Physiological Roles of CoQ$_{10}$ in Humans

Subjects: Nutrition & Dietetics

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Coenzyme Q$_{10}$ (CoQ$_{10}$) is a compound with a crucial role in mitochondrial bioenergetics and membrane antioxidant protection. Despite the ubiquitous endogenous biosynthesis, specific medical conditions are associated with low circulating CoQ$_{10}$ levels. However, previous studies of oral CoQ10 supplementation yielded inconsistent outcomes. In this text, previous CoQ10 trials are reviewed, either single or in combination with other nutrients, and stratified the study participants according to their metabolic statuses and medical conditions. The CoQ10 supplementation trials in elders reported many favorable outcomes. However, the single intervention was less promising when the host metabolic statuses were worsening with the likelihood of multiple nutrient insufficiencies, as in patients with an established diagnosis of metabolic or immune-related disorders. On the contrary, the mixed CoQ10 supplementation with other interacting nutrients created more promising impacts in hosts with compromised nutrient reserves. Furthermore, the results of either single or combined intervention will be less promising in far-advanced conditions with established damage, such as neurodegenerative disorders or cancers. With the limited high-level evidence studies on each host metabolic category, it could only be concluded that the considerations of whether to take supplementation varied by the individuals' metabolic status and their nutrient reserves. Further studies are warranted.

coenzyme Q10   dietary supplements   ubiquinone   mitochondria   bioenergetics

1. Introduction

In 1957, Crane et al. isolated a new quinone compound, initially referred to as Q-275, from beef heart mitochondria and described its ability to undergo reversible oxidation and reduction [1]. With its functional quinone moiety and its ubiquitous presence in living cells, this compound was later officially named 'ubiquinone' by the IUPAC-IUB Commission on Biochemical Nomenclature [2][3]. However, there were other common names for ubiquinone, including Coenzyme Q$_{10}$ (CoQ$_{10}$), CoQ, ubiquinone-Q10, vitamin Q10, and ubidecarenone [4].

CoQ$_{10}$ consists of two functional groups, i.e., the five-carbon isoprene 'tail' and the benzoquinone 'head'. The lipid-soluble tail consists of ten isoprenes, with a total of 50 carbon atoms, hence the name 'CoQ$_{10}$' [5][6]. Humans can internally synthesize CoQ$_{10}$. The synthesis of the benzoquinone head requires amino acids, either tyrosine or phenylalanine, while the mevalonate pathway provides the acetyl coenzyme A for the polyisoprenoid tail synthesis [5][7][8]. The CoQ$_{10}$ head and tail are synthesized in the cytosol but the joining of both functional groups occurs in the mitochondria [5][9]. The CoQ$_{10}$ biosynthesis requires support from various macro- and micronutrients, such as

pantothenic acid for the CoA precursor, pyridoxine for the benzoquinone production, and s-adenosyl methionine for methylation support and isoprene production [10].

Humans can internally synthesize CoQ$_{10}$, while the dietary CoQ$_{10}$ sources additionally contribute to its total tissue pool. The main dietary sources of CoQ$_{10}$ include fish and meat, while vegetables generally contain low CoQ$_{10}$ quantities. Dietary CoQ$_{10}$ sparsely absorbs in the hydrophilic intestinal environment due to its lipophilic and high molecular weight properties. Following the gut uptake, CoQ$_{10}$ circulates in the lymphatic system and ultimately drains into the blood circulation [11]. Consequently, the CoQ$_{10}$ level in the liver and plasma lipoproteins appears shortly after absorption, but the elevation of plasma CoQ$_{10}$ level varies by the blood cholesterol and lipoprotein concentrations [6][12]. The CoQ$_{10}$ turnover in the body is relatively fast, with a 49 to 125 h half-life, depending on the tissue type [13].

The combination of endogenous biosynthesis and dietary intake is largely sufficient to prevent the CoQ$_{10}$ deficiency state in a healthy individual [14][15]. However, cumulative studies reported the association of low CoQ$_{10}$ levels in specific conditions such as following strenuous exercise, during aging, after taking some prescribed medications, in patients with various metabolic disorders, and in individuals with cancers [6][8][16][17][18][19][20][21][22]. Despite the documented low CoQ$_{10}$ levels, the clinical outcomes of CoQ$_{10}$ interventions, either single or in combination with other nutrients, were generally inconsistent.

2. Physiological Roles of CoQ$_{10}$ in Humans

2.1. CoQ$_{10}$ Roles in Mitochondrial Bioenergetics

CoQ$_{10}$ roles are crucial to the mitochondrial respiratory chain as the electron acceptor. It modulates the electron transferring from the bioenergetic-derived reducing equivalents, i.e., nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH$_2$), through the complex I, II, and III in the electron transport chain (ETC). The concurrent proton flow, from the mitochondrial matrix to the intermembrane space, generates the intermembrane proton gradients, which are essential for oxidative phosphorylation and subsequent adenosine triphosphate (ATP) synthesis [5]. Accordingly, CoQ$_{10}$ intervention could have potential bioenergetic benefits in clinical conditions with mitochondrial dysfunction.

While mitochondria are the bioenergetic hub of the cells, they are also the predominant source of reactive oxygen species (ROS) production, oxidative stress, and immunologic and apoptotic regulation. The imbalances of these physiological processes underly diverse metabolic conditions [23]. As the critical supporter of mitochondrial functions, the importance of CoQ$_{10}$ might extend beyond bioenergetics.

2.2. CoQ$_{10}$ Role as an Antioxidant

With its reversible redox potential and membrane-associated locations, CoQ$_{10}$ renders antioxidant protection to the organelles and cell lipid membranes [13][24][25][26]. Inside the cells, the benzoquinone head of CoQ$_{10}$ exists in three

interchangeable oxidation states, i.e., the fully reduced ubiquinol (CoQ$_{10}$H$_2$), the ubisemiquinone intermediate (CoQ$_{10}$H•), and the fully oxidized ubiquinone (CoQ$_{10}$). These redox states are culpable for the scavenging of ROS as well as the mediation of electrons transferring in the mitochondrial ETC.

Nevertheless, the integrated redox modulation of CoQ$_{10}$ requires support from other nutrients, specifically α-tocopherol, vitamin C, and other micronutrients. **Figure 1** depicts this integrated antioxidant network of CoQ$_{10}$ against lipid peroxidation [27][28]. While the ROS induces unsaturated lipid peroxidation, it yields the highly reactive lipid peroxyl radicals, which are quickly neutralized by α-tocopherol through the donation of its hydrogen to the peroxyl radicals, thus holding their propagations within membranes and circulating lipoproteins. The reduced ubiquinol then helps regenerate the α-tocopherol antioxidant capacity through their redox interactions. Thereafter, the ubisemiquinone intermediate can either react with the oxygen molecule and produce the superoxide anion radicals or oxidize further to the fully oxidized ubiquinone that does not react with oxygen. Reduced NADP (NADPH), glutathione, and other antioxidants such as vitamin C then help to regenerate the oxidized ubiquinone and α-tocopherol back and maintain their reduction states [13][29][30][31]. In this integrated manner, CoQ$_{10}$ limits the production of lipid peroxyl radicals and protects the circulating lipoproteins, the cellular membrane proteins, the mitochondrial DNA, and the ETC membranes [24][32][33][34].
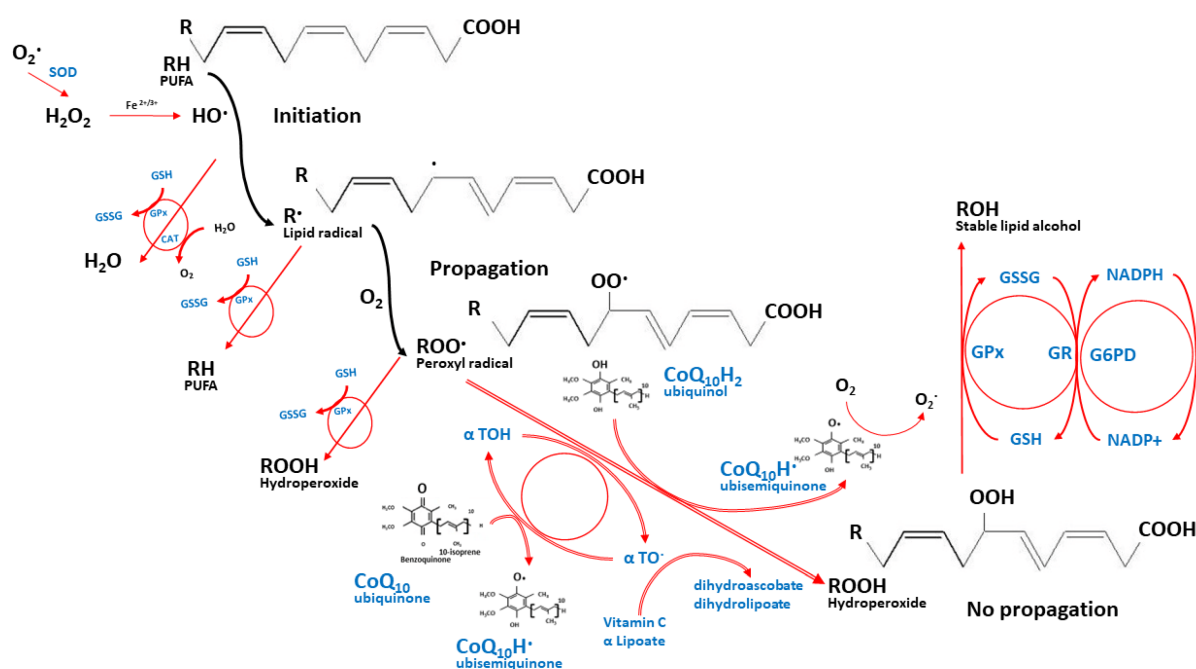

Figure 1. The integrated antioxidant defenses against lipid peroxidation. The nutrient network halts the propagation of lipid peroxyl radicals while their redox interactions maintain their reduction states. These nutrients include coenzyme Q$_{10}$, α tocopherol, vitamin C, α lipoic acid, glutathione, and the micronutrients that support the activities of antioxidant enzymes such as selenium, manganese, copper, and zinc (not shown in the figure). O$_2$•—superoxide anion radical, H$_2$O$_2$—hydrogen peroxide, Fe$^{2+/3+}$—ferrous or ferric iron, PUFA—polyunsaturated fatty acids, GSH—reduced glutathione, GSSG—glutathione disulfide, GPx—glutathione peroxidase, CAT—catalase, H$_2$O—water, O$_2$—oxygen, α TOH—reduced α tocopherol, α TO•—oxidized α tocopherol.

For oral CoQ$_{10}$ supplementation, a 2020 meta-analysis of 17 randomized clinical trials (RCT) documented its antioxidant potentials, comprising the reduction of membrane oxidative damage level, the enhancement of total antioxidant capacity, and the activation of antioxidant defense system enzymes [28]. As a dietary supplement, the antioxidant capability of CoQ$_{10}$ might provide benefits to clinical conditions with underlying oxidative stress pathophysiology.

2.3. Other Physiological Roles of CoQ$_{10}$

CoQ$_{10}$ also serves as the structural component of the ETC membrane supercomplexes that ascertains the efficient ETC functions and prevents the leakage of the electron from the respiratory chain [26][35][36][37]. The combined result of its structural contribution, lipid peroxidation protection, ROS scavenging, and uncoupling protein activations contribute to the pivotal role of CoQ$_{10}$ in mitochondrial membrane integrity [13][38]. Besides this, the conservation of mitochondrial membrane permeability is also crucial for cellular survival and functions [13][39][40].

Apart from the mitochondria, the containment of highly acidic enzymes within the lipid-membrane boundary of lysosomes requires the CoQ$_{10}$-induced intermembrane proton gradient [8][41]. Furthermore, CoQ$_{10}$–redox interaction maintains the balance of cytosolic redox intermediates such as NADH, NADPH, and FADH$_2$. The CoQ$_{10}$-mediated reaction also supplies orotate for the de novo pyrimidine synthesis through the oxidative activity of dihydroorotate dehydrogenase [42]. These intracellular redox balances influence several cellular signalings and gene transcriptions. Such homeostasis modulates apoptosis, bioenergetics, cell growth, and inflammatory responses [26][43].

Interestingly, the oral CoQ$_{10}$ supplementation showed different 115 gene expressions in the muscle tissue samples from aged individuals compared to their placebo controls [44]. These findings supported the diverse physiologic roles of CoQ$_{10}$ and the potential benefit of its intervention. Several clinical studies also reported that oral CoQ$_{10}$ supplementation showed anti-inflammatory effects, including the reduction of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) [45][46][47][48]. This immunomodulatory potential of CoQ$_{10}$ supplementation also suggests its potential benefit to various immune-mediated clinical conditions.

3. Potential Roles of CoQ$_{10}$ Supplementation in Specific Medical Conditions

Despite the ubiquitous endogenous biosynthesis, specific medical conditions are associated with low circulating CoQ$_{10}$ levels. However, the inconsistent results of CoQ10 interventions, from previous studies, implied the presence of unaccounted factors that contributed to clinical outcomes. After reviewing the participants' status in previous CoQ10 clinical trials, two potentially confounding aspects are proposed herein, i.e., differences in host metabolic status and the need for CoQ10 interacting nutrients.

Human metabolism fundamentally relies on host macro- and micronutrient reserves. Depleted host nutrient reserve leads to metabolic triage of nutrients toward the preservation of short-term metabolic survival, usually at the cost of

compromised long-term health [49][50]. The protein deformations, with altered enzyme binding constants for various coenzymes, underly these nutrient triage processes [51]. Compromised host nutrients induce metabolic triage and accelerate the pathophysiologies of degenerative and metabolic diseases [52]. Therefore, nutrient interventions could hinder mitochondrial decay and delay age-associated illnesses [50].

Even the so-called healthy subjects were still prone to conditional micronutrient inadequacies following intense physical activities, despite their good metabolic statuses and no established clinical diagnosis at baseline. The combined nutrient interventions hold better chances to address the conditional nutritional insufficiencies than a single nutrient. To support this notion, previous studies showed the favorable trends of combined CoQ$_{10}$ intervention in healthy adults and athletes performing exercise sessions, as compared to single supplementation.

Elders and patients with diagnosed metabolic and immune-related disorders likely had compromised metabolic status, along with multiple nutrient insufficiency. The depleted nutrient reserves increased with the advancement of these chronic situations. Hosts with specific nutrient depletion, such as primary CoQ$_{10}$ deficiencies, benefited from single CoQ$_{10}$ supplementation, even though the outcomes were mostly palliative, not curative. The single intervention was also beneficial in hosts with early stages of declined metabolic status, such as the elderly. The benefits decreased with the advancement of metabolic conditions, as seen in patients with diabetes, cardiovascular diseases, or kidney failure. Despite the improvement of some surrogate biomarkers such as proinflammatory cytokines, antioxidative capacities, and lipid or glycemic profiles, the positive trends in clinical outcomes were less promising with single supplementation. Contrarily, combined CoQ$_{10}$ interventions provided more encouraging results in hosts with impaired metabolic status due to the readily available interacting nutrients in the formulations.

However, both CoQ$_{10}$ interventions would be less beneficial in far-advanced conditions with established damage such as neurodegenerative conditions or cancers. The results of both single and combined supplementation, at best, affected some surrogate biomarkers but not the overall clinical outcomes. Therefore, nutrient interventions are preventive or protective rather than curative measures.

In conclusion, no single nutrient could magically drive whole physiological processes. Single CoQ10 supplementation will be beneficial only for hosts that specifically require it, such as hereditary CoQ10 deficiencies. The single intervention will be less promising when the host metabolic status worsens with the likelihood of multiple nutrient insufficiencies. On the contrary, the mixed CoQ10 supplementation with other interacting nutrients will create more promising impacts in hosts with compromised nutrient reserves. However, the results of either single or combined intervention will be less promising in far-advanced conditions with established damage.

With the limited amount of high-level evidence, such as provided by systematic reviews and meta-analyses, the researchers could only conclude that the considerations of whether to take supplementation varied by the individuals' metabolic status and their nutrient reserves, which span across the continuum of metabolic triage processes that lead to chronic health issues. Future studies are warranted, particularly for the RCT with the design

to control the host metabolic and nutrient status of participants and the meta-analysis of upcoming CoQ10 studies on each subject's metabolic status.

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