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Overview of CoQ10 Role in Health and Diseases

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Abstract

Coenzyme Q10 (CoQ10), also known as ubiquinone or ubidecarenone, is a lipid-soluble, vitamin-like compound found in all human cells, primarily in the mitochondria, cell membranes, and lipoproteins. It plays a vital role in cellular energy production by participating in the electron transport chain (ETC) in mitochondria, converting metabolic products into ATP through oxidative phosphorylation. The reduced form, ubiquinol (CoQH2), acts as a potent antioxidant, scavenging reactive oxygen species (ROS) to prevent oxidative damage to lipids, proteins, DNA, and mitochondria. CoQ10 levels decline with age, reducing antioxidant capacity and increasing oxidative stress, which may contribute to age-related and metabolic conditions. Supplementation of CoQ10 has been proposed as a potential treatment for certain chronic diseases due to its antioxidant properties. CoQ10 was first isolated in 1955, and its chemical structure was fully characterized shortly after. It gained prominence in the 1960s when it was linked to mitochondrial energy production and cardiovascular health. Research advanced further when Dr. Peter Mitchell's work on ATP synthesis, dependent on CoQ10, won the Nobel Prize in 1978. CoQ10's critical biological roles and therapeutic potential continue to make it a focus in health and disease management.

Keywords: *CoQ10, Heart Diseases, Lipid Peroxidation, Oxidative Stress.*

Introduction

Coenzyme Q10 (CoQ10) is a lipid-soluble benzoquinone, first isolated from beef heart in 1957. Its oxidized form is ubiquinone, while the reduced form is ubiquinol, the bioactive version. Structurally similar to vitamin K, CoQ10 is not classified as a vitamin due to its synthesis in the body. It plays a key role in producing ATP in mitochondria via the respiratory chain and acts as an antioxidant, protecting cellular components from oxidative damage. CoQ10 also supports the regeneration of antioxidants like tocopherol and ascorbate and influences gene expression through mitochondrial transcription factors [1, 2]. Synthesized in tissues from farnesyl diphosphate and tyrosine, CoQ10 is also obtained from dietary sources like meat, fish, milk, fats, and seeds. Organs such as the heart, liver, kidneys, and pancreas contain the highest levels. However, CoQ10 production declines after age 20 and is affected by factors like age, cancer, cardiovascular diseases, and degenerative conditions. Approximately 25% of CoQ10 comes from dietary sources, absorbed in the small intestine and distributed to tissues via blood and lymph [3].

Chemical Structure and Synthesis of CoQ 10

Coenzyme Q10 (CoQ10) is a naturally occurring benzoquinone with a 10-unit isoprenyl tail (Figure 1). Although structurally similar to vitamin K, it is not classified as a vitamin because the body can synthesize it. CoQ10 has a molecular weight of 865 g/mol, a melting point of 49°C, and is only slightly soluble in fats and oils. It becomes unstable when exposed to light and heat (above 55°C), with better stability in a solid state. Adding

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antioxidants like vitamins E and C enhances CoQ10 stability, as does combining it with ascorbic acid and EDTA. CoQ10 exists in two forms: oxidized (ubiquinone) and reduced (ubiquinol), which act as a redox pair based on the body's needs [4]. Ubiquinol, the reduced form, is the primary antioxidant form and makes up 95% of circulating CoQ10. The balance between ubiquinone and ubiquinol reflects oxidative stress, which can be affected by aging and disease. CoQ10 is abundant in the heart, liver, and kidneys, playing a vital role in aerobic cellular respiration and ATP production. Its synthesis is a complex process involving tyrosine, methionine, and the mevalonate pathway, linking CoQ10 production to cholesterol biosynthesis. Deficiencies in these components can impair endogenous CoQ10 synthesis [5].

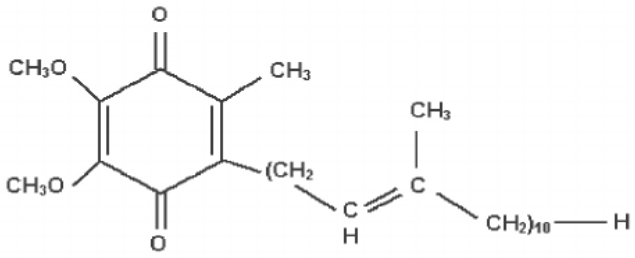

Figure 1. Chemical Structure of CoQ10 Enzyme

Commercially, CoQ10 is produced through yeast or bacterial fermentation, yielding the natural all-trans isomer, which is biologically identical to human CoQ10 (Figure 2). Synthetic versions often contain a mix of cis- and trans-isomers, but the cis-isomer's efficacy and safety are less understood. CoQ10, a lipophilic compound, requires lipids for effective absorption. Its absorption begins in the small intestine, aided by pancreatic and bile secretions that form micelles [6]. Once absorbed, CoQ10 is reduced to ubiquinol, incorporated into chylomicrons, and transported to the liver before being distributed in lipoproteins such as LDL and HDL. Plasma concentrations increase with dosage but plateau at higher amounts, with diminished absorption efficiency. Along with alpha-tocopherol, CoQ10 helps protect lipoproteins from lipid peroxidation, underscoring its antioxidant role [7].

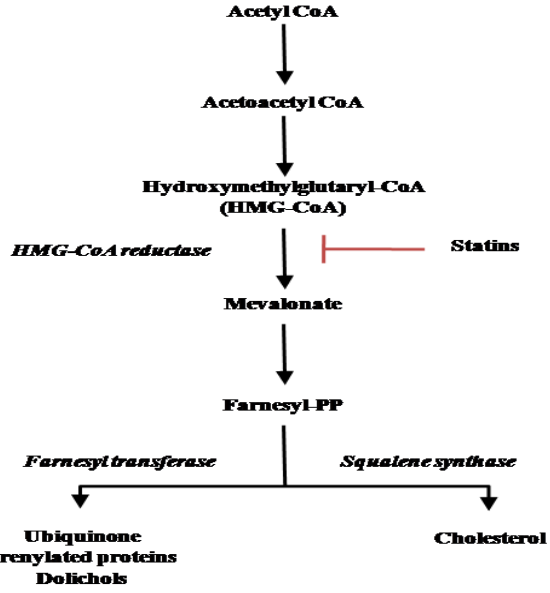

Figure 2. Mevalonate Pathway for Synthesis of CoQ10 Enzyme [8]

Dietary Resources and Daily Intake

CoQ10 is widely found in nature, present in both plants and animals, with animal products generally containing the highest concentrations. It is abundant in tissues with high energy demands, such as the heart, liver, and kidneys. Plant-based sources like broccoli, spinach, nuts, legumes, and oils (soybean, canola, and palm) also contain moderate amounts of CoQ10. However, dietary intake contributes only 3–5 mg per day, roughly 1% of the total body pool, while the majority is produced endogenously. The body's CoQ10 reserves range between 0.5 and 1.5 g, with a half-life of 35 to 100 hours depending on tissue activity [9]. Early CoQ10 supplements, made from ubiquinone powder in tablets, capsules, and oil-based softgels, had low bioavailability due to their hygroscopic nature. Modern formulations, such as Q-Gel, Q-Nol, and Kaneka QH, use ubiquinol to enhance stability and absorption. Standard supplemental doses range from 15 to 100 mg, with higher doses (up to 1,200 mg) used safely in conditions like heart disease, neurodegenerative disorders, cancer, and diabetes. In studies, even doses as high as 3,000 mg in Parkinson's disease patients were well-tolerated, with minimal side effects such as mild nausea or abdominal discomfort [10]. CoQ10 levels are typically measured using high-performance liquid chromatography with ultraviolet or electrochemical detection, capable of assessing both ubiquinone and ubiquinol. However, plasma levels may not reflect tissue-specific deficiencies, such as those in the heart or muscles. In such cases, a skeletal muscle biopsy is preferred for accurately evaluating endogenous CoQ10 status [11].

Consequences of CoQ10 Deficiency

The CoQ10 deficiency associated with diseases, these deficiency are two types and treatment needs supplementation as outlined below [12] (Figure 3):

Primary CoQ10 Deficiency

This type is caused by mutations in COQ genes and presents diverse clinical signs, including: Steroid-resistant nephrotic syndrome often accompanied by deafness, retinopathy, or neurological issues. Mitochondrial encephalopathy, including hypotonia, ataxia, strokes, spasticity, and intellectual disability. Unexplained ataxia, especially with a recessive autosomal inheritance pattern. Exercise intolerance, with muscle weakness and elevated creatine kinase levels.

Secondary CoQ10 Deficiency

This type arises from mutations affecting mitochondrial or cellular functions unrelated to direct CoQ10 biosynthesis, such as defects in glucose transport (e.g., GLUT1 mutations). These deficiencies may reflect an adaptive response to altered energy demands.

Treatment and Therapeutic Advances

High-dose oral CoQ10 supplementation can improve outcomes in primary CoQ10 deficiency, reducing encephalopathy progression and recovering kidney function. Preclinical studies have shown promising results, with ubiquinol (the reduced form of CoQ10) approved as an orphan drug in Europe for treating primary CoQ10 deficiency. However, patients with secondary CoQ10 deficiency may not respond to supplementation, underscoring the complexity of these disorders.

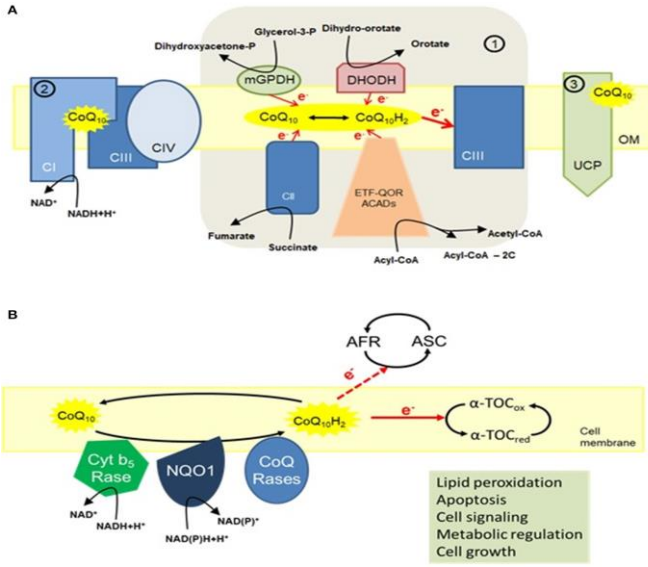

Figure 3. The Multiple Functions of CoQ10 [12]

Role of CoQ10 in Health

CoQ10 primarily functions in energy production due to its location in the mitochondria. It is situated between flavoprotein complexes I, II, and III, where it serves as a mobile electron carrier [13]. Utilizing its redox properties, CoQ10 transfers electrons from Complex I (NADH–ubiquinone reductase) and Complex II (succinate–ubiquinone reductase) to Complex III (ubiquinol cytochrome c reductase). This process, essential for sustaining human life, creates a high demand for ubiquinone. Consequently, ubiquinol is swiftly converted back to oxidized ubiquinone, maintaining a cycle critical for ATP production [14]. In the mid-1970s, Peter Mitchell proposed a theory suggesting that the redox properties of CoQ10 might have a role beyond electron transport. He observed that during reduction, protonation occurs inside the mitochondria, while during oxidation, deprotonation takes place outside the membrane. This process generates an electrical gradient across the membrane, which ultimately drives the conversion of adenosine diphosphate (ADP) to ATP [15]. Additionally, uncoupling proteins (UCPs) located in the inner mitochondrial membrane facilitate the movement of protons from the outside to the inside of the membrane. Mitchell's theory suggested that any proton leak not directly linked to ATP synthesis could lead to uncoupling of respiration and thermogenesis. Since reactive oxygen species (ROS) production in mitochondria is influenced by respiratory activity and sometimes by semi-ubiquinone, UCP activity that reduces the mitochondrial proton gradient could potentially lower ROS generation [15, 16].

Echtay et al. discovered that in the presence of oxidized CoQ10, fatty acids could more effectively deliver protons to UCPs in the inner mitochondrial membrane, facilitating their transport into the mitochondrial matrix [17]. In its reduced form, ubiquinol, CoQ10 functions as a powerful fat-soluble antioxidant outside the mitochondrial membrane. It not only recycles and regenerates other antioxidants like vitamins E and C but also uniquely influences the initiation and propagation of reactive oxygen species (ROS). Mitochondria, being significant producers of O2− and H2O2 due to their role in ATP production, contribute to oxidative stress when electron leakage and free radical formation occur, particularly during respiration [18]. This oxidative stress can damage DNA, lipids, and proteins. Lipid peroxidation, the most extensively studied form, involves the removal of hydrogen from a polyunsaturated fatty acid,

leading to the formation of a peroxyl radical. Reduced $CoQH_2$ (ubiquinol) loosely retains electrons and eliminates lipid peroxyl radicals, either by directly forming the semiquinone radical (CoQH·) or by scavenging other peroxyl radicals. Additionally, $CoQH_2$ plays a role in regenerating vitamin E by converting α-tocopherol radicals back to their active form. Animal studies have shown that when α-tocopherol levels are depleted, ubiquinol undergoes oxidation, indicating that α-tocopherol and ubiquinol work synergistically to neutralize free radicals [5].

Another important function of CoQ10 is its interaction with dihydrolipoic acid, a potent radical scavenger, through the transfer of electron pairs. This process helps maintain CoQ10 in its reduced state, thereby enhancing its antioxidant capacity in extra-mitochondrial membranes. CoQ10 has also been associated with improving the activity of superoxide dismutase (SOD) [16]. In vascular homeostasis, endothelial nitric oxide (NO) plays a critical role by preventing platelet aggregation and inflammation. However, in conditions such as heart failure and diabetes, oxidative stress can lead to the production of ROS, which reacts with NO· to form peroxynitrite, a highly reactive and damaging oxidizing species that exacerbates oxidative stress. As an antioxidant, CoQ10 protects NO· from converting into pro-oxidant species, preserving endothelial function and potentially enhancing SOD activity [19].

CoQ10 Status in Disease States

Role in Cardiovascular Disease (CVD)

Cardiovascular disease (CVD) claims over 2,150 American lives daily, averaging one death every 40 seconds. Conditions such as hypertension, heart failure, and coronary artery disease (CAD) are significant contributors, with CAD alone causing one in six deaths in 2010 [20]. Studies have shown that patients with CVD often have a deficiency in CoQ10, with lower levels of ubiquinol (the reduced form of CoQ10) linked to increased oxidative stress [21]. Extracellular superoxide dismutase (ecSOD), which mitigates oxidative damage, is also reduced in CAD patients [22]. Supplementing with 100 mg of CoQ10 three times daily significantly increases ecSOD activity, potentially preserving nitric oxide (NO^-) and protecting endothelial function, which may help lower blood pressure in hypertensive patients [23].

Clinical trials have demonstrated CoQ10's effectiveness in reducing blood pressure, with an average decrease of 16 mm Hg systolic and 10 mm Hg diastolic. Higher dosages have shown similar results, with some patients able to discontinue antihypertensive medications. CoQ10 supplementation has also improved symptoms in heart failure patients and reduced arrhythmias and pulmonary complications. Additionally, combining CoQ10 with vitamin B6 has shown potential in reducing CAD risk by enhancing CoQ10 synthesis and lowering inflammation [24]. CoQ10 supplementation has further benefits for patients undergoing cardiovascular surgeries. Administering 150–180 mg daily for a week before coronary artery bypass surgery reduced ischemic reperfusion (IR) injury, arrhythmias, blood loss, and complications. Overall, CoQ10 plays a vital role in reducing oxidative stress, inflammation, and improving cardiovascular outcomes [23].

Role of CQ10 in Inflammation

Chronic inflammation and oxidative stress are linked to various age-related diseases, including cardiovascular diseases, diabetes, cancer, and chronic kidney disease. A meta-analysis examined the effects of CoQ10 supplementation on inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), in conditions like cardiovascular disease, multiple sclerosis, obesity, renal failure, rheumatoid arthritis, diabetes, and fatty liver disease. CoQ10 supplementation (60–500

mg/day for 1 week to 4 months) significantly reduced inflammatory cytokines, particularly in elderly individuals with low CoQ10 levels [25]. Metabolic diseases characterized by chronic low-grade inflammation showed positive responses to CoQ10, with notable reductions in TNF-α levels, though effects on CRP and IL-6 were inconsistent. For rheumatoid arthritis patients, CoQ10 (100 mg/day for 2 months) lowered TNF-α compared to a placebo. Similarly, doses of 60–300 mg/day reduced IL-6 levels without affecting CRP [26]. CoQ10 has also been shown to mitigate inflammation and thrombotic risk in antiphospholipid syndrome, improving endothelial function and mitochondrial activity. In Down syndrome patients, who typically exhibit low CoQ10 levels and elevated proinflammatory cytokines (IL-6 and TNF-α), CoQ10 supplementation has demonstrated protective effects against oxidative damage and mitochondrial dysfunction, potentially slowing the progression of neurological symptoms [27].

Role of CoQ10 in Diabetes

Hyperglycemia contributes to vascular complications by promoting ROS (reactive oxygen species) formation. CoQ10 levels in diabetes are inconsistent due to disease variability, with type 2 diabetes (T2D) patients typically showing lower total CoQ10 levels and a decreased ubiquinol-to-CoQ10 ratio. Some studies observed increased ubiquinone levels in T2D, indicating altered antioxidant status. Conversely, individuals with type 1 diabetes may exhibit elevated plasma CoQ10, suggesting that diabetes type and severity influence CoQ10 status [28]. T2D patients, who often have reduced CoQ10 levels, may benefit from CoQ10 supplementation due to its antioxidant properties. Early research shows that supplementation with ubiquinone can modestly improve glycemic profiles, potentially due to impaired conversion of ubiquinone to ubiquinol. However, newer studies using ubiquinol supplements have demonstrated more significant benefits, including improved HbA1c levels and reduced formation of advanced glycation end products, though lipid profiles and blood pressure effects are inconsistent. Some studies have reported improved blood pressure and heart function in diabetics, particularly those with congestive heart failure [29]

Role of CoQ10 in Obesity

Obesity is characterized by reduced fat metabolism, increased fat deposition, and associated conditions like hyperglycemia, insulin resistance, dyslipidemia, and hypertension. Obese individuals often exhibit mitochondrial dysfunction and lower CoQ10 levels. CoQ10 plays a role in preventing fat accumulation by inhibiting adipogenesis, as demonstrated in studies using rosiglitazone-induced adipogenesis in mice and 3T3-F442A cell lines. Enhanced CoQ10 synthesis inhibits adipocyte differentiation, while its suppression triggers it [30]. CoQ10 promotes fat oxidation and energy expenditure, particularly in inguinal white adipose tissue. It reduces the expression of lipogenic enzymes like fatty acid synthase (FAS), acetyl-CoA carboxylase 1 (ACC1), and phosphoenolpyruvate carboxykinase (PEPCK), contributing to its lipid-lowering effects. Additionally, CoQ10 enhances the expression of mitochondrial biogenesis proteins (PGC-1), oxidative phosphorylation proteins (COIV), fatty acid transporters (M-CPT1), and energy expenditure regulators (UCP1) [31]. CoQ10's effects are mediated through AMP-activated protein kinase (AMPK), which regulates lipogenic genes. By increasing cytoplasmic calcium concentrations, CoQ10 activates CaMKK, leading to AMPK phosphorylation. This, in turn, enhances fatty acid oxidation and upregulates PPARα, a key regulator of lipid metabolism, at both protein and mRNA levels. This AMPK-driven PPARα activation helps suppress adipocyte differentiation and supports

fatty acid utilization, particularly in high-fat diet models [32].

Role of CoQ 10 in Neurodegenerative Diseases

Like lipids and proteins, nucleic acids are vulnerable to oxidative stress, with mitochondrial DNA being particularly susceptible due to its proximity to ROS formation. Damage to mitochondria can result in irreversible gene mutations affecting ATP synthesis, potentially leading to energy production issues and cell apoptosis. Decreased CoQ10 levels have been observed in Alzheimer's disease (AD) and Parkinson's disease (PD) patients [33]. Mischley et al suggested that CoQ10 becomes conditionally essential in PD and may offer clinical benefits through supplementation. Since CoQ10 is involved in the electron transport chain, increasing its levels could help restore mitochondrial function. Wadsworth et al proposed that CoQ10's effects may stem from its antioxidant properties or activation of UCP molecules, which reduce mitochondrial stress. While this study found no significant changes in CoQ10 levels in the brain or mitochondria, further in vivo research is needed to clarify its neuroprotective mechanisms [34].

Role of CoQ10 in Cancer

In the 1970s, Karl Folkers proposed that CoQ10 is essential for normal cell respiration and that a reduction in its availability could impair cell function, leading to increased lipid peroxidation, inflammation, oxidative damage, and potentially cancer development. Observational studies have linked low plasma CoQ10 levels to a higher prevalence of lung, pancreatic, and breast cancers [35]. Animal studies have demonstrated CoQ10's anticancer potential. In mice, CoQ10 injections delayed tumor onset, reduced tumor size, and improved survival rates. Similarly, in rats with hepatocellular carcinoma, CoQ10 supplementation suppressed lipid peroxidation, preserved glutathione levels, and reduced inflammatory markers like tumor necrosis factor-α and nitric oxide [36]. CoQ10 has also shown benefits in combination with chemotherapy, particularly in breast cancer patients treated with Tamoxifen, where it counteracted oxidative stress and improved blood profiles, including reducing hyperlipidemia. The anticancer effects of CoQ10 are attributed to its antioxidant and anti-inflammatory properties, highlighting its therapeutic potential in cancer management [37].

Role of Q10 and Male Fertility

Oxidative stress is linked to male infertility, with CoQ10 levels in seminal fluid serving as a key biomarker of sperm health. Supplementing with CoQ10 has been shown to improve semen parameters in idiopathic male infertility, enhancing sperm concentration, density, motility, and morphology at doses of 200–300 mg/day [38]. In female infertility, CoQ10 deficiency may impair mitochondrial activity, reducing granulosa cells' ability to produce ATP. Studies on PDSS2-deficient mice with low oocyte CoQ10 levels revealed oocyte deficits and infertility. Although clinical trials on CoQ10 supplementation for female infertility are lacking, research suggests promising potential for improving fertility during the prime reproductive years [39].

Role of CoQ10 in Smoking

Antioxidant levels, including CoQ10, are often reduced in smokers, particularly those at risk for cardiovascular diseases (CVD), chronic heart failure, or with altered cholesterol metabolism. However, research on CoQ10 levels in healthy smokers without medical conditions is limited. A study by Al-Bazi et al examined 55 young healthy smokers (30 males, 25 females) and 51 nonsmokers (26 males, 25 females), finding that smokers had significantly lower plasma CoQ10 levels than nonsmokers. Female smokers also exhibited

lower total cholesterol, HDL, LDL, and CoQ10/LDL ratios compared to male smokers [40]. Conversely, research by Zita et al showed that healthy men who smoked 1–10 cigarettes daily had higher baseline CoQ10 levels than nonsmokers. Additionally, 90% of the men in this study experienced increased CoQ10 levels after supplementation with 30–100 mg/day for two months, regardless of smoking frequency [41].

Role of CoQ10 in Aging

A decline in CoQ biosynthesis is thought to occur with aging and age-related diseases, though the relationship between CoQ levels and aging remains debated. For instance, mice with one COQ7 allele missing show increased longevity despite normal CoQ levels, suggesting factors beyond CoQ itself may influence lifespan. However, other studies in senescence-accelerated mice models have linked higher mitochondrial CoQ levels to extended longevity, with ubiquinol supplementation shown to delay aging by promoting mitochondrial biogenesis [42]. In elderly individuals, plasma CoQ10 levels correlate positively with physical activity, cholesterol levels, and reduced lipid oxidative damage. High CoQ10H2/CoQ10 ratios are associated with improved muscle strength, while lower ratios may predict sarcopenia. A 4-year study combining selenium and CoQ10 supplementation reported improved vitality, physical performance, and quality of life in older adults. Additionally, CoQ10 helps mitigate chronic oxidative stress, reducing risks for cardiovascular and neurodegenerative diseases [43].

Conclusion

CoQ10 is a vitamin-like compound synthesized in the body, with mitochondria containing the highest concentrations due to its critical role in ATP production. Organs with high energy demands, like the heart and muscles, require substantial CoQ10. Beyond energy production, CoQ10 functions as a lipophilic antioxidant, protecting cells from oxidative damage caused by reactive oxygen species (ROS). While the body can produce CoQ10, factors such as aging, oxidative stress, and metabolic imbalances can reduce its levels, making dietary supplementation beneficial in certain conditions. Age-related mitochondrial changes often lead to tissue-specific declines in CoQ10, and increased levels of its oxidized form may further lower total CoQ10 availability. Diet alone may not sufficiently replenish CoQ10 due to its slow and inefficient absorption, attributed to its large molecular weight and hydrophobicity. Supplementation offers a reliable therapeutic option to address CoQ10 deficiencies, supporting mitochondrial and antioxidant functions. Clinical studies suggest that CoQ10 supplementation could help mitigate conditions linked to oxidative stress, such as cardiovascular diseases, diabetes, neurodegenerative disorders, and cancer. CoQ10 has a strong safety profile, but its cost and absorption efficiency pose limitations. Additionally, most clinical studies involve small sample sizes and short durations, underscoring the need for long-term research with larger populations to better understand its therapeutic potential.

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