Chapter 17
Effects of Coenzyme Q_{10} Supplementation on Elderly People

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Abstract Coenzyme Q_{10} (CoQ_{10}) is an essential component of the electron transport system and the only lipid-soluble compound synthesized endogenously present in all cell membranes with bioenergetics and antioxidant properties.

Aging, neurodegenerative disorders, cardiovascular disease and other aged-related diseases, as well as genetic mutations, have been associated with CoQ_{10} deficiency. Since both limited uptake and low bioavailability of dietary CoQ_{10} might influence in this deficiency, supplementation with CoQ_{10} must be considered in those cases as therapeutic solution. However, more research is needed in order to identify the appropriate dose, the effectiveness and the bioavailability of orally-administered CoQ_{10}. Furthermore research must be developed in order to design therapeutic agents to induce the endogenous synthesis CoQ_{10} specially in elderly people.

This review will focus in the most relevant biochemical characteristics of this important antioxidant, including its main functions, levels and distribution in human organism and the therapeutic potential of CoQ_{10}, especially, during aging and the associated diseases.

Keywords Coenzyme Q_{10} · Aging · Oxidative stress · Antioxidant · Aging-related diseases · Therapeutic approach

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17.1 Coenzyme Q_{10}

Coenzyme Q_{10}, also known as CoQ_{10}, vitamin Q_{10}, ubiquinone, and ubidecarenone, is a benzoquinone compound, identified as a component of the mitochondrial respiratory chain (Crane et al. 1989; Schultz and Clarke 1999). It has been isolated and characterized as an ubiquitous quinone substance that received the name of ubiquinone (Festenstein et al. 1955). After its isolation, CoQ_{10} was identified as an essential electron carrier in the inner membrane of mitochondria as member of the mitochondrial electron transport chain (Festenstein et al. 1955; Crane et al. 1957).

CoQ_{10} is the short name of 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone. It is a lipid-soluble quinone with a very high biological activity. CoQ_{10} has two different parts, a polar benzoquinone ring and a lipidic isoprenoid side chain whose length depends on the organism. Its structure is similar to vitamin E. The name CoQ_{10} indicates that the quinone ring is bound to ten isoprenyl subunits that are part of this compound's structure. This is the predominant human form of this molecule. Moreover, the term "coenzyme" denotes it as an organic (contains carbon atoms), non-protein molecule necessary for the proper functioning of its protein partner (an enzyme or an enzyme complex) (Jeya et al. 2010). The principal characteristic of CoQ_{10} is its presence in three redox states: the fully oxidized *ubiquinone* form, a *semiquinone* form (that acts as free radical) and the fully reduced *ubiquinol* (Fig. 17.1) (Alcazar-Fabra et al. 2016). CoQ_{10} is found in all cell membranes but the highest presence is in the inner membrane of mitochondria in every cell in the human organism. In mitochondria, CoQ_{10} is essential as a cofactor in the

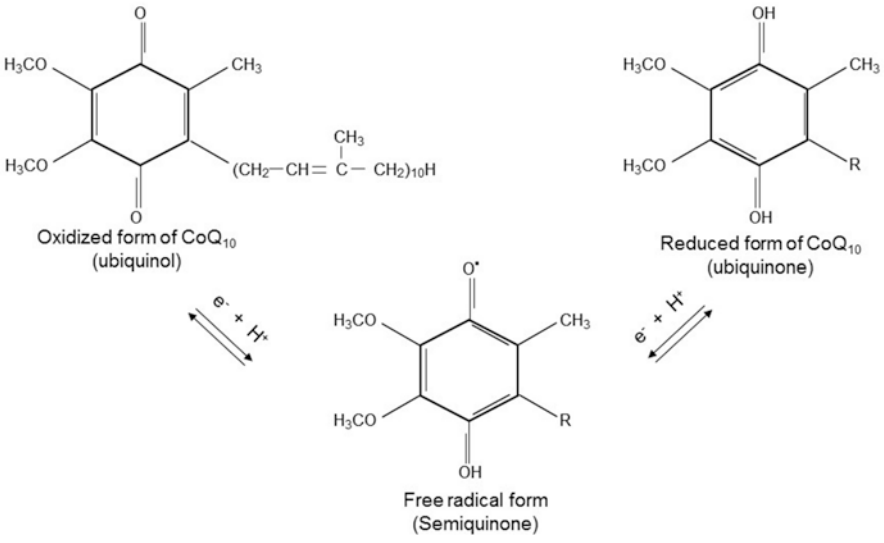

Fig. 17.1 Chemical structure of different forms of coenzyme Q_{10}
Chemical structure of different forms of coenzyme Q_{10} (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone). Ubiquinone is reduced to ubiquinol through a semiquinone intermediate

mitochondrial electron transport chain, and them, indispensable for aerobic cellular respiration and for the production of ATP and cell bioenergetics in aerobic organisms (Alcazar-Fabra et al. 2016; Acosta et al. 2016).

17.1.1 Coenzyme Q_{10} Functions

As member of the mitochondrial electron transport chain, CoQ_{10} accepts electrons from different donors named reductases, mainly NADH-coenzyme Q oxidoreductase (Complex I) and succinate-dehydrogenase (Complex II). The reduced form is later oxidized by transferring electrons to ubiquinol-cytochrome c reductase complex (Complex III) (Fig. 17.2). Its electron transport activity is accompanied by a pumping capacity that transfers protons from mitochondrial matrix to the intermembrane space contributing to create a proton gradient between mitochondrial matrix and cytosol (Crane 2001). This redox activity permits to mitochondria to participate in cell growth and maintenance (Overvad et al. 1999). Through this process, CoQ_{10} maintains a permanent redox equilibrium between the reduced form (ubiquinol) and

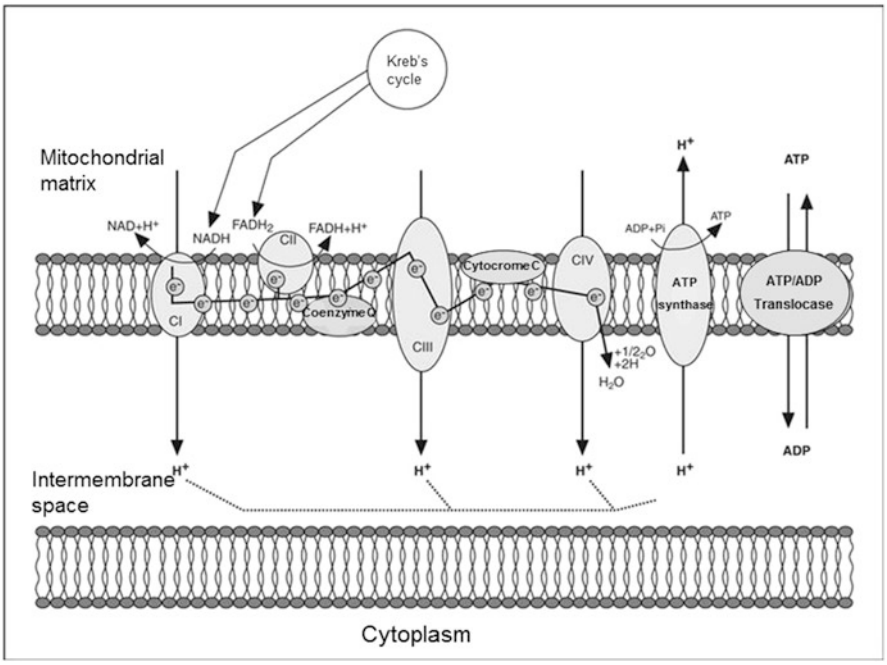

Fig. 17.2 Electron transport chain
The electron transport chain uses the electrons from electron carriers to generate an electrochemical gradient that will be used by ATP synthase to produce ATP. Coenzyme Q_{10} accepts the electrons from both complex I and complex II and delivers them to complex III

the oxidized form (ubiquinone). This equilibrium is maintained in mitochondria mainly by the activity of complexes I and II as electron donors and Complex III as acceptor. Other researches have revealed that CoQ_{10} is also a co-factor for the function of uncoupling proteins. For these reasons, CoQ_{10} is essential in the control of bioenergetics homeostasis in cells (Littarru and Tiano 2007; Potgieter et al. 2013).

In other cell membranes, at least three enzymes are known as CoQ_{10}-reductases: NADH/NADPH oxidoreductase (DT diaphorase), NADH cytochrome b_5 reductase and NADPH coenzyme Q reductase (Villalba and Navas 2000). In these membranes, ubiquinol acts as a potent antioxidant protecting cells from oxidative damage and contributing to the stability of the cell membranes, proteins, glycoproteins and DNA. Further reduced CoQ_{10} form has also been reported to protect LDL from oxidation (Lopez-Lluch et al. 2010). LDLs tend suffer more oxidation during aging probably by the reduction of the levels of CoQ_{10}. For this reason, CoQ_{10} supplementation could be a good therapy to decrease LDL oxidation reducing the high risk of cardiovascular disease during aging (Yubero-Serrano et al. 2011).

In addition to direct antioxidant radical scavenging, CoQ_{10}, and particularly the semiquinone intermediate (Fig. 17.1), recycles and regenerates other membrane antioxidants, such as α-tocopherol and also cytosolic and extracellular antioxidants such as ascorbic acid. CoQ_{10} is essential to maintain them in their reduced and activity state (Navas et al. 2007). All these activities make CoQ_{10} as the main lipidic antioxidant, more powerful than vitamin E, present in relative high concentrations and able to regenerate intracellular reducing mechanisms (Forsmark-Andree et al. 1995).

17.1.2 Levels and Distribution of Coenzyme Q_{10} in the Humans

All human cells studied so far can synthesize CoQ_{10}. Its amount in these cells depends on the organs and tissues. In humans, CoQ_{10} ranges from 8 μg/g in lung to 114 μg/g in heart. In some determinations, a shorter form, CoQ_9 has been found but only in small quantities (2–7%) (Jeya et al. 2010). In general, ubiquinol levels are higher than the levels of the oxidized form, ubiquinone, in most of the human tissues except in the case of lung and brain (Bhagavan and Chopra 2006). In the case of brain, the increase in the ratio ubiquinol/ubiquinone can be associated with neurological diseases due to mitochondrial dysfunction (Spinazzi et al. 2019).

Generally, tissues with high metabolic activity, such as the heart, kidney, liver and muscle, contain relatively high concentrations of CoQ_{10} (Ernster and Dallner 1995). At the cellular levels, most of the CoQ_{10} (40–50%) is localized at the mitochondrial inner membrane. It is present in the rest of cell membranes although at smaller amounts in the other organelles and in the cytosol.

Cell and tissue CoQ_{10} is coming from endogenous synthesis although it can be also obtained from food intake or oral supplementation. Interestingly, the range of CoQ_{10} concentration in humans show a high range and also depend on age, sex and race, and on the health of the individual (Sohal and Forster 2007). In healthy young

individuals, total body content of CoQ_{10} is around 0.99 ± 0.3 mg/L (from 0.55 mg/L and 1.87 mg/L). However, these levels decrease during aging, and in age-related diseases such as in patients with cardiomyopathies, congestive heart failure and degenerative diseases (Fotino et al. 2012; Shetty et al. 2012).

17.1.3 Biosynthesis and Transport of CoQ_{10}

The main although not unique source of CoQ_{10} in humans is the endogenous synthesis. This synthesis depends on the mevalonate pathway (Fig. 17.3). CoQ_{10} synthesis Shares the mevalonate pathway with cholesterol, dolichol, dolychil-phoshate and isoprene chains that bind to aminoacid residues in proteins (Villalba et al. 2010). *De novo* CoQ_{10} synthesis in humans is initiated by the union of the benzoquinone ring precursor, 4-hydroxybenzoate, and the isoprenoid side chain produced from farnesyl pyrophosphate. These two molecules are condensed by the polyprenil-4-hydroxybenzoate transferase, COQ2. After that, a complex with many other components, at least eight enzymes (encoded by COQ3–10) modify the benzene ring with subsequent methylation, decarboxylation and hydroxylation reactions to (Quinzii et al. 2007; Turunen et al. 2004).

It seems clear that CoQ_{10} synthesis is located in mitochondria and from this, it is distributed in all the subcellular compartments. Then, a transport system from the mitochondria to the rest of cellular membranes must exist. Using *in vivo* labeling

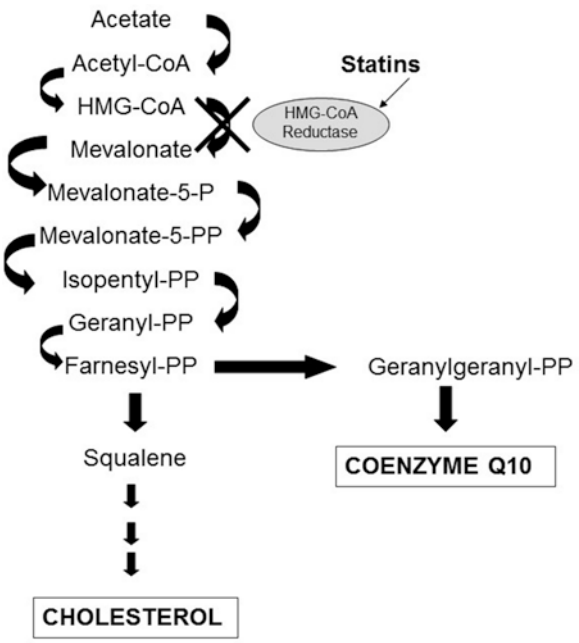

Fig. 17.3 Cholesterol and Coenzyme Q_{10} pathways share Mevalonate intermediate and Statin interruption **3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) is changed into Mevalonate by the action of the enzyme HMG-CoA reductase. From here, Mevalonate can be used to synthesize both cholesterol and coenzyme Q_{10}. Statins work by inhibiting the action of HMG-CoA reductase, thereby decreasing the amount of mevalonate available to make either cholesterol or coenzyme Q_{10}**

and cell fractionation in spinach leaves, it was demonstrated that CoQ_{10} is transported from the endoplasmic reticulum to other compartments through a vesicle-mediated process involving the Golgi system (Wanke et al. 2000). This cellular transport system was also found in human cells in culture (Fernández-Ayala et al. 2005a). Interestingly, exogenous CoQ_{10} can enter the cell through plasma membrane and incorporate to cell organelles including mitochondrial inner membrane (Fernández-Ayala et al. 2005b).

17.1.4 Uptake and Distribution of CoQ_{10}

CoQ_{10} is found in many dietary sources including animals and vegetables and can be also obtained from many dietary supplements. Large amounts are present in food from animal sources such as chicken legs, heart, liver and herrings. In comparison with meat and fish, lower levels are found in vegetables probably by the lower amount of mitochondria in comparison with animal cells (Table 17.1). In general, dietary intake of CoQ_{10} has been estimated as 3–5 mg/day. However, this intake is not necessary in situations without endogenous CoQ_{10} synthesis dysfunction in which the quinone reaches a saturation level in cells and tissues (Bhagavan and Chopra 2006).

Table 17.1 Content in coenzyme Q_{10} in food

Food Sources		CoQ_{10} content (μg/g)
Meat	Pork heart	203
	Pork liver	3.1
	Pork ham	20
	Beef heart	41
	Beef liver	19
	Lamb leg	2.9
	Chicken leg	17
Fish	Trout	11
	Sardines	64
	Red mackerel	43–67
	Tuna canned	0.3
Vegetables	Spinach	2.3
	Pea	0.1
	Cauliflower	0.6
Fruits	Orange	2.2
	Strawberry	0.1
	Apple	0.2
Cereals	Bread (rye)	4.7
	Bread (wheat)	2.1

To understand the distribution of CoQ_{10} in tissues after oral ingestion it is necessary to take into consideration its lipophilic nature. The absorption of CoQ_{10} is enhanced in the presence of lipids, then supplementation with CoQ_{10} must be performed with fat-rich meals. Due its biochemical characteristics, CoQ_{10} is absorbed slowly from the small intestine, possibly because it has a high molecular weight and is not very water soluble, passes into the lympha, and finally to the blood bound to chylomicrons and further to tissues, mainly liver. This mechanism is the same than vitamin E used to be incorporated from dietary sources (Zhang et al. 1995). In blood plasma, the reduced form, ubiquinol, is bound to lipoproteins, mostly to LDL (Bhagavan et al. 2007; Zhang et al. 1995). It has been considered that circulating concentrations of CoQ_{10} may be a putative biomarker to indicate their general status in the body and for monitoring the bioavailability of CoQ_{10} supplementation.

Accordingly, the number of different formulations developed to improve the incorporation of CoQ_{10} into human body, the importance of the vehicle and the solubility of CoQ_{10} in the preparation is clear in order to increase its bioavailability (López-Lluch et al. 2019). During the last decade, CoQ_{10} supplements have been developed as oil-based, softgel or powder-filled capsules and hard tablets. Comparisons between studies have indicated that CoQ_{10} bioavailability is influenced by the type of formulation, and that it is better to take CoQ_{10} with fatty foods (Villalba et al. 2010).

17.2 CoQ_{10} and Aging

We can define aging as the normal decline in survival suffering by all organisms along time. Understanding the molecular and cellular mechanisms underlying aging process would permit to develop strategies to resolve the problems associated to the increase of aged population that affects the whole world. Aging events have been studied from different points of view. One of the most accepted theories suggest that aging, is associated with the increase of oxidative damage in cells and tissues that drives aging and the age-related degenerative diseases (Su et al. 2010). In this theory, reactive oxygen species (ROS) are the factors that trigger the deleterious, irreversible changes and macromolecular damage associated with aging (Fig. 17.4) (Miquel 1998; Sohal et al. 2002).

Normal aerobic cell metabolism releases ow amounts of ROS as results of the partial reduction of molecular oxygen. These low ROS levels have beneficial effects maintaining antioxidant machinery. However, when there is a ROS overproduction, the accumulation of these reactive species produces oxidative modifications affecting many cell components including all the organic molecules present in cells (Valko et al. 2006). To avoid oxidative damage, organisms contains antioxidant mechanisms (Fig. 17.4) such as enzymes (superoxide dismutase, catalase, glutathione peroxidase) and small hydrophilic and hydrophobic molecules that act directly as non-enzymatic antioxidants (ascorbic acid, tocopherol, glutathione, CoQ_{10}, and others). Thus, we can define oxidative stress as the damage produced by the

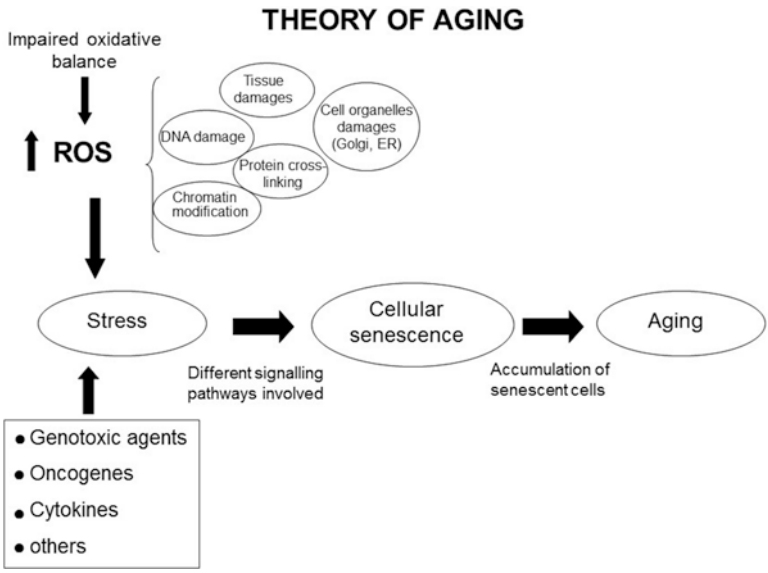

Fig. 17.4 Theory of aging
One of the most accepted theory of aging suggest that aging is produced by the deleterious, irreversible changes and macromolecular damage produced by ROS. Some modifications (mainly those related to DNA) are not completely repaired and thus accumulate, leading to cell death, organism malfunction, and the "aging phenotype"

imbalance between ROS production rate and the capacity to eliminate ROS by and antioxidant defences, in favour of ROS. This imbalance seems to be a hallmark of aging since oxidative stress has been associated with many age-associated diseases such as chronic-degenerative disease, such as cancer, metabolic and disease cardiovascular diseases.

Oxidative stress causes some of the modifications that cannot be completely repaired by antioxidant and cell turnover mechanisms and thus accumulate. The accumulation of oxidized structures in cells leads to cell senescence, cell death, organism malfunction, and the "aging phenotype." Nowadays, a version of the free-radical theory to explain aging, related with mitochondria as the main source and, at the same time target for ROS-dependent damage, is one of the most popular theories of aging (Barja 2007; Miquel et al. 1980). This theory postulates that mitochondrial DNA (mtDNA) suffer higher oxidative damage as the organism ages and this leads to the accumulation of mtDNA. This accumulation produces a vicious cycle in which an initial ROS-induced mtDNA damage increases oxidants production that, in turn, leads to more mitochondrial damage that produces more mtDNA damage (Gilmer et al. 2010).

According to this concept, mitochondria and mitochondrial ROS would play an important role in the development of strategies to delay and improve the aging process. These strategies must be focused on extending lifespan and/or retarding age-associated biological changes, including age-related diseases (Lee et al. 2004).

Among these strategies, nutritional and pharmacological interventions studied in several model organisms, including *yeast, flies,* mice and rats, as well as monkeys. Accordingly, with this strategy, some antioxidants have proved to be useful as dietary antiaging therapies (Duntas 2011; Lopez-Dominguez et al. 2012).

17.2.1 Coenzyme Q_{10} Deficiency in Aging

As it has been indicated before, all cells in the organism synthesize CoQ_{10} (Schultz and Clarke 1999). Along human life, CoQ_{10} increases until 20 years; however, it seems that the organism begin to lose its ability to synthesise CoQ_{10} during maturity and aging when and the coenzyme becomes deficient (Blatt and Littarru 2011; Gutierrez-Mariscal et al. 2011; Ochoa et al. 2007). Besides a decrease in biosynthetic capacity, other factors or situations may affect the levels of CoQ_{10}, including an increase in its degradation (Nakamura et al. 1999) or changes in membrane composition as occurs in different age-related diseases (Kagan and Quinn 1996). However, it is difficult to determine the importance of the changes in CoQ_{10} levels during aging since they are tissue- and organ-dependent. It has been shown that levels of CoQ_{10} in mitochondria of old rat brain increase (Battino et al. 1997) whereas they decrease in skeletal muscle (Lass et al. 1999). These differences make very complex the study of the importance of CoQ_{10} in aging process and further research is needed in order to clarify the importance of CoQ_{10} in aging progression.

Furthermore, dietary supplementation with CoQ_{10} does not affects all the organs. In young and healthy rodents, dietary CoQ_{10} is easily incorporated into liver and spleen; however, in older animals supplemental CoQ_{10} seems to restore normal levels (Beal 1999; Rosenfeldt et al. 1999).

This decrease in CoQ_{10} during aging has been related to a higher oxidative stress associated with aging and its related diseases. Thus, oral CoQ_{10} supplementation could be an effective antioxidant strategy to many age-associated diseases such as neurodegenerative disorders, diabetes, and cancer, muscular and cardiovascular diseases in which oxidative stress is an important factor.

17.3 Therapeutic Uses of CoQ_{10} in Age-Related Diseases

The fundamental role of CoQ_{10} in mitochondria, bioenergetics and antioxidant protection is the base of the therapeutic importance of CoQ_{10} supplementation. The studies performed in animals demonstrate that large doses of CoQ_{10} can reach all tissues and subcellular components including heart and brain mitochondria. This capacity has implications in therapies for many human diseases in which oxidative stress is a main factor. Several evidence have been recorded about the beneficial effects in cardiovascular, neurodegenerative and many other aged-related diseases

(Bhagavan and Chopra 2006; Villalba et al. 2010; Gonzalez-Guardia et al. 2015; Gutierrez-Mariscal et al. 2012; Gutierrez-Mariscal et al. 2014; Yubero-Serrano et al. 2013).

17.3.1 CoQ_{10} and Cardiovascular Disease

Cardiovascular disease (CVD) is one of the major causes of death and disability worldwide. We can suspect that the importance of disease will increase with the increase of elderly and the higher levels of obesity and sedentary lifestyles. Today, around 17 million deaths per year are associated to CVD (Flowers et al. 2014).

One of the main priorities in public health systems is to design a strategy to prevent CVD by modifying lifestyle. In this strategy, diet plays an important role. Several dietary factors have been related with a rise in the risk to suffer CVD, such as a low consumption of fruit and vegetables, a high intake of saturated fat and salt (Eilat-Adar et al. 2013). In the pathogenesis of CVD, oxidative stress plays a central role.

Oxidative stress has been also associated with congestive heart failure, hypertension and ischemic heart disease. The high-energy requirements and high mitochondria amount in heart muscle cells is the main cause of the high levels of CoQ_{10} found in this cell type. In samples from human heart it has been detected a significant decrease of the CoQ_{10} content in cardiomyopathies. This deficiency showed a direct correlation with the severity of disease (Folkers et al. 1985; Nobuyoshi et al. 1984). A recent meta-analysis demonstrated that CoQ_{10} supplementation in the clinical treatment of CVD shoes improvement of congestive heart failure, indicated by best left ventricular ejection fraction (LVEF). Further, the New York Heart Association classification (NYHA), showed that subjects treated with CoQ_{10} supplements improved in the ejection fraction in comparison with controls (placebo) (Fotino et al. 2013). Moreover, a prospective, randomized, double-blind, placebo-controlled, multicentre trial in which CoQ_{10} (Q-SYMBIO) is used as an adjunctive treatment of chronic heart failure has demonstrated that the treatment with this quinone is safe, well tolerated, and associated with a reduction in general symptoms (Mortensen et al. 2014). These clinical results could be based on the important molecular functions of CoQ_{10}, as integral component of mitochondrial respiratory chain (Littarru and Tiano 2010), and the only lipid-soluble antioxidant that slows lipid peroxidation in the circulation (Littarru and Tiano 2007).

CVD in elderly is accompanied with other complications such as diabetes and hypercholesterolemia. Certain drugs used in hypercholesterolemic disease can cause depletion of CoQ_{10} in particular statins that affect the first enzyme (hydroxylmethylglutaryl-coenzyme A reductase; HMG-CoA reductase) in cholesterol and CoQ_{10} synthesis pathway (Schaars and Stalenhoef 2008) (Fig. 17.3). Statins are widely prescribed to reduce cholesterol levels by inhibiting HMG-CoA reductase (Folkers et al. 1990). Chronic statin treatment can reduce endogenous-synthesized cholesterol levels but, at the same time, they also lower CoQ_{10} levels. This can be the

reason why chronic statin treatment is associated with muscle-related symptoms, pain or myopathies that can be improved with CoQ_{10} supplementation (Caso et al. 2007).

In relationship with the treatment of heart diseases several studies have concluded that supplementation with CoQ_{10} (50–300 mg/day) can be the safe and optimal dose, although higher doses such as 1200 mg/day have been also safely used (Gao et al. 2011). The majority of these clinical studies indicate that the treatment with CoQ_{10} significantly improve the heart muscle function, increasing ATP synthesis and enhancing myocardial contractility (Folkers et al. 1985). Importantly, these treatments have demonstrated no adverse effects or drug interactions (Kaikkonen et al. 2002).

17.3.2 CoQ_{10} and Hypertension

Hypertension is also associated with aging. Hypertension is also a key risk factor for stroke, myocardial infarction, congestive heart failure, kidney failure, and peripheral vascular disease. Although many pharmacological treatment have shown efficacy lowering blood pressure and modestly decrease stroke, myocardial infarction, and mortality, hypertension remains with high prevalence especially in old population and additional treatments are needed (Musini et al. 2009). The health effects of CoQ_{10} as additional treatment have been investigated in several controlled intervention studies in human subjects in a range of CoQ_{10} doses from 100 mg to 200 mg/day (Young et al. 2011; Yubero-Serrano et al. 2011, 2013). CoQ_{10} affects vasodilatation by improving endothelium and vascular smooth muscle activity, counteracting vasoconstriction and lowering blood pressure. Among treated patients, it has been reported a decrease in systolic blood pressure ranged from 11–17 mmHg and 8 mmHg decrease in diastolic blood pressure after the treatment with CoQ_{10}. These results indicate a putative role of CoQ_{10} as a hypotensive agent and probably a safe adjuvant in the treatment with conventional anti-hypertensive pharmacological products.

17.3.3 CoQ_{10} and Endothelial Function

The progression and clinical manifestations of atherosclerosis and cardiovascular diseases depends on the dysfunction of endothelium. Several studies have determined the effect of oral CoQ_{10} supplementation on the physiology of endothelium in patients suffering coronary artery disease or diabetes mellitus or in elderly people (Gao et al. 2011; Tiano et al. 2007; Watts et al. 2002). In most of the individuals treated with CoQ_{10}, endothelial function, determined by flow-mediated dilation (FMD) or by nitro-glycerine-mediated dilation (NMD) and the activity of extracellular superoxide dismutase, improved. This effect has been associated with the

antioxidant and anti-inflammatory activity of CoQ_{10} (Yubero-Serrano et al. 2012). CoQ_{10} treatment decreases the rate of production of peroxynitrite from nitric oxide (NO) that reacts with superoxide radicals. Likely, under conditions of oxidative stress, CoQ_{10} can reduce the levels of superoxide radicals (Yubero-Serrano et al. 2011, 2013; Tiano et al. 2007). Furthermore, *in vitro* studies have demonstrated that CoQ_{10} can efficiently prevent apoptosis of endothelial cells produced by high glucose and the adhesion to monocytes. This effect is very important in the prevention of the development of atherosclerosis (Tsuneki et al. 2007). Further, the inhibition of the LDL-oxidation by ubiquinol adds an important factor in the prevention of atherogenesis (Thomas et al. 1997).

17.3.4 CoQ_{10} and Renal Failure

Chronic kidney (CKD) and end-stage renal (ESRD) diseases are also associated with oxidative stress (Himmelfarb and Hakim 2003). Five hundred thousand patients in the United States receive maintenance haemodialysis for ESRD, with life expectancies less than 17–34% than those of the general population (US Renal Data System 2013). In these patients, the balance between ROS and antioxidants is disturbed and oxidative stress is produced. The high ratio of mortality has been attributed to an increased risk of cardiovascular disease produced by this high oxidative stress (Kuchta et al. 2011). The putative role of CoQ_{10} in CKD patients has been studied only in a few studies. Lippa et al. (1994) determined the levels of CoQ_{10} in 48 patients under chronic haemodialysis, in comparison with 15 uremic patients and a control group of healthy subjects (Lippa et al. 2000). In this study, CoQ_{10} levels were significantly lower in CKD patients. In a recent study, the levels of CoQ_{10} and oxidative stress biomarkers were determined in CKD, haemodialysis and peritoneal dialysis (PeD) patients. Contrary to the study of Lippa et al. (1994), in this study, researchers did not find differences in CoQ_{10} levels between those of CKD and haemodialysis groups. However, they did observe higher levels of members of the antioxidant system in patients undergoing PeD in comparison with CKD patients (Gokbel et al. 2011).

In other study, supplementation with CoQ_{10} (120 mg/day) to patients with CKD, reduced the number of patients on dialysis in comparison with placebo after 28 days of treatment (Singh et al. 2000). As in other cases, the tolerability and safety of oral CoQ_{10} administration was determined until doses as higher as 1800 mg/day in CKD patients (Yeung et al. 2015). Authors conclude that in these patients, CoQ_{10} supplementation is important since it reduces systemic oxidative stress and improves mitochondrial function in patients receiving haemodialysis (Yeung et al. 2015).

17.3.5 CoQ_{10} and Neurodegenerative Diseases

Mitochondrial dysfunction is a common characteristic of the neurodegenerative diseases. This dysfunction is accompanied by abnormal energy metabolism and higher oxidative stress. As we have previously described, CoQ_{10} levels in the brain and other tissues in humans and animals have been shown to decline with age. As an antioxidant molecule, CoQ_{10} has been involved in the development of neurodegenerative diseases such as Parkinson's disease (PD), Huntington's disease (HD) and other neurodegenerative disorders (Koroshetz et al. 1997; Shults et al. 1997). There is, therefore, a robust scientific rationale for testing this agent in neuroprotective therapies.

CoQ_{10} has shown protective effects in the nigrostriatal dopaminergic system in many preclinical studies of PD (Liu et al. 2011). Mitochondrial dysfunction has been strongly associated with PD and, probably for this reason, CoQ_{10} levels are significantly lower in mitochondria from PD patients. A randomised, placebo controlled and double-blind study performed in these patients demonstrated that a CoQ_{10} dose as high as 1200 mg/day, was safe and reduced the worsening of PD (Shults et al. 2002). Treatment with CoQ_{10} was accompanied by significant increases in plasma levels of CoQ_{10} and a higher NADH-cytochrome C reductase activity in white blood cells (Shults et al. 2002). Everyday activities of the patients, such as dressing, bathing and feeding, were significantly improved with the treatment with CoQ_{10}. Accordingly with this study, another placebo-controlled, double-blind trial showed that CoQ_{10} supplementation provided a mild but significant benefit on PD patients in comparison with (Muller et al. 2003).

In the case of HD, strong evidence indicate the existence of early oxidative stress. As in the other cases, this oxidative stress is coupled with mitochondrial dysfunction and the impairment of energy metabolism in which the deficiency in CoQ_{10} can be an important factor (Stack et al. 2008). In HD patients, CoQ_{10} doses, ranging from 600 to 1200 mg/day were tested during six-months in an open-label trial. Although no significant effect on clinical scores were found, the treatment with CoQ_{10} significantly decreased the levels of cortical lactate concentrations. This decrease was reversed following withdrawal of therapy indicating a protective effect of CoQ_{10} supplementation (Delanty and Dichter 1998). Again, the effect of CoQ_{10} in the behaviour of metabolic markers indicate the bioenergetics effect of oral CoQ_{10} in the mitochondrial metabolism of brain (Koroshetz et al. 1997).

17.4 Conclusions

The importance of CoQ_{10} is because this quinone is not just an agent in the transit of electrons in energy transduction in mitochondria. CoQ_{10} is a strong antioxidant able to regenerate the redox capacity in many tissues and organs. In normal conditions, its biosynthesis in mitochondria and endoplasmic reticulum provides

sufficient CoQ_{10}, but in some conditions such as genetic failure or aging and age-related diseases, CoQ_{10} deficiency can be an important factor in the progression of incapacity or disease. A number of studies have demonstrated that CoQ_{10} can be easily and safely used as nutritional supplement to delay and mitigate the effects caused by its depletion.

The clear beneficial effects of CoQ_{10} are reinforced because its excellent safety record. CoQ_{10} is very well tolerated even at high doses and for prolonged periods with null or very limited side effects. However, it is necessary to increase the research to determine the appropriate dose, effectiveness, and to increase the bioavailability of orally administered CoQ_{10}, specially, in the elderly. Further, a promising strategy can be centred in the design of therapeutic agents that increment the endogenous synthesis of CoQ_{10}.

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