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Mechanisms of action and effects of the administration of Coenzyme Q10 on metabolic syndrome

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HIGHLIGHTS

- Explaining what Coenzyme Q10 is;
- Action and effects of Coenzyme Q10 in the body.
- How to dose Coenzyme Q10 in the body.
- Food containing Coenzyme Q10.
- Supplementation.
- Supplementation of Coenzyme Q10 in the Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease.

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ABSTRACT

Coenzyme Q_{10} (CoQ_{10}) is an essential component of the mitochondrial electron transport chain responsible for different functions, among them its action as an antioxidant compound. Low CoQ_{10} levels are related to inflammatory processes and oxidative stress, factors implicated in atherosclerosis, obesity, nonalcoholic fatty liver (NAFLD), as well as metabolic syndrome (MS). MS is a disease characterized by cardiovascular risk factors linked to obesity, dyslipidemia and hyperglycemia. NAFLD is recognized as a hepatic manifestation of MS and, together with the latter, has a high incidence in the world population. Recent investigations have underscored the positive effects of CoQ10 supplementation on the treatment of obesity, oxidative stress, MS, and NAFLD. The objective of the present study was to analyze the evidence of the effects of CoQ10 supplementation on MS and NAFLD and to provide a general view of the mechanisms of action of CoQ10 in both diseases.

1. Introduction

Coenzyme Q10 (CoQ10) is a benzoquine (2,3-dimethoxy-5 methyl-6-decaprenyl-benzoquinone) [1] chemically similar to a liposoluble vitamin consisting of a crystalline powder in its pure form [2]. This molecule can be found in many aerobic organisms ranging from bacteria to mammals and is present in almost all the cells of the human body. In the human organism, this enzyme plays an important role in the respiratory chain, acting as an electron transporter for the production of adenosine triphosphate (ATP) inside the mitochondria..

In its reduced form, CoQ10 acts as an antioxidant, protecting the biological membranes against oxidation, inhibiting lipid peroxidation [3], indirectly stabilizing the calcium channels to prevent calcium overload [4], and participating in the recycling of α-tocopherol. However, some factors may reduce its plasma concentrations, such as aging, genetic factors, the use of certain drugs, and certain diseases. Metabolic syndrome (MS) is a disease involving several signs and symptoms such as dyslipidemia, arterial hypertension, hyperglycemia accompanied by insulin resistance, and abdominal obesity [5], factors that play a crucial role in mitochondrial dysfunction. The inflammatory responses present in MS, such as the increase in tumor necrosis factor-α (TNF-a), interleukin-6 (IL-6) and monocyte chemotactic protein-1 (MCP-1) can be clearly seen in the adipocyte dysfunction and insulin resistance present in obesity and in metabolic disorders. Adipocyte inflammation may be a causal factor of reduced mitochondrial biogenesis and energy homeostasis [6].

Because of the wide gamut of cellular properties of COQ10 favoring the treatment of numerous diseases including MS by its antioxidant

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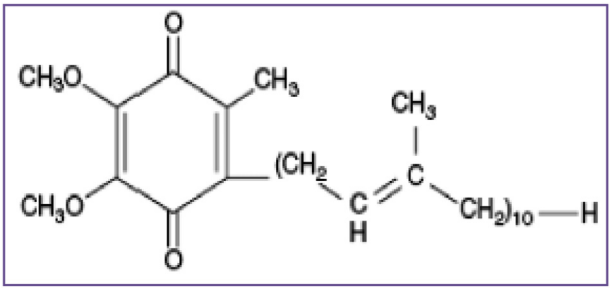

Fig. 1. Chemical structure of CoQ10 (reproduced from Prakash S et al., 2010) [10].

action, supplementation with this enzyme can be an ally in the stabilization and restoration of the natural defenses of the organism. Thus, in view of the above considerations, the objective of the present study was to elucidate what Coenzyme Q10 is, its origin and characteristics, form of absorption, and its relationship with MS and related diseases.

2. Characteristics of Coenzyme Q10

2.1. Chemical form

CoQ10 is synthesized from the mevalonate cycle, obtained from acetyl-CoA, which goes on to produce cholesterol, dolichol and CoQ10 as the final product [7]. CoQ10 is also known as ubiquinone in its oxidized form and ubiquinol in its reduced form. In humans, ubiquinone (2,3-dimethoxy-5 methyl-6-decaprenyl-benzoquinone) [1] has a chain with isoprene units [8] and derives from the conjunction of the benzoquinone ring with a chain of hydrophobic isoprenoids, all of them with a double bond and trans configuration [9] (Fig. 1).

2.2. Function in the organism

In the respiratory chain, CoQ10 is responsible for electron transport from the protein I complex (NADH dehydrogenase) to the protein II complex (succinate dehydrogenase), and from complex II to complex III (bc1 complex) [11]. When receiving the electrons from both complex I and complex II, it remains in its reduced form as ubiquinol and, after transferring the electrons to complex III it resturns to its oxidized form as ubiquinone [7]. The organs that require higher energy concentrations such as the brain, heart, kidneys and liver show higher CoQ10 rates [12] (Fig. 2).

2.3. Antioxidant function

By being vital for ATP synthesis, CoQ10 plays a crucial role in mitochondrial bioenergy, acting on all cells of the organism and thus being essential for health. Due to its redox property, it is useful for the neutralization of reactive oxygen species, i.e., free radicals [13]. CoQ10 is the only endogenously synthesized liposoluble antioxidant that can participate in redox reactions, acting on the prevention of damage to DNA and proteins and on lipid peroxidation, and indirectly stabilizing the calcium channels by preventing calcium overload [4]. The enzyme acts on lipid peroxidation by either sequestering free radicals or reducing the α–tocopheryl radical to α-tocopherol [14]. Its role is closely similar to that of vitamin E, although vitamin E depends exclusively on the diet and on hepatic reserves, with no endogenous synthesis, in contrast to CoQ10.

2.4. CoQ10 sources

In healthy individuals, normal CoQ10 levels are maintained through two pathways, i.e., the exogenous pathway by food ingestion and endogenous synthesis by the mevalonate cycle. In the endogenous production, the mevalonate cycle involves acetyl-CoA as the initial substrate and cholesterol, CoQ10 and dolichol as the final products, the last being crucial for protein glycosylation. In this pathway, the enzyme prenyltransferase is responsible for the synthesis of the isoprenoid side chain of CoQ10, with the later occurrence of another condensation of this chain formed with 4-hydroxybenzoate [11]. In the exogenous pathway, CoQ10 is ingested in its oxidized form, being later transformed to its reduced form at the erythrocyte level. It is found naturally in small amounts in different foods, but it occurs in significant amounts in dark vegetables such as spinach and in legumes such as broccoli, grains such as soy and peanuts, oleaginous fruits such as nuts and almonds, and mainly in read meats such as heart and liver and in some fish like mackerel and sardines [15]. However, the dose of CoQ10 that can be obtained from food is 2–5 mg/day and only about 10% of what is ingested is absorbed by the gastrointestinal tract due to the low water solubility and high molecular weight of the enzyme, an insufficient amount to meet the demands of the organism in the presence of redox imbalance [1,16].

2.5. Absorption

In healthy individuals, about 95% of the CoQ10 circulating in plasma is in the reduced ubiquinol form [2]. Because it is hydrophobic and has a high molecular weight, CoQ10 is absorbed from the diet in a slow and limited manner, as is the case for lipids. Plasma CoQ10 levels start to increase 1–2 h after oral intake, with maximum concentration occurring within 6–8 h and with a half-life that may reach 34 h [17]. CoQ10 is mainly absorbed in the small bowel and is then transported to the liver, forming the lipoprotein complex [18]. For transport, CoQ10 is coupled to the chylomicrons, being taken up by the liver[17] and being then incorporated into LDL, which transports 58% of it, and into HDL, which transports 26% of it. CoQ10 is then distributed to various tissues such as the spleen, adrenals, lungs, kidneys, and myocardium [8]. The main pathways of CoQ10 elimination are the bile ducts and the feces, and a small fraction of what is absorbed ends up by being eliminated in urine [19].

2.6. Supplementation

Several brands of commercial products containing CoQ10 are available on the market as powders, capsules or oil, in the reduced or oxidized form and in different doses, representing different forms of bioavailability [7]. Solubilized CoQ10 formulations have greater bioavailability and are absorbed at faster rates than powders, tablets, capsules or oil powder suspensions [20]. Comparison of the solubilized forms of ubiquinol and ubiquinone has shown that ubiquinol is better absorbed [2].

Several clinical trials involving the most diverse diseases have administered a variety of CoQ10 doses and have reported that adverse effects were more common at doses above 1200 mg/day [21], with doses of 22–400 mg/day being considered safe [22].

2.7. Contraindication and adverse effects

CoQ10 supplementation is quite safe. Several clinical trials using high doses did not show adverse effects significant enough to compromise the therapy [23]. The enzyme should be administered with caution to pregnant or breastfeeding women or to small children since its effects during these periods have not been fully clarified. Gastrointestinal effects such as abdominal discomfort, diarrhea, vomiting, and nauseas, as well as headache and allergic skin rashes have been reported to occur in less than 1% of patients in clinical trials [24]. Due to the antiplatelet and hypotensive potential of this medication [18], patients who use it should be monitored. Several studies have reported reduced CoQ10 values after its use in combination with HMG-CoA reductase inhibitors (statins) due to the fact that both CoQ10 and