31] and in a more recent study the use of di-propoxy CoQ10 as an internal standard has been described [37]. According to Kishi et al. [26] plasma CoQ10 reflects not only the amount of absorbed CoQ10 but also tissue CoQ10 content. Although plasma CoQ10 concentrations may not necessarily reflect tissue status [37,38], it still serves as a useful measure of overall CoQ10 status and also as a guide to CoQ10 dosing. This is particularly true of degenerative neurologic and muscular diseases where clinical monitoring of plasma CoQ10 concentration and also its redox status is highly desirable that could provide valuable information as to the course of treatment [38]. Lymphocyte and platelet CoQ10 concentrations could also be considered as potential surrogates for tissue CoQ10 status. However, not much work has been done in this area probably because of the additional steps in sample preparation and processing required. Assay of the activities of CoQ10-dependent enzyme systems in the respiratory chain in biopsy samples is some times carried out in a few a laboratories in order to localize the biochemical lesions in such disorders and thus aid in the treatment strategy.

Reference intervals for plasma and tissue CoQ10 values

Normal range for plasma CoQ10 concentrations in adult subjects is available and there is also some data on tissue CoQ10 values. Since plasma CoQ10 is associated with lipoproteins, values adjusted for plasma lipids are also available that may serve as a better indicator of status under certain situations. Kaikkonen et al. [39] reported plasma CoQ10 values ranging from 0.40 to 1.72 μmol/l for males and 0.43 to 1.47 μmol/l for females in a Finnish population. Similar data are available for a US population. Miles et al. [12] reported a range of 0.50–1.91 μmol/l that included blacks and whites of both sexes. Breakdown by sex and race and also the redox status of plasma CoQ10 were also provided in this study. Plasma CoQ10 concentration ranges were higher in white males than in white females and this is consistent with the findings of Kaikkonen et al. [39]. Furthermore, significant differences in plasma CoQ10 values attributable to racial factors have also been observed. In the study by Miles et al. [12], blacks had higher plasma CoQ10 values than whites although their reference interval fitted within the reference interval for whites. The reasons for this difference are not clear. Somewhat lower values that range from 0.227 to

1.432 μmol/l with a mean of 0.675 μmol/l have been reported in a British population [37]. Lipid-corrected reference intervals for plasma CoQ10 area also available. Data on total CoQ10/total cholesterol (μmol/mmol) for a US population are reported to be in the range of 0.113–0.329 for males and 0.119–0.326 for females [38].

Plasma concentrations of both the total and the reduced CoQ10 (ubiquinol) were found to be significantly lower in Asian Indian males than those in Chinese males in a Singaporean population, and this was presumed to be one reason for the higher risk for coronary artery disease in Asian Indians [40]. Data on normal CoQ10 content of plasma in a healthy pediatric population are also available. In European children, a mean value of 0.84 μmol/l has been reported [41] that is in very close agreement with a value of 0.87 μmol/l obtained earlier [42]. In addition to plasma cholesterol and triglycerides, other confounding factors have been identified that might affect plasma CoQ10 concentrations in epidemiologic research [35].

There is limited data on reference intervals for CoQ10 concentrations in skeletal muscle. Duncan et al. [37] recently reported a range of 140–580 pmol/mg protein with a mean value of 241 pmol/mg protein for skeletal muscle and this is similar to the findings of Miles et al. [43]. Data on mononuclear cells were also obtained in this study that show a range of 37–133 pmol/mg protein with a mean of 65 pmol/mg protein. There was a close association between mononuclear cell and skeletal muscle CoQ10 concentrations but not with plasma CoQ10 [37].

Plasma/serum response to orally-administered CoQ10

Under normal circumstances plasma CoQ10 concentrations are not significantly affected by dietary components such as dairy products, eggs, fish and vegetables [35]. CoQ10 supplementation on the other hand leads to increases in plasma CoQ10 concentrations, the extent of which depends upon the dosage, duration and also the type of formulation. There are numerous reports in the literature on plasma CoQ10 response to oral administration of CoQ10 in several species of animals and also in humans. Data from representative human studies with various CoQ10 formulations are presented in Table IV showing the dose, duration and net increase in plasma CoQ10 concentration. Incidentally, it should be noted that in the paper by Lyon et al. [44] the plasma CoQ10 values throughout the paper are erroneously stated as moles rather than as micromoles (and the baseline plasma CoQ10 values of 0.27 and 0.29 μmol/l for the two groups reported are extremely low for "normal" subjects).

Large single doses of CoQ10 either as a powder or as an oil-suspension elicit practically no response in human subjects [15,45] or only a marginal response [39]. With chronic dosing, there appears to be a somewhat dose-dependent increase in plasma CoQ10 up to daily dose of 200 mg CoQ10 administered as an oil-suspension [39]. In this study, the increases in plasma CoQ10 were from 2.8-fold (at 30 mg) to 6.5-fold (at 200 mg) over a 2–3 month period (actual values not given). In another controlled trial, supplementation with either 30 or 100 mg CoQ10 as an oil suspension for two months resulted in increases in serum CoQ10 values of 0.637 and 1.575 μmol/l from baseline values of 1.483 and 1.332 μmol/l, respectively [46]. However, with solubilized formulations of CoQ10, plasma response is much higher [14]. In this study, plasma CoQ10 values increased from 0.579 to 3.834 μmol/l with the solubilized formulation as opposed to from 0.579 to 1.587 μmol/l with an oil suspension in just three weeks, clearly indicating the superiority of the

Table IV. Plasma CoQ10 response to following daily CoQ10 supplementation.

Formulation	Dose (mg)	Duration	Plasma CoQ10 increase (μmol/l)	Reference
Oil based	90	9 months	1.214*	Folkers et al. [47]
Oil based	90	2 weeks	1.200†	Weber et al. [48]
Oil based	100	2 weeks	0.524‡	Lonnrot et al. [19]
Powder based	90	2 months	1.810	Kaikkonen et al. [45]
Oil based	90	2 months	1.900	Kaikkonen et al. [45]
Powder based	120	3 weeks	1.309	Chopra et al. [14]
Oil based	120	3 weeks	1.008	Chopra et al. [14]
Solubilized	120	3 weeks	3.255	Chopra et al. [14]
Oil based	300	1 week	0.530	Lyon et al. [44]
Emulsion	300	1 week	0.500	Lyon et al. [44]
Powder based	50	1 week	0.568	Lu et al. [49]
Powder—SR	50	1 week	1.124	Lu et al. [49]

Plasma CoQ10 values corrected for baseline.
* Whole blood; CoQ10 in divided doses.
† Extrapolated from figure.
‡ With 500 mg vitamin C.

solubilized formulation of CoQ10. Similar observation has been made by Miles et al. [15] in a single-dose pharmacokinetic study. A great deal of individual variability in plasma response to ingested CoQ10 has been observed in all these studies as indicated by rather large standard deviations.

Pharmacokinetics of CoQ10

There are only a few reports on the pharmacokinetics of CoQ10 in humans and in animal models. In one of the early rat studies, radioactivity from an orally administered dose of ^{14}C-labeled CoQ7 was found to peak at 6 h in blood [25] and this is similar to what has been observed in subsequent studies with humans. However, in another rat study using ^{14}C-labeled CoQ10, Kishi et al. [26] found that plasma radioactivity peaked at 2 h following oral administration. The reasons for the discrepancy between the two rat studies are not clear other than the fact that in addition to differences in experimental design they were using two different labeled homologs of CoQ, but none using CoQ9, the predominant form in the rat.

Data on half-lives of CoQ9 in various rat tissues are also available. In a study by Thelin et al. [50] rats were injected intraperitoneally with labeled mevalonate, a precursor of CoQ, and the decay of radioactivity incorporated into CoQ9 in various tissues were examined. The data, presented in Table V, show observed half-lives ranging from a low of 49 h for thyroid to 125 h for kidney. This indicates that CoQ9 is subjected to rapid catabolism and turnover in all the tissues in rats and this may reflect a similar phenomenon in humans too.

Among the few studies related to the pharmacokinetics of CoQ10 in humans, the study by Tomono et al. [51] is recognized as an important contribution in this area and is cited often. Using deuterium-labeled CoQ10, they reported a T_{max} of 6.5 h and an elimination half-life of 33.19 h. Lucker et al. [48] employing unlabeled CoQ10 in their study have reported similar data. In both studies powder-based CoQ10 products were used. In a more recent study, Miles et al. [9] compared a powder-based formulation with three different solubilized formulations of CoQ10 with enhanced bioavailability. The powder and two solubilized formulations showed a T_{max} of about 6 h consistent with previous reports and one solubilized formulation had a T_{max} of about 8 h. The pharmacokinetic parameters obtained in this study are shown in Table VI.

In another study where a straight tablet formulation of CoQ10 was compared with a sustained release tablet formulation, both showed a T_{max} of 6 h and also similar C_{max} values indicating that the sustained release feature did not significantly delay the absorption rate of CoQ10 [49].

The T_{max} value of about 6 h or longer indicates that CoQ10 is absorbed slowly from the gastrointestinal tract and this is attributable to both its hydrophobicity and high molecular weight. A second plasma CoQ10 peak has been observed at about 24 h following oral ingestion [51–53] which may be due to both enterohepatic recycling and redistribution from the liver to circulation. A similar phenomenon has been reported in guinea pigs injected intravenously with ^{14}C-labeled CoQ10 where a second peak appeared 8 h post-injection [54]. This type of plasma CoQ10 response renders it difficult to analyze the data based on a simple compartment model, and according to Tomono et al. [51] the absorption rate constant could be better expressed in this situation by assuming a zero-order rate constant rather than first-order kinetics. This model designed to fit the unusual plasma response curve is based upon the assumption that absorbed CoQ10 is taken up by the liver and then transferred mainly to VLDL and redistributed from the liver to systemic circulation.

Therapeutic uses of CoQ10

CoQ10 is a popular dietary supplement because of its recognition by the public as an important nutrient in supporting human health. The rationale for the use of CoQ10 as a therapeutic agent in several cardiovascular and degenerative neurologic and neuromuscular diseases is based upon its fundamental role in mitochondrial function and cellular bioenergetics.

Table V. Half-lives of CoQ9 in rat tissues.

Tissue	Half-life (h)
Heart	59
Kidney	125
Liver	79
Muscle	50
Brain	90
Intestine	54
Pancreas	94
Thyroid	49

Adapted from Thelin et al. [50].

Table VI. Pharmacokinetic profile of single-dose oral CoQ10 in humans.

Formulation	Dose (mg)	C_{max}* (μmol/l)	T_{max} (h)	AUC* (μmol h/l)
Powder	180	0.14	6.70	–
Liquid 1†	180	1.16	6.20	59.85
Liquid 2†	180	1.47	8.10	64.01
Liquid 3†	180	1.16	5.80	44.94

Adapted from Miles et al. [15].
* Corrected for baseline values.
† Solubilized formulations of CoQ10.

There is data to support the therapeutic value of CoQ10 as an adjunct to standard medical therapy in cardiovascular diseases [3,4,17]. The importance of CoQ10 as a treatment modality in mitochondrial diseases is well recognized [55,56]. Preliminary results on the use of CoQ10 in Parkinson's and Huntington's diseases are indeed promising [5,57], and there is some evidence for a role of CoQ10 in amyotrophic lateral sclerosis [5,57]. There is also data to indicate a beneficial effect of CoQ10 in diabetes [58], cancer [59], and in a few other indications as well [60].

CoQ10 dosage

CoQ10 is available as a dietary supplement in strengths generally ranging from 15 to 100 mg. In cardiovascular disease patients CoQ10 dosages generally range from 100 to 200 mg a day [61]. Dosages of up to 15 mg/kg/day are being employed in the case of mitochondrial cytopathy patients [55]. A dosage of 600 mg a day was used in the Huntington's disease trial [62] whereas a dosage of up to 1200 mg a day was employed in the Parkinson's disease trial [63].

CoQ10-drug interactions

The adverse effects of two classes of drugs, viz. anthracyclines and statins are well documented by both preclinical and clinical studies. Anthracyclines such as doxorubicin and daunorubicin are excellent anticancer drugs but they are also cardiotoxic. They cause irreversible damage to myocardial mitochondria, and this can be prevented by CoQ10 administration during cancer chemotherapy without compromising their antineoplastic action [64]. Cholesterol-lowering drugs known as statins (HMG–CoA reductase inhibitors) in addition to inhibiting cholesterol synthesis also block the endogenous synthesis of CoQ10 resulting in its depletion. This leads to myopathy in some cases, and life-threatening rhabdomyolysis in extreme cases, and these adverse effects can be prevented by CoQ10 supplementation [65,66]. Beta-blockers have shown to decrease endogenous serum CoQ10 content by inhibiting CoQ10-dependent enzymes [67]. Certain oral hypoglycemic agents such as glyburide, phenformin and tolazamide have also been shown to decrease endogenous CoQ10 content, whereas CoQ10 supplementation has been reported to improve glycemic control in diabetics. Therefore, diabetic patients taking CoQ10 may require dosage adjustments of hypoglycemic agents [58,68]. Because of its structural similarity to vitamin K, it has been suggested that CoQ10 may have procoagulant activity [69]. This indicates that patients on anticoagulant therapy may need to have their INR monitored and anticoagulant dosage adjusted accordingly.

Safety of CoQ10

CoQ10 has an excellent safety record. The safety of high doses of orally-ingested CoQ10 over long periods is well documented in human subjects [70,71] and also by chronic toxicity studies in animals [72]. The side effects reported in human studies are generally limited to mild gastrointestinal symptoms such as nausea and stomach upset seen in a small number of subjects. No adverse effects were observed with daily doses ranging from 600 to 1200 mg in two trials on Huntington's [62] and Parkinson's [63] diseases. More recent data document the safety and tolerability of CoQ10 at doses as high as 3000 mg a day in patients with Parkinson's disease [73] and amyotrophic lateral sclerosis [74].

In summary, CoQ10 is a vitamin-like nutrient that belongs to a homologous series of compounds that occur widely in nature. CoQ10 is present in all tissues in humans. Mitochondria contain relatively high concentrations of CoQ10, attributable to its fundamental role in mitochondrial bioenergetics in facilitating the production of ATP. Tissues with high-energy requirements and metabolic rates such as the heart and the skeletal muscle contain relatively high concentrations of CoQ10. Another important function of CoQ10 is as a lipophilic antioxidant.

CoQ10 is synthesized de novo by every cell in the body and it is therefore presumed that under normal conditions an exogenous supply of CoQ10 is not required. However, under certain conditions including oxidative stress and aging, endogenous production may not meet the demands for CoQ10.

Because of its hydrophobicity and large molecular weight, the absorption of dietary CoQ10 is slow and very limited. In the case of CoQ10 as dietary supplements, products containing solubilized formulations of CoQ10 show enhanced bioavailability as compared with powder-based capsules, tablets and oil-suspensions. The T_{max} of CoQ10 is about 6 h that indicates a slow absorptive process. The reference intervals for plasma CoQ10 values range from 0.4 to 1.91 μmol/l in healthy adults. With CoQ10 supplements there is reasonable correlation between increase in plasma CoQ10 concentrations and ingested dose up to a certain point. Solubilized formulations of CoQ10 yield higher plasma concentrations. Animal studies show that when administered in large doses on a chronic basis CoQ10 is taken up by all tissues including heart and brain mitochondria, leading to biochemical and also functional improvements. This has implications for therapeutic applications in human diseases, and there is evidence for its beneficial effect in cardiovascular and mitochondrial diseases. Preliminary results with CoQ10 in neurodegenerative diseases are promising. Finally, as a nutrient and also as a drug CoQ10 has an excellent safety record.

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