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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.

## ARTICLE INFO

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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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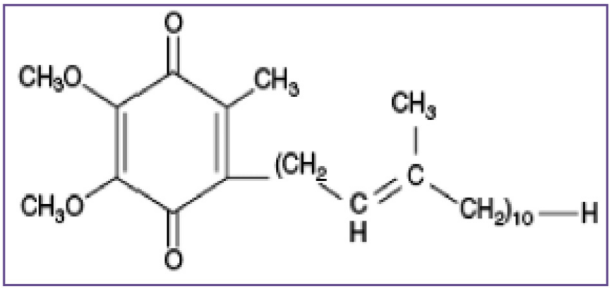


**Fig. 1.** Chemical structure of CoQ10 (reproduced from Prakash S et al., 2010) [10].

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

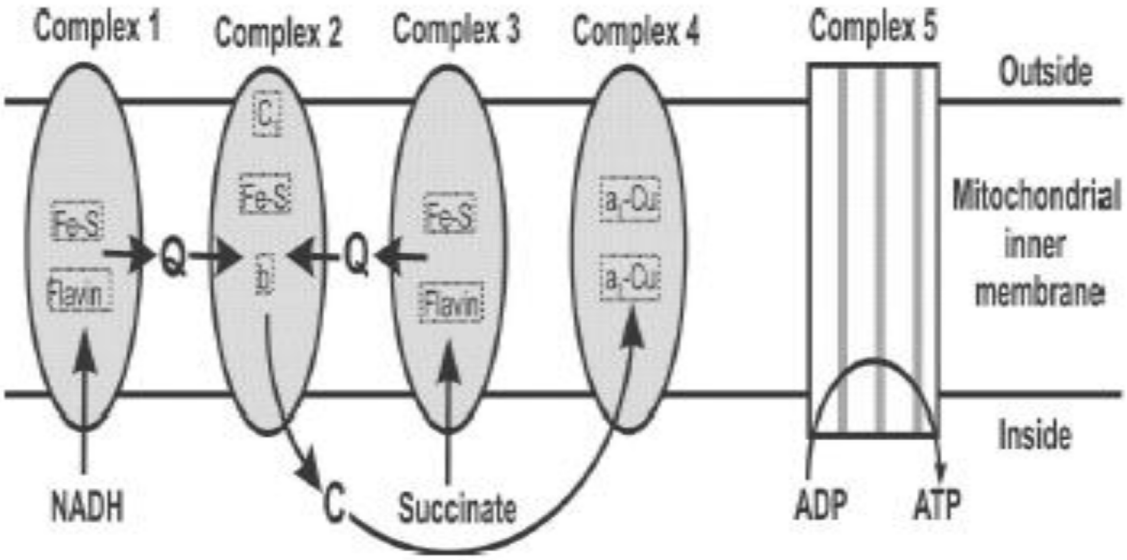


**Fig. 2.** Mirochondrial electron transport chain. NADH = nicotinamide adenine dinucleotide, Q = CoQ10, C = cytochrome C, Fe-S = iron-sulfur agglomerates, C1 = cytochrome C1, b = cytochrome *b*, *a*1-Cu = copper-containing cytochrome a1, ADP = adenosine diphosphate, ATP = adenosine triphosphate. The arrows indicate the electron flow through the pathway (reproduced from Molyneux SL et al., 2008) [7].

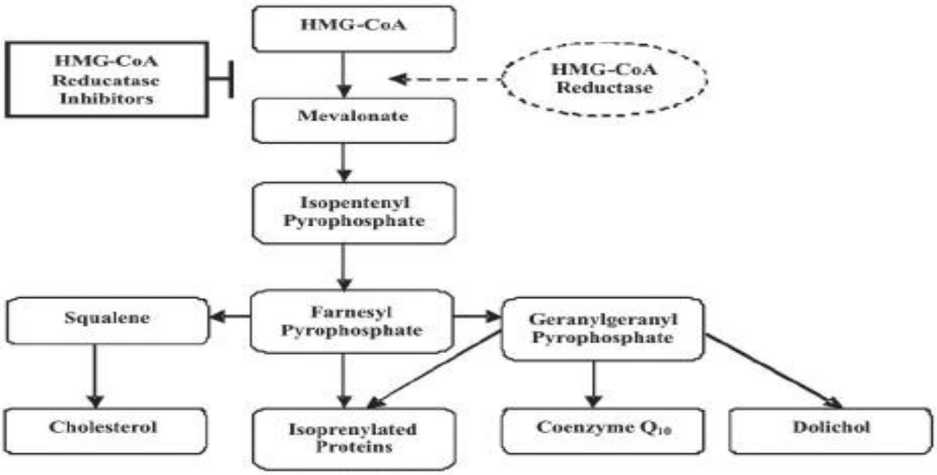


**Fig. 3.** Mevalonate cycle. Inhibition of HMG-CoA reductase by statins, including CoQ10 (reproduced from Molyneux SL et al., 2008) [7].

cholesterol are synthesized through the mevalonate pathway. The reduction of serum CoQ10 concentrations may be as high as 54% [25,26]. The magnitude of the reduction of CoQ10 in combination with statins has been shown to be dose related and reversible with the cessation of treatment. It has been hypothesized that this reduction may be the cause of the adverse effects of statins, and CoQ10 supplementation during treatment with statins could be a possible mediator treatment as long as it is properly monitored [27,28] (see Fig. 3).

### 2.8. Measurement in plasma and analytical methods

In human beings, CoQ10 concentration peaks at about 20 years of age [29]. Its plasma concentration in adults may range from 0.5 to 1.7 μg/ml [30–32], with approximately 75% of it being the reduced form, and the highest concentrations are found in the muscles [33]. However, several factors may interfere with CoQ10 levels, both in terms of an increase and a decrease. The presence of free radicals and of other reactive oxygen and nitrogen species related to certain diseases such as diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, Alzheimer's disease and vitamin A deficiency in some organs cause an increase in CoQ10 in order to increase the antioxidant defenses against the production of free radicals due to these diseases. With aging, CoQ10 levels in the organs may decrease by 30–60%. Persons with heart or thyroid diseases and certain genetic deficiencies such as primary and secondary mutations affecting the biosynthesis of CoQ10, and even high performance athletes appear to suffer the influence of CoQ10 levels [34]. According to Bentinger et al. [11], the quantity, structure and size of mitochondria may also be an additional factor inducing an increase or a decrease in CoQ10 levels in the organism.

HPLC is the technique most frequently used to determine CoQ10 levels after extraction from plasma or tissue. Since CoQ10 is highly hydrophobic, its analysis is carried out in two phases. In the first, separation is carried out using a highly hydrophobic inverse phase with a C18 column with a high carbon load, and in the second a mobile phase is used based on inferior alcohols such as hexane or included heptane [7].

### 2.9. Effects of CoQ10 on inflammation and fat metabolism

Inflammation is the response to injury caused by endogenous or

exogenous factors to tissues or organs and is of help in the restoration of impaired homeostasis [35]. During this process, various inflammatory cytokines are generated, such as TNF-α and IL-1 and IL-6. In local inflammation, macrophage infiltration and fibroblast activation are two responses that, on a chronic basis, will trigger inflammation of adipose tissue [36,37].

The mitochondria play a fundamental role in adipocyte differentiation and maturation [38], in addition to generating sufficient ATP to support the lipogenic processes that consume energy during preadipocyte differentiation [39]. Mitochondrial dysfunction and the consequent reduction of CoQ10 levels can occur in obese individuals who exhibit increased fat deposition in the organism [40]. Among the factors contributing to mitochondrial dysfunction is an excessive nutrient supply which will later contribute to the formation of reactive oxygen species and to the production of toxic lipid species, stress of the endoplasmic reticulum, aging and/or proinflammatory processes and mitochondrial fission. Individually or in combination these events contribute to the development of insulin resistance and obesity in the organism as a whole [41]. Fat deposition in the organism is related to high levels of hyperglycemia, hypertriglyceridemia and arterial hypertension, common characteristics of MS. Among the effects of CoQ10 is its ability to prevent the adipogenesis induced by rosiglitazone in obese rats [42] and to inhibit adipocyte differentiation [43], and treatment with CoQ10 has been reported to increase fat oxidation and energy expenditure in inguinal white adipose tissue [42].

### *2.10. Relationship of CoQ1O with metabolic syndrome and nonalcoholic fatty liver disease*

Metabolic syndrome is characterized by a complex ensemble of risk factors such as abdominal obesity, hyperglycemia, dyslipidemia and arterial hypertension and, when present, it increases the risk of cardiovascular events and of type 2 diabetes mellitus by about 2–6 times [5,44]. The growing MS epidemic and its complications have been accompanied by increased liver changes including NAFLD. As a result of insulin resistance, NAFLD is considered to be a metabolic disorder manifested in the liver [45]. NAFLD is the main cause of abnormal hepatic function [46] and is represented by excessive fatty acid accumulation in the hepatocytes favoring lipogenesis and inhibiting lipolysis, with an excessive increase in the supply of fatty acids followed by an increase in oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction and chronic endotoxemia [47]. With time, this steatotic liver becomes susceptible to hepatocellular damage, inflammation and fibrosis.

Diabetic hyperglycemia and metabolic disorders are among the main factors responsible for the inactivity of the antioxidant system and for the reduction of mitochondrial function. CoQ concentrations may be reduced in diabetic patients [48,49]. Supplementation with 100 mg/day CoQ10 for 8 weeks improved the serum levels of insulin, HOMA-IR an HOMA-B in obese patients with MS, type 2 diabetes mellitus and coronary disease and increased the plasma levels of total antioxidant capacity [50]. Gholami et al. [51] also supplemented with 100 mg/day for 12 weeks women, with diabetes mellitus 2 and noted the decrease in fasting blood glucose values, HOMA-IR and other markers such as total cholesterol, LDL cholesterol, ferritin and an increase in HDL cholesterol. Zahedi et al. [52] found a similar result, where supplementation with CoQ10 significantly reduced levels of fasting glycemia in patients with diabetes mellitus 2. However, Eriksson et al. [53] did not found improve the glycemic control or lipid levels in type 2 diabetic patients during 6 months of supplementation. Additional investigations are needed to assess the action of CoQ10 on glycemic control.

Increased glucose intolerance and oxidative stress play a crucial role in the development of endothelial dysfunction and arterial hypertension in patients with MS. A meta-analysis evaluating the effects of CoQ10 supplementation on the treatment of hypertension detected beneficial results of this treatment. Among the findings, the final blood pressure was lower than the initial levels before CoQ10 supplementation [54]. Another study showed that supplementation with 50 mg/day of CoQ10 administered twice daily for 10 weeks reduced the arterial hypertension of the evaluated patients [55]. However, perhaps, supplementation is not as beneficial for patients with inadequate blood pressure control, because in a study conducted on subjects with MS patients with decompensated pressure, supplementation with 100 mg/day CoQ10 for 12 weeks was not associated with any clinically relevant changes in blood pressure [56]. One of the theories proposed to explain the effects of CoQ10 on the reduction of blood pressure is the decreased peripheral vascular resistance by the preservation of nitric oxide bioavailability [16].

There are some controversies regarding the role of CoQ10 in the lipid profile. Moasen et al. [57] after 8 weeks of supplementation did not find differences in the lipid profile of patients with diabetes mellitus 2. While some authors [51] [58] [59], highlight the positive effects of supplementation on the reduction of total cholesterol, LDL-cholesterol and increase of HDL-cholesterol in patients with MS and DM2. CoQ10 has beneficial effects on lipid metabolism through the oxidation of fatty acids and increased PPARα (Peroxisome proliferator-activated receptor α), involved in the increase of β-oxidation of fatty acids and lipolysis [57].

NAFLD is associated with central obesity, insulin resistance and dyslipidemia, common characteristics of MS, and has been reported to be the hepatic manifestation of the syndrome [45]. Available data show that 60% of persons with MS have NAFLD, indicating a strong correlation between the two disorders [60]. Oxidative stress and inflammation are responsible for hepatic injury. As a result of disorders related to fatty acid absorption, synthesis, degradation and secretion, macrovesicular steaosis occurs in the liver, mainly due to fatty acid esterification to triglycerides and to the reduced triglyceride transport outside the liver. In addition, oxidative stress occurs as a consequence of hepatic changes, triggering lipid peroxidation and the consequent release of inflammatory cytokines [61]. Among the consequences of NAFLD is steatohepatiis which can potentially progress to fibrosis and cirrhosis, the latter involving dramatic complications such as the development of hepatocarcinoma [62].

Recent studies have shown that CoQ10 supplementation may be an ally in the treatment of NAFLD. Some biochemical markers are specific for fatty infiltration in the liver such as IL-6 [63] and GGT (gamma-glutamyl transferase). GGT is one of the markers indicative of infiltration and shows a direct relationship with insulin resistance. Previous studies highlight the improvement in GGT activity after supplementation with CoQ10 [51] [64] [65], in patients with NAFLD.

After 4 weeks of supplementation with 100 mg/day CoQ10, Farhangi et al. [66] detected changes in serum vaspin, chemerin and pentaxin values, as well as a reduction of liver enzymes and of abdominal circumference in patients with NAFLD. In another study, CoQ10 administration improved systemic inflammation and the biochemical variables present in NAFLD [64]. CoQ10 supplementation was also effective for the protection of the liver in various models leading to hepatic dysfunction and in aging by means of its antioxidant action [67,68] (Table 1).

## 3. Conclusion and perspectives

In view of the above discussion, we may conclude that CoQ10 deficiency interferes in a negative manner with inflammatory and oxidative parameters. Supplementation with CoQ10 in the treatment of pathologies such as obesity, MS and NAFLD is still not clear. Finally, additional investigations are needed about the basic aspects of the roles of $CoQ_{10}$ in this pathologies, as well as clinical studies for the determination of the ideal time of supplementation, the dose and the effects of the enzyme on inflammation and oxidative stress.

**Table 1**
Studies of CoQ10 in metabolic syndrome or nonalcoholic fatty liver disease.

| Study | Author/Year | Methods | Results |
|---|---|---|---|
| Effects of Coenzyme Q10 supplementation on serum salues of samma-glutamyl transferase, sseudocholinesterase, silirubin, serritin, and sigh-sensitivity C-reactive protein in women with type 2 diabetes | *Mahsa Gholami et al, 2018* [51] | • A randomized, double-blind, placebo-controlled study<br>• 70 women with type 2 diabetes mellitus<br>• 100 mg/day<br>• 12 weeks | ↓ Fasting glycemia<br>↓Serum insulin levels (HOMA – IR)<br>↓ Ferritin<br>↓ Total Cholesterol<br>↓LDL-C<br>↑ HDL-C |
| Functions of coenzyme Q10 supplementation on liver enzymes, markers of systemic inflammation, and adipokines in patients affected by nonalcoholic fatty liver disease: A double-blind, placebo-controlled, randomized clinical trial | *Farnaz Farsi et al, 2016* [64] | • A randomized, double-blind, placebo-controlled study<br>• 41 subjects with NAFLD<br>• 100 mg/day<br>• 12 weeks | ↓ AST<br>↓ GGT<br>↓ C-reactive protein<br>↓ Tumor necrosis factor<br>↓ NAFLD<br>↑Adiponectin<br>↑Serum leptin |
| The effects of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome | *Fariba Raygan et al, 2015* [50] | • A randomized, double-blind, placebo-controlled study<br>• 60 overweight or obese patients with type 2 diabetes mellitus and coronary disease.<br>• 100 mg/day<br>• 8 weeks | ↓Serum insulin levels (HOMA – IR and HOMA – B);<br>↑ TAC (although this difference disappeared when the value was adjusted for BMI and age);<br>↑Plasma glutathione (tendency)<br>↓ Malondialdehyde |
| Effect of coenzyme Q10 on glycaemic control, oxidative stress and adiponectin in type 2 diabetes | *M Moasen et al,* 2015 [57] | • A randomized, single-blind, placebo-controlled study<br>• 52 patients with type 2 diabetes mellitus<br>• 100 mg/twice day<br>• 8 weeks | ↓ Fasting glycemia<br>↓Glycated Haemoglobin<br>↓Adiponectin |
| Effects of CoQ10 supplementation on lipid profiles and glycemic control in patients with type 2 diabetes: a randomized, double blind, placebo-controlled trial | *Hoda Zahedi et al, 2014* [52] | • A randomized, double-blind, placebo-controlled study<br>• 40 subjects with type 2 diabetes mellitus<br>• 150 mg/day<br>• 12 weeks | ↓ Fasting glycemia<br>↓Glycated Haemoglobin<br>↓triglyceride<br>↓HDL-C<br>↑LDL-C |
| Oral coenzyme Q10 Supplementation in patients with nonalcoholic fatty liver disease: effects on serum vaspin, chemerin, pentraxin 3, insulin resistance and oxidative stress | *Mahdieh Abbasalizad Farhangi et al, 2014* [66] | • A randomized, double-blind, placebo-controlled study<br>• 44 subjects with NAFLD<br>• 100 mg/day<br>• 4 weeks | ↓Abdominal circumference<br>↓ AST<br>↓ TAC<br>↓ Fasting glycemia (stepwise) was a significant predictor of changes in serum vaspin, chemerine and pentraxin 3. |
| Effects of coenzyme q10 supplementation on serum lipoproteins, plasma fibrinogen, and blood pressure in patients with hyperlipidemia and myocardial infarction | *Mona Mohseni, et al 2014* [59] | • A randomized, double-blind, placebo-controlled study<br>• 52 subjects with hyperlipidemia and myocardial infarction<br>• 200 mg/day<br>• 12 weeks | improve blood pressure;<br>↑HDL-C<br>↓Total Cholesterol<br>↓LDL-C<br>↓ Fibrinogen |
| The effect of coenzyme Q10 supplementation on metabolic status of type 2 diabetic patients. | *Mohammadi R Kolahdouz et al, 2013* [58] | • A randomized, double-blind, placebo-controlled study<br>• 64 subjects with type 2 diabetes mellitus<br>• 200 mg/day<br>• 12 weeks | ↓ Fasting glycemia<br>↓Glycated Haemoglobin |
| A randomized, double-blind, placebo-controlled crossover study of coenzyme q10 therapy in hypertensive patients with metabolic syndrome | *Joanna M. Young et al, 2012* [56] | • A randomized, double-blind, placebo-controlled study<br>• 30 subjects with MS, type 2 diabetes mellitus and inadequate control of blood pressure<br>• 100 mg (twice a day)<br>• 12 weeks | Coenzyme Q10 was well tolerated and was not associated with any clinically relevant changes in blood pressure. |
| * Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials | *Rosenfeldt FL et al, 2007* [54] | • 12 clinical trials<br>• 362 subjects<br>• Arterial hypertension or inadequate control of pressure | ↓ Systolic and diastolic arterial pressure |
| The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus | *Eriksson JG et al, 1999* [53] | • A randomized, double-blind, placebo-controlled study<br>• 23 subjects with type 2 diabetes mellitus<br>• 200 mg/day<br>• 24 weeks | No significant changes in metabolic parameters were observed. |

HOMA – IR: Homeostatic model assessment insulin resistance; HOMA – B Homeostatic model assessment beta-cell function; TAC: Total antioxidant capacity; BMI: Body mass index; AST: Aspartate transaminase; GGT: Gamma glutamyl transpeptidase; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol. * Meta-analysis.

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## Conflicts of interest

Nothing to declare.

## Author contributions

Daniela Casagrande (primary author).
Paulo Henrique Waib (co-author).
Alceu Afonso Jordão Júnior (co-author).

## References

[1] A. Kumar, H. Kaur, P. Devi, V. Mohan, Role of coenzyme Q10 (CoQ10) in cardiac disease, hypertension and Meniere-like syndrome, Pharmacol. Therapeut. 124 (2009) 259-9.
[2] H. Bhagavan, R. Chopra, Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations, Mitochondrion 7 (2007) 78-10.
[3] A. Mellors, A.L. Tappel, The inhibition of mitochondrial peroxidation by ubiquinone and ubiquinol, J. Biol. Chem. 241 (1966) 4353–4356.
[4] S. Sugiyama, M. Kitazawa, T. Ozawa, K. Suzuki, Y. Izawa, Anti-oxidative effect of coenzyme Q10, Experentia 36 (1980) 1002–1003.
[5] E. Kassi, P. Pervanidou, G. Kaltsas, G. Chrousos, Metabolic syndrome: definitions and controversies, BMC Med. 9 (2011) 48.
[6] G.S. Hotamisligil, B.M. Spiegelman, Tumor necrosis factor alpha: a key component of the obesity-diabetes link, Diabetes 43 (1994) 1271–1277.
[7] S.L. Molyneux, J.M. Young, C.M. Florkoski, M. Lever, P.M. George, Coenzyme Q10: is there a clinical role and a case for measurement? Clin. Biochem. 29 (2008) 71-11.
[8] E. Mas, T. Morri, Coenzyme Q10 and statin myalgia: whats is the evidence? Curr. Atherosclerosis Rep. 12 (6) (2010) 407-6.
[9] G. Litarru, L. Tiano, Clinical aspects of coenzyme Q10: an update, Nutrition 26 (3) (2010) 250–254.
[10] S. Prakash, J. Sunitha, M. Hans, Role of coenzyme Q10 as a antioxidant and bioenergizer in periodontal diseases, Indian J. Pharmacol. 42 (6) (2010) 334-3.
[11] M. Bentinger, M. Tekle, G. Dallner, Coenzyme Q – biosynthesis and functions, Biochem. Biophys. Res. Commun. 396 (2010) 74–75.
[12] Y. Shindo, E. Witt, D. Han, W. Epstein, L. Packer, Enzymic and nonenzymic antioxidants in epidermis and dermis of human skin, Invest. Dermatol. 102 (1994) 122-2.
[13] J.G. Maraver, M.D. Cordero, M.O. Ávila, A.F. Vega, M. Mata, A. Pavón, et al., Coenzyme Q10 therapy, Mol. Syndromol. 5 (2014) 187-10.
[14] V. Kagan, E. Serbinova, L. Packer, Antioxidant effects of ubiquinones in microsomes and mitochondria are mediated by tocopherol recycling, Biochem. Biophys. Res. Commun. 169 (3) (1990) 851–857.
[15] M. Kitano, K. Hosoe, N. Fukutomi, T. Hidaka, R. Ohta, K. Yamakage, T. Hara, Evaluation of the mutagenic potential of ubidecarenone using three short-term assays, Food Chem. Toxicol. 44 (2006) 364–366.
[16] S. Pepe, S. Marasco, S. Haas, F. Sheeran, H. Krum, F. Rosenfeldt, Coenzyme Q10 in cardiovascular disease, Mitochondrion 7 (2007) 154-13.
[17] M. Miles, The uptake and distribution of Coenzyme Q10, Mithocondrion 7 (2007) 72–75.
[18] S. Greenberg, W.H. Frishman, Co-enzyme Q10: a new drug for cardiovascular disease, J. Clin. Pharmacol. 30 (1990) 596-12.
[19] H. Bhagavan, R. Chopra, Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics, Free Radic. Res. 40 (5) (2006) 445–448.
[20] C. Schulz, J.U.C. Obermuller, O. Hasselwander, J. Bernhardt, H.K. Biesalski, Comparison of the relative bioavailability of different coenzyme Q10 formulations with a novel solubilizate (Solu Q10), Int. J. Sci. Nutr. 57 (7/8) (2006) 546–549.
[21] J.N. Hathcock, A. Shao, Risk assessment for coenzyme Q10 (ubiquinone), Regul. Toxicol. Pharmacol. 45 (2006) 282–288.
[22] Drugs and supplements: Coenzyme Q10. [Internet]. Arizona: Mayo Clinic 2017 [cited 2017 set 9]. Available from: http://www.mayoclinic.org/drugs-supplements/coenzyme q10/interactions/hrb-20059019.
[23] T. Hidaka, K. Fujii, I. Funahashi, N. Fukutomi, K. Hosoe, Safety assessment of coenzyme Q 10 (CoQ 10 ), Biofactors 32 (2008) 199–9.
[24] C. Fuke, S.A. Krikorian, R.R. Couris, Coenzyme Q10: a review of essential functions and clinical trials, U.S. Pharm. 25 (2000) 1–12.
[25] C.H. Strey, J.M. Young, S.L. Molyneux, P.M. George, C.M. Florkowski, R.S. Scott, et al., Endotheliumameliorating effects of statin therapy and coenzyme Q10 reductions in chronic heart failure, Atherosclerosis 179 (2005) 201–206.
[26] G. Ghirlanda, A. Oradei, A. Manto, S. Lippa, L. Uccioli, S. Caputo, et al., Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a doubleblind, placebo-controlled study, J. Clin. Pharmacol. 33 (1993) 226–229.
[27] K. Folkers, P. Langsjoen, R. Willis, P. Richardson, L.J. Xia, C.Q. Ye, et al., Lovastatin decreases coenzyme Q levels in humans, Proc. Natl. Acad. Sci. U.S.A. 87 (1990) 8931–8934.
[28] M.A. Silver, P.H. Langsjoen, S. Szabo, H. Patil, A. Zelinger, Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction, Am. J. Cardiol. 94 (2004) 1306–1310.
[29] G.C. Santos, L.M.G. Antunes, A.C. Santos, M.L.P. Bianchi, Coenzyme Q10 and its effects in the treatment of neurodegenerative diseases, Braz. J. Pharmaceut. Sci. 45 (4) (2009) 607–611.
[30] S.L. Molyneux, C.M. Florkowski, M. Lever, P.M. George, Biological variation of coenzyme Q10, Clin. Chem. 51 (2005) 455–457.
[31] J. Kaikkonen, K. Nyyssönen, J.T. Salonen, Measurement and stability of plasma reduced, oxidized and total coenzyme Q10 in humans, Scand. J. Clin. Lab. Invest. 59 (1999) 457–466.
[32] J. Kaikkonen, T.P. Tuomainen, K. Nyyssönen, J.T. Salonen, Coenzyme Q10: absorption, antioxidative properties, determinants, and plasma levels, Free Radic. Res. 36 (2002) 389–397.
[33] K. Overvad, B. Diamant, L. Holm, G. Holmer, S.A. Mortensen, S. Stender, Coenzyme Q10 in health and disease, Eur. J. Clin. Nutr. 53 (1999) 764–766.
[34] M. Bentinger, K. Brismar, G. Dallner, The andioxidant role of coenzyme Q, Mitochondrion 7 (2007) 41–49.
[35] A.M. Alam, M.M. Rahman, Mitochondrial dysfunction in obesity: potential benefit and mechanism of Coenzyme Q10 supplementation in metabolic syndrome, J. Diabetes Metab. Disord. 13 (2014) 60.
[36] S.P. Weisberg, D. McCann, M. Desai, M. Rosenbaum, R.L. Leibel, A.W. Ferrante, Obesity is associated with macrophage accumulation in adipose tissue, J. Clin. Invest. 112 (2003) 1796–12.
[37] H. Xu, G.T. Barnes, Q. Yang, G. Tan, D. Yang, C.J. Chou, J. Sole, A. Nichols, J.S. Ross, L.A. Tartaglia, H. Chen, Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance, J. Clin. Invest. 112 (2003) 1821–1829.
[38] A. De Pauw, et al., Mitochondrial dysfunction in adipocyte differentiation and systemic metabolic alterations, Am. J. Pathol. 175 (2009) 927-12.
[39] R.H. Lu, et al., Mitochondrial development and the influence of its dysfunction during rat adipocyte differentiation, Mol. Biol. Rep. 37 (2010) 2173–2179.
[40] I. Mehmetoglu, F.H. Yerlikaya, S. Kurban, Correlation between vitamin A, E, coenzyme Q-10 and degree of insulin resistance in obese and non-obese subjects, J. Clin. Biochem. Nutr. 49 (2011) 159–4.
[41] C.M. Kusminski, P.E. Scherer, Mitochondrial dysfunction in white adipose tissue, Trends Endocrinol. Metabol. 23 (9) (2012) 435–438.
[42] M.C. Carmona, P. Lefebvre, B. Lefebvre, A. Galinier, A. Benani, Y. Jeanson, et al., Coadministration of coenzyme Q prevents rosiglitazone-induced adipogenesis in ob/ob mice, Int. J. Obes. 33 (2009) 204–207.
[43] S. Bour, M.C. Carmona, A. Galinier, S. Caspar-Bauguil, L. Van Gaal, B. Staels, L. Penicaud, L. Casteilla, Coenzyme Q as an antiadipogenic factor, Antioxid. Redox Signal. 14 (2011) 403–410.
[44] E.S. Ford, Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome a summary of the evidence, Diabetes Care 28 (2005) 1769–9.
[45] F. Angelico, et al., Insulin resistance, the metabolic syndrome, and nonalcoholic fatty liver disease, J. Clin. Endocrinol. Metab. 90 (2005) 1578–4.
[46] J.M. Clark, F.L. Brancati, A.M.E. Diehl, Nonalcoholic fatty liver disease: the most common cause of abnormal liver enzymes in the US population, Gastroenterology 120 (2001) 65.
[47] G.C. Farrel, D.V. Rooyen, L. Gan, S. Chitturi, NASH is an inflammatory disorder: pathogenic, prognostic and therapeutic implications, Gut and Liver 6 (2) (2012) 149-22.
[48] A. Gvozdjakova, J. Kucharska, S. Mizera, Z. Braunova, Z. Schreinerova, E. Schramekova, et al., Coenzyme Q10 depletion and mitochondrial energy disturbances in rejection development in patients after heart transplantation, Biofactors 9 (1999) 301–305.
[49] M.G. McDonnell, G.P.R. Archbold, Plasma ubiquinol/cholesterol ratios in patients with hyperlipidaemia, those with diabetes mellitus and in patients requiring dialysis, Clin. Chim. Acta 253 (1996) 117–119.
[50] F. Raygan, Z. Rezavandi, S.D. Tehrani, A. Farrokhian, Z. Asemi, The effects of coenzyme Q10 administration on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation and oxidative stress in patients with metabolic syndrome, Eur. J. Nutr. 55 (8) (2015) 2357-7.
[51] M. Gholami, R.M. Rezvanfar, M. Delavar, M. Adbollahi, A. Khosrowbeygis, Effects of Coenzyme Q10 supplementation on serum salues of samma-glutamyl transferase, sseudocholinesterase, silirubin, serritin, and sigh-sensitivity C-reactive protein in women with type 2 diabetes, Exp. Clin. Endocrinol. Diabetes 126 (1) (2018) 1–9.
[52] H. Zahedi, S. Eghtesadi, S. Seifirad, et al., Effects of CoQ10 supplementation on lipid profiles and glycemic control in patients with type 2 diabetes: a randomized, double blind, placebo-controlled trial, J. Diabetes Metab. Disord. 13 (2014) 81.
[53] J.G. Eriksson, T.J. Forsen, S.A. Mortensen, M. Rohde, The effect of coenzymeQ10 administration on metabolic control in patients with type 2 diabetes mellitus, Biofactors 9 (1999) 315–318.
[54] F.L. Rosenfeldt, S.J. Haas, H. Krum, A. Hadj, K. Ng, J.Y. Leong, G.F. Watts, Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials, J. Hum. Hypertens. 21 (2007) 297–299.
[55] V. Digiesi, F. Cantini, A. Oradei, G. Bisi, G.C. Guarino, A. Brocchi, et al., Coenzyme Q10 in essential hypertension, Mol. Aspect. Med. 15 (1994) 257-6.
[56] J.M. Young, C.M. Florkowski, S.L. Molyneux, R.G. McEwan, C.M. Frampton, M.G. Nicholls, R.S. Scott, P.M. George, A Randomized, double-blind, placebo-controlled crossover study of coenzyme Q10 therapy in hypertensive patients with the metabolic syndrome, Am. J. Hypertens. 25 (2) (2012) 261–269.
[57] M. Moazen, Z. Mazloom, A. Ahmadi, et al., Effect of coenzyme Q10 on glycaemic control, oxidative stress and adiponectin in type 2 diabetes, J. Pakistan Med. Assoc.

65 (2015) 404-4.
[58] M.R. Kolahdouz, M. Hosseinzadeh-Attar, M. Eshraghian, et al., The effect of coenzyme Q10 supplementation on metabolic status of type 2 diabetic patients, Minerva Gastroenterol. Dietol. 59 (2013) 231–235.
[59] M. Mohseni, M.R. Vafa, S.J. Hajimiresmail, et al., Effects of coenzyme q10 supplementation on serum lipoproteins, plasma fibrinogen, and blood pressure in patients with hyperlipidemia and myocardial infarction, Iran. Red Crescent Med. J. 16 (2014) e16433.
[60] G. Marchesini, M. Brizi, G. Bianchi, S. Tomassetti, E. Bugianesi, M. Lenzi, et al., Nonalcoholic fatty liver disease: a feature of the metabolic syndrome, Diabetes 50 (2001) 1844–1850.
[61] A.E. Reid, Nonalcoholic steatohepatitis and focal fatty liver, in: M. Feldman, L.S. Friedman, L.J. Brandt (Eds.), Sleisenger and Fordtran's Gastrointestinal and Liver Disease, ninth ed., Saunders, Philadelphia, 2010.
[62] D. Festi, A. Colecchia, T. Sacco, M. Bondi, E. Roda, G. Marchesini, Hepatic steatosis in obese patients: clinical aspects and prognostic significance, Obesity 5 (2004) 27-15.
[63] G. Tarantino, P. Conca, F. Pasanisi, M. Ariello, M. Mostralia, A. Arena, et al., Could inflammatory markers help diagnose nonalcoholic steatohepatitis? Eur. J. Gastroenterol. Hepatol. 21 (2009) 504–508.
[64] F. Farsi, M. Mohammadshahi, P. Alavinejad, A. Rezazadeh, M. Zarei, K.A. Engali, Functions of coenzyme Q10 supplementation on liver enzymes, markers of systemic inflammation, and adipokines in patients affected by nonalcoholic fatty liver disease: a double-blind, placebo-controlled, randomized clinical trial, J. Am. Coll. Nutr. 35 (4) (2016) 346–353.
[65] S. Onur, P. Niklowitz, G. Jacobs, et al., Ubiquinol reduces gamma glutamyltransferase as a marker of oxidative stress in humans, BMC Res. Notes 7 (2014) 42.
[66] M.A. Farhangi, B. Alipour, E. Jafarvand, M. Kloshbaten, Oral coenzyme Q10 supplementation in patients with nonalcoholic fatty liver disease: effects on serum vaspin, chemerin, pentraxin 3, insulin resistance and oxidative stress, Arch. Med. Res. 45 (7) (2014) 589-6.
[67] R.I. Bello, C. Gomez-Diaz, M.I. Buron, F.J. Alcain, P. Navas, J.M. Villalba, Enhanced anti-oxidant protection of liver membranes in long-lived rats fed on a coenzyme Q10-supplemented diet, Exp. Gerontol. 40 (2005) 694–12.
[68] A.A. Fouad, I. Jresat, Hepatoprotective effect of coenzyme Q10 in rats with acetaminophen toxicity, Environ. Toxicol. Pharmacol. 33 (2012) 158–159.