The preventive role of coenzyme Q10 and other antioxidants in injuries caused by oxidative stress

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Abstract

Oxidative stress contributes to the generation of many different pathological conditions. Its key feature is an imbalance between free radical formation and their elimination processes. In this mini-review the authors give an introduction to the basic mechanisms of free radical formation, their physiological and pathological roles and the possible defective mechanisms involved in the maintenance of the living organism's balanced oxidative state. Antioxidants are very important in the battle against harmful oxidative stress. Therefore they can be used to prevent several diseases and even to cure them. In this short overview the authors discuss the role of some antioxidants such as coenzyme Q10 (ubidecarenone), lipoic acid, selenium, omega-3 fatty acids and vitamin E, emphasizing their increased effectiveness with their combined applications.

Key words: oxidative stress, antioxidants, coenzyme Q10, ubidecarenone, lipoic acid, selenium, omega-3 fatty acids, vitamin E.

Introduction

In the scientific literature of the previous decades there were increasing numbers of references to free radicals present in the living organism and the role played by their beneficial and harmful effects in physiological and pathological processes [1-10]. Atoms, molecules or molecular particles having an unpaired electron in orbit are called free radicals. This unfilled state makes these particles very active and aggressive in physicochemical processes, leading to the formation of newer and newer radicals in the course of chemical reactions [5].

The mitochondrial electron transport system consumes more than 85% of all oxygen used by cells, and up to 5% of the oxygen consumed by mitochondria is converted to superoxide anion, hydrogen peroxide and other reactive oxygen species (ROS) under normal physiological conditions. Formation of free radicals in the biological environment and an imbalance between radical formation and antioxidant defences, i.e. oxidative stress, are the causes of many pathological processes [6, 7].

Generation of excessive free radicals certainly plays a central role in several pathological conditions such as age-related diseases, malignancy, infective diseases and injuries. However, these diseases may have

multifactorial origin in addition to oxidative stress. Furthermore, several environmental risk factors may influence – usually accelerate or enhance – the harmful effects of free radicals [5, 11].

All these data strongly suggest that a combination of antioxidants may be of greater value than antioxidant monotherapy. In this mini-review we present some well established combinations of coenzyme Q10 (with other names: ubiquinone, ubidecarenone) with other antioxidants.

Free radicals originating from oxygen and nitrogen

Free radicals appearing in the living organism originate from molecular oxygen or nitrogen (Table I). Oxygen-derived radicals are generated by excitation or by reduction of electrons. Sigma singlet and the delta singlet oxygen are produced by excitation, while perhydroxy radical, superoxide anion as well as the hydroxyl radical are the results of reduction [5, 7]. Hydrogen peroxide is also an active molecule with electron reduction originating from oxygen. However, it is not a free radical, but in its reaction it behaves very aggressively, similarly to them [5, 12, 13]. Nitric oxide ($NO^{\bullet}$) is another free radical with cell signalling functions [14]. Besides its role in dilatation of blood vessels, $NO^{\bullet}$ and related species have other functions. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are important groups of free radicals that are capable of eliciting direct damaging effects or acting as critical intermediate signalling molecules, leading to oxidative and nitrosative stress and to a series of biological consequences [15, 16]. RNS refers to all oxidation states and reactive adducts of nitrogenous products, from NO up to but excluding nitrate (NO_3^-), that arise in physiological settings, including nitroxyl (NO^-), nitrosonium (NO^+), higher oxides of nitrogen, S-nitrosothiols (RSNOs), peroxynitrite ($OONO^-$), and dinitrosyl iron complexes [16, 17]. A mixture of nitrogen oxides make up nitrous radicals causing acidic rainfall [11, 18].

Table I. Free radicals originating from oxygen and nitrogen

Free radicals originating from oxygen
by reduction
Superoxide anion
Perhydroxy radical
Hydroxyl radical
by excitation
Sigma singlet oxygen
Delta singlet oxygen
Some free radicals originating from nitrogen
Nitrogen oxide ($NO^{\bullet}$)
Nitrogen dioxide ($NO_2^{\bullet}$)
Higher oxides of nitrogen
S-nitrosothiols (RSNOs)
Peroxynitrite ($OONO^-$)
Dinitrosyl iron complexes

Hydrogen peroxide is also a molecule with electron reduction originating from oxygen. It is not a free radical, but it does behave very aggressively in its reaction like free radicals

Physiological and pathological role of free radicals

The main processes producing free radicals in mammals are the following: mitochondrial oxidative metabolism providing energy supply, microsomal drug-metabolizing enzyme system, biosynthesis of prostaglandins, constitutive and inducible NO-synthase activity, free radical-producing reactions of phagocytes, monocytes, macrophages and Kupffer's cells, and auto-oxidation of hydrogen peroxide produced in peroxisomes. Another consequence of free radical activity is lipid peroxidation. In regulated circumstances it is part of the phospholipid turnover. Free radicals are generated in the organism in hypoxia, also in hyperoxia and at normal oxygen tension as well [5].

Oxidative stress is the result of pathologic accumulation of free radicals that have escaped the physiological controlling mechanism. The mechanism of oxidative stress and also its biological consequences are demonstrated in the figures (Figures 1, 2). Free radicals can attack small molecules containing thiol and amine groups as well as macromolecules building up the cells [19]. Proteins, polypeptides and peptides containing amino acids with free functional groups tryptophan, tyrosine, phenylalanine, histidine, methionine and cysteine are especially susceptible to oxidative damage. As a consequence the macromolecules undergo structural changes: polymerization, aggregation or fragmentation. Proteins that possess enzymatic function may become inactive. Due to

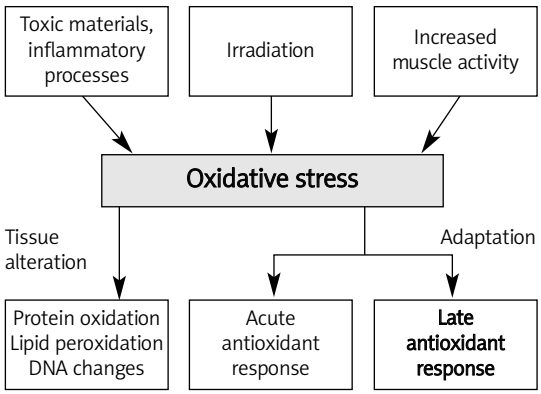

Figure 1. The mechanism of oxidative stress and its consequences

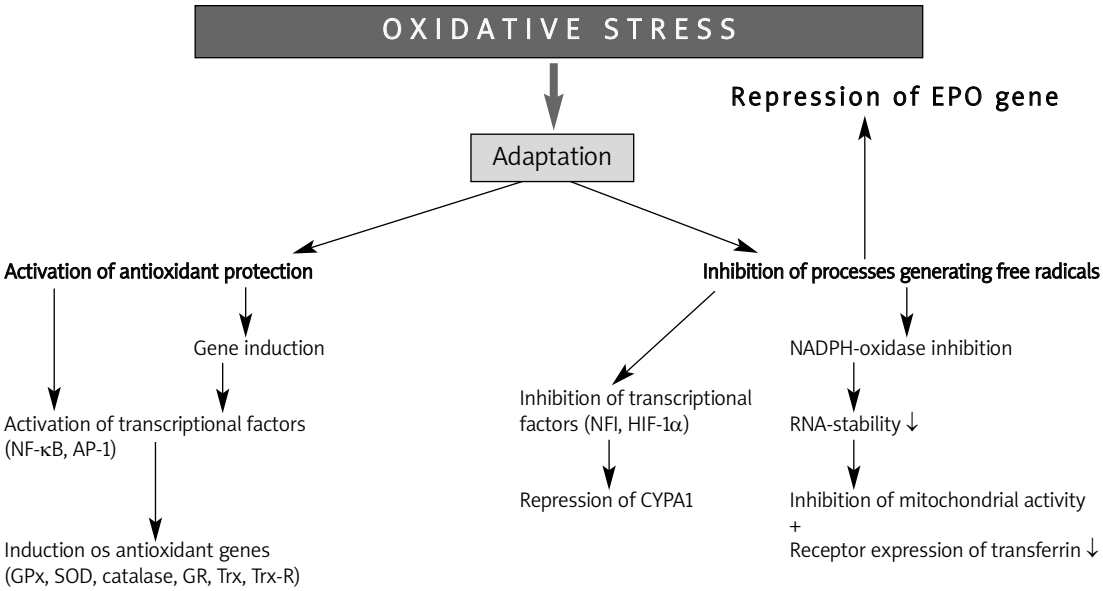

Figure 2. The molecular consequences of oxidative stress in the cells

peroxidative damage of the lipids in the cell membrane, permeability changes may occur. Nucleic acid injury can lead to mutation and neoplastic processes of the cells [5, 10, 18, 19].

It has been established that oxidative stress plays a role in aging, in various diseases such as arteriosclerosis and reperfusion, in inflammation and immunological processes, in toxic injury as well as in carcinogenesis. In addition it has some causative role in the pathogenesis of numerous other diseases [2, 13, 19].

Protection against injury caused by free radicals

Defensive mechanisms strictly based on each other in the living organism permit free radical reactions to happen to a certain extent without damaging the membranous structures and the enzymatic functions, so that the physiological role of free radicals is secured. The healthy organism is able to prevent the overproduction of free radicals (Table II).

Low oxygen tension of the tissues is a basic condition. Its value is about 26 mmHg or less. The primary line of antioxidants consists of representatives of the enzymatic defence: superoxide dismutases (SODs), catalase, peroxidase, glutathione-S-transferase and reductases. The enzymatic defence is supplemented by antioxidant vitamins with scavenger property (vitamins C, A, E, K), the cofactors, compounds containing thiol, phosphor, amine, polyamine, phenols, quinolines, ubiquinone (coenzyme Q), flavonoids, polyenes, glucose, urate, bilirubin, etc. [19-24].

In the maintenance of the redox balance an indispensable role is played by some trace elements such as copper, zinc, manganese and selenium [25-27]. The protection of the extracellular space is provided by albumin, ceruloplasmin, transferrin and the tetramer SOD (Table III).

If the elimination of free radicals is not sufficient, scavenging of the damaged molecules can still give some protection [19]. The representatives of this line are repairing mechanisms eliminating the degraded DNA, proteins and lipids. Exonucleases, endonucleases, glycosylases, polymerases and ligases repair the damaged DNA molecules. Proteinases, proteases, peptidases and macroxyproteases take part in scavenging the degraded proteins. Phospholipases,

Table II. Possibilities in prevention of oxidative stress in order to maintain homeostasis

Possibilities in prevention of oxidative stress in order to maintain homeostasis
Reduced oxygen tension in tissues
Enzymatic prevention (superoxide dismutase, catalase, peroxidase)
Antioxidants, scavengers
Repair mechanisms (elimination of DNA, protein and lipid degradants)
Improvement of mitochondrial functions (dietary omega-3 FA, CoQ10, carnitine)

Table III. Free radical scavengers in biological systems

Antioxidants in the living organism
Vitamins: C, A, E, K
Selenium
Substances containing thiol
Gallus acid
Protection of the extracellular space against free radicals
Ceruloplasmin
Transferrin
Pyruvate
Uric acid
Glucose

glutathione peroxidase breaking down the organic hyperoxidases, transferases and reductases help in the elimination of the oxidized lipids [5, 18].

Coenzyme Q (ubidecarenone, ubiquinone) and lipoic acid

There are two important metabolic oxidants in the mitochondria, namely coenzyme Q (CoQ10) and lipoic acid. The name coenzyme Q is misleading because it does not function as a coenzyme in mitochondrial oxidation. Lipoic acid is a cofactor of the pyruvate dehydrogenase enzyme system. The presence of these molecules shows that mitochondria as individual organisms can defend themselves against harmful effects of the oxygen atmosphere [19, 28, 29].

Coenzyme Q, also called ubiquinone or ubidecarenone, is derived from benzoquinone bound to an isoprene chain usually consisting of 6-10 units (Figure 3). The quinonoid structure makes the uptake of hydrogen possible and the isoprene chain ensures the localization within the membrane. Coenzyme Q in its reduced form is an excellent antioxidant. Its presence has been demonstrated in numerous other cellular organisms. The name "ubi quinone" also indicates that it can occur in various places. The endogenous coenzyme Q can capture perferril, carbon-centred lipids, lipid-peroxyl and alkoxyl radicals. Coenzyme Q is a component of the mitochondrial electron transport chain and it is also a constituent of various cellular membranes. It acts as an important in vivo antioxidant but it is also a primary source of $O_2^{-\bullet}/H_2O_2$ generation in cells [30, 31].

Experimental studies

There are data about the beneficial effect of exogenous coenzyme Q entering the body with food or as a nutritional supplement in numerous publications [31]. After induction of ischaemia in the rat liver the exogenous coenzyme Q has been proved to be beneficial due to its inhibitory effect on lipid peroxidation and on the oxidation of endogenous coenzyme Q-9 as well as by improving mitochondrial respiration [30]. Based on these data it was concluded that coenzyme Q-10 can possess a beneficial effect in the prevention of injury caused by oxidative stress developing during liver transplantation. The liver cell protective effect has also been reported during administration of coenzyme Q-analogue idebenone in an in vitro experiment where oxidative stress was induced by adding hydrophilic bile acids to rat hepatocytes [31].

Clinical trials

There are remarkable epidemiological studies performed by administration of certain food supplements (such as vitamins and coenzyme Q10) in relation to the prevention of aging,

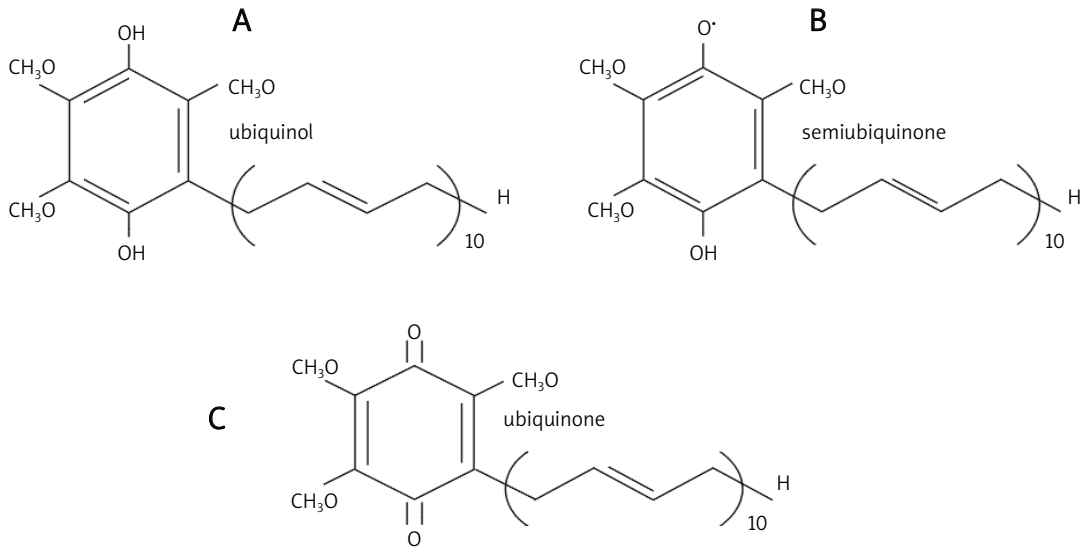

Figure 3. The chemical structure of coenzyme Q10

arteriosclerosis and ischaemic heart disease [19, 30, 31]. Based on these data it could be demonstrated that the Western diet (rich in fat and carbohydrates) plays a role in the development of arteriosclerosis while the Mediterranean diet (rich in fruits and vegetables and many sorts of fish) reduces the incidence of coronary disease and the Asian diet (containing plenty of soy and fish) increases the frequency of haemorrhagic cerebral diseases. In addition to this, some alcoholic beverages (about 10-15 g alcohol a day) can reduce mortality of cardiac origin. Antioxidant supplementation – especially coenzyme Q and selenium – reduces the risk of arteriosclerosis. There are also data suggesting that coenzyme Q plays a role in vitamin E regeneration [31-38].

Since CoQ10 is fat soluble, it is preferred to be taken with dietary fat. However, biliary and liver disorders may significantly influence both absorption from dietary sources and biosynthesis of endogenous CoQ10. Furthermore, people suffering from angina, HIV, male infertility, diabetes, periodontal disease, high blood pressure, thyroid diseases, cancer and those receiving chemotherapy could benefit from CoQ10 supplementation. Good sources are found in beef, soy, mackerel, sardines, spinach, peanuts, soybeans and vegetable oil. There is a considerable body of evidence that CoQ10 supplementation results in an elevation of CoQ10 in tissues and their mitochondria, a selective decrease in protein oxidative damage and an increase in antioxidant potential [19, 37]. The clinical disorders treated with coenzyme Q10 are listed in Table IV.

The other important antioxidant of the mitochondria is lipoic acid [37, 39]. It is synthesized both in the animal and in the human body. This fatty acid with eight carbon atoms containing disulphide groups at the sixth and eighth carbon atoms closed in a pentamerous ring is essential for the function of mitochondrial pyruvate dehydrogenase. Both lipoic acid and its reduced form are excellent metabolic antioxidants. They take part in the antioxidant redox cycle of the organism [30, 38].

Dosage of coenzyme Q10

Coenzyme Q10 is present naturally in a number of foods, including meats (e.g. beef, chicken) and fish (e.g. herring, rainbow trout), and on average people are estimated to consume 2-20 mg/day of this metabolically important substance [39-41]. Conventionally, in most EU countries and also in the US the adequate supply is 20 mg/day [19, 42]. However, this dosage is the minimum that we require per day to ward off serious deficiency of this particular nutrient. In therapeutic use the dosage is usually considerably increased (50-100 mg/day). As a therapeutic agent the dosage of Coenzyme Q10 varies according to the treated disease (50-3000 mg/day) [22, 42, 43].

Table IV. Clinical indications of coenzyme Q10 treatment

Cardiovascular disease
All-cause chronic heart failure (cardiomyopathy, congestive heart failure, etc.)
Dyslipidaemia and statin drugs
Hypertension
Other cardiovascular diseases
Neurological conditions
Parkinson's disease
Huntington's disease
Other diseases
Mitochondrial disorders
Cancer
Diabetes
Male infertility
HIV/AIDS
Asthma
Thyroid disorders
Periodontal disease
Renal failure
Friederich's ataxia
Migraine
Pregnancy
Veterinary indications

Currently, relatively little formal evidence regarding the safety of coenzyme Q10 has been identified in the toxicology literature, despite its consumption by humans for centuries without reported notable adverse effects. As such, a series of toxicological studies, including mouse bone marrow micronucleus, chromosomal aberration and bacterial reverse mutation tests, were conducted to evaluate the in vivo and in vitro mutagenic potential of CoQ10. The test article, coenzyme Q10 (ubidecarenone), was devoid of clastogenic activity when administered orally to mice at doses up to 2000 mg/kg/day [41].

Several companies distribute CoQ10 as a dietary supplement. In the United States, dietary supplements are regulated as foods, not drugs. Therefore, pre-market evaluation and approval by the U.S. Food and Drug Administration (FDA) are not required unless specific disease prevention or treatment claims are made. The FDA can, however, remove from the market dietary supplements that it deems unsafe. The FDA has not approved CoQ10 for the treatment of cancer or any other medical condition. In animal studies, CoQ10 has been administered by injection (intravenous, intraperitoneal, intramuscular or subcutaneous). In humans, it is usually taken orally as a pill (tablet or capsule), but intravenous infusions have been given. CoQ10 is absorbed best with fat; therefore, lipid preparations are better absorbed than

the purified compound. Reviewed in human studies, supplementation doses and administration schedules have varied, but usually have been in the range of 90 to 390 mg/day [30, 42, 43]. There are no official RDA levels for intake of CoQ10, but it is estimated that an intake of 10-30 mg/day should provide an adequate supply of CoQ10. There are no reported side effects at these low levels of intake. At more than 100 mg/day of CoQ10 some people may experience nausea, diarrhoea and mild insomnia [31, 44].

In two clinical trials the dosage of CoQ10 was 3 times 100 mg in a day. In one of these studies the ubiquinone was found to be effective in migraine prophylaxis [45]. These authors compared CoQ10 (3×100 mg/day) and placebo in 42 migraine patients in a double-blind, randomized, placebo-controlled trial. CoQ10 was superior to placebo for attack-frequency, headache-days and days-with-nausea in the third treatment month and well tolerated. In the ongoing Q-Symbio study the dosage is also 100 mg t.i.d. as adjunctive therapy in chronic heart failure [44]. An open-label dose-escalation trial was performed to assess the safety and tolerability of high doses of CoQ10 in amyotrophic lateral sclerosis (ALS), in order to improve the mitochondrial dysfunction in ALS. In this study, CoQ10 was safe and well tolerated in 31 subjects treated with doses as high as 3,000 mg/day for 8 months [46].

No serious toxicity associated with the use of CoQ10 has been reported. According to a review [47] doses of 100 mg/day or higher have caused mild insomnia in some individuals. Liver enzyme elevation has been detected in patients taking doses of 300 mg/day for extended periods of time, but no liver toxicity has been reported. In one cardiovascular study the CoQ10 caused rashes, nausea and epigastric (upper abdominal) pain that required withdrawal of a small number of patients from the study [48]. The observed safe level risk assessment method indicates that the evidence of safety is strong at intakes up to 1200 mg/day. Much higher levels have been tested without adverse effects and may be safe, but the data for intakes above 1200 mg/day are not sufficient for a confident conclusion of safety [49, 50].

Coenzyme Q10 and selenium

The role of selenium has been studied in several diseases. In the case of a decreased level of selenium (under 0.57 µmol/l) the relative risk of myocardial infarction is 2.1 [51] and the relative risk of fatal stroke at a diminished intake of selenium is 3.2-3.7 [52]. In the last decade several authors have suggested a relationship between selenium level in the plasma or serum and neoplastic diseases. An inverse correlation has been demonstrated between tumour mortality and selenium supply. There was a close correlation especially in the case of breast and colon cancers. It has also been demonstrated that selenium possesses immunostimulant and anti-inflammatory effects by promoting antibody production. The lasting deficit of selenium in animals has led to a decrease in the coenzyme Q-9 and Q-10 content of the liver [53-55].

Several studies suggest that selenium supply of the Hungarian population is scarce. With coworkers [27] we have demonstrated that the Hungarian soil systems are poor in selenium, especially the rocks with acidic volcanic origin as well as the loess and sandy soils, and this may be mirrored by the population's serum selenium concentration. In the case of less selenium entering plants and similarly animals, the food with low selenium concentration results in decreased level of selenium in the human body as well. Taking international data into consideration, it is possible that one of the important causes of the high cardiovascular mortality and cancerous morbidity may be the lack of selenium as well [30, 38].

According to the recommendation determined by the National Research Council of the United States, which is accepted in many countries worldwide, the optimal daily intake of selenium for adult men is at least 70 µg and 55 µg for women. The requirement increases during pregnancy and breastfeeding [27].

Therefore in Hungary selenium supplementation is recommended because of the low serum selenium content. There are various methods to fulfil this demand. In Finland and New Zealand adding sodium selenide to the artificial fertilizer during cultivation has been introduced. In Scotland sodium selenide supplementation is given to domestic animals in the hope of improving human selenium deficiency. In the United States selenium supplementation of drinking water has begun. In Hungary bread baked with yeast rich in selenium is sporadically used for selenium replacement. This latter method is easy to accomplish and it is effective. As food supplementation controlled administration of commercially available selenium products should be taken into consideration. As a result of the selenium supplementation mortality indices due to cardiovascular causes and malignant diseases may decrease to some degree as happened in Finland following systematic selenium food supplementation [27, 36, 56].

Coenzyme Q10 and statins

HMG-CoA reductase inhibitors, known as statins, represent a potent anti-cholesterol therapy. Cholesterol lowering therapy plays an essential, well recognized role in the secondary prevention of several atherosclerosis-related diseases, in particular that of coronary heart disease. As CoQ10 and cholesterol share the same biosynthetic pathway it was reasonable to hypothesize that statin therapy may also lead to decreased levels of CoQ10. In fact, several studies reported decreased levels of coenzyme Q10 during statin administration both in animals and in humans [57-63].

Statins are widely used, powerful and effective drugs, usually safe, with an apparently low frequency of side effects, but in some cases they were found to be very serious. A clear relationship between the use of cerivastatin [64] and rhabdomyolysis with consequent death of some patients has recently been established. Side effects of statins include muscle weakness, pain and elevated plasma levels of CK and/or transaminases and these symptoms could, at least in part, be related to a certain degree of CoQ10-deficiency. We may reasonably hypothesize that in some conditions where other CoQ10-impoverishing causes exist treatment with HMG-CoA reductase inhibitors may seriously impair levels of CoQ10 in plasma and possibly in tissues. For instance physiological decline in CoQ10 has been implicated in aging, which would make the elderly more susceptible to statin-induced CoQ10 depletion [61]. In a limited number of patients who had been on CoQ10 therapy for congestive heart failure, a sudden deterioration of their cardiac function was documented when statins were added to the therapy. This worsening was overcome by increasing their daily dosage of CoQ10. Besides the plasma CoQ10 lowering effects animal studies have also demonstrated tissue depletion in the course of statin treatment [62, 63]. Decrease in tissue coenzyme Q10 during statin therapy may have adverse effects on cellular ATP production. In particular it was shown that simvastatin treatment leads to a significant decrease in the myocardial level of CoQ10 and to an impairment of oxidative phosphorylation in the ischaemic dog and guinea pig hearts [65, 66]. However, lovastatin is able to decrease the cardiac levels of CoQ10 and to hamper oxidative phosphorylation only in aged animals.

CoQ10 deficiency may manifest in humans as cystolic and diastolic left ventricular dysfunction with symptoms of fatigue and exercise dyspnoea. Although statin therapy has been shown to have benefits, the long-term response in ischaemic heart disease may have been blunted due to the CoQ10 depleting effect. Further evidence of this was also shown in diabetic patients receiving HMG-CoA reductase inhibitors whose cardiothoracic ratio decreased upon CoQ10 treatment [67, 68]. Dosage of statins may also be important. In fact a 12-week lipid-lowering treatment with a daily dosage of 20 mg simvastatin was not found to negatively alter left ventricular function during exercise [66]. Thus, statin therapy supplemented with CoQ10 could make the use of statins even more effective and safe [69-71].

Coenzyme Q10 and omega-3 fatty acids

Mitochondrial membranes are rich in omega-3 fatty acids and several experimental and clinical studies have shown that these compounds determine, among others, functions of the electron transport chain (oxidative phosphorylation). In particular, omega-3 fatty acids play an essential role by stabilizing complexes III and IV [72, 73]. We should imagine respiratory complexes as clusters of enzymatic proteins embedded in the phospholipid bilayer of the inner mitochondrial membrane. CoQ10 serves to transport electrons from Complex I and Complex II to Complex III. Respiratory complexes of the oxidative phosphorylation pathway are essential for the production of the high-energy phosphate (ATP) upon which all cellular functions depend. Thus, there is a strong structural and functional correlation between omega-3 fatty acids and CoQ10 in the inner mitochondrial membrane [74, 75].

There is accumulating evidence that mitochondrial dysfunctions play a central role in the pathogenesis of several diseases, particularly in age-related diseases. Apart from being the main source of ROS, mitochondria are also the primary target of oxidative damage, which may result in mutation of mitochondrial DNA (mtDNA) and alteration of mitochondrial membranes (mtMEM) [76, 77]. Furthermore, mitochondrial dysfunctions also include reduced production of energy, disorders of cellular Ca^{2+} homeostasis, impairment in oxidation of fatty acids, impairment in the biosynthesis of amino acids and lipids, disorders of steroid metabolism and in extremis activation of apoptosis pathways [78]. Recent studies suggested that peroxidation of cardiolipin (a mitochondria-specific phospholipid) might have an initiating role in the liberation of cytochrome c from the inner membrane and in the opening of the permeability transition pore via inactivation of adenine nucleotide translocator, which regulates the opening and closing of the permeability transition pore [79, 80].

These findings suggested that an intervention in mitochondrial metabolism, i.e. attenuating generation of ROS, a metabolic rather than simple antioxidant approach, may be a more specific and more effective way for treating diseases caused by excessive generation of ROS [81]. In fact, in vivo studies showed that a diet rich in omega-3 fatty acids reverses the age-associated membrane omega-3:omega-6 fatty acid imbalance and dysfunctional Ca^{2+} metabolism, facilitating increased efficiency of mitochondrial energy production and improved tolerance of ischaemia and reperfusion [82]. There is a considerable body of evidence that these compounds from dietary uptake preferentially accumulate in the mitochondrial membranes of various organs [83, 84] and there is a well defined synergy between them [85, 86]. Recent clinical studies showed that dietary supplementation with omega-3 and CoQ10 (and acetyl-L-carnitine) improved both visual functions and retinal alterations in early age-related macular degeneration, the most common progressive neurodegenerative disease of the retina [87, 88].

Coenzyme Q10 and vitamin E

Vitamin E can directly regulate hydrogen peroxide production in mitochondria. Recent studies [89]

revealed several details of these processes and they suggest that the overproduction of mitochondrial ROS is the first event leading to tissue damage observed in vitamin E-deficiency syndromes:

(i) deprivation of vitamin E resulted in an approximately 5-fold increase in mitochondrial hydrogen peroxide production in skeletal muscle and a 1-fold increase in liver when compared with the vitamin E-supplemented group;
(ii) disruption of mitochondrial ultrastructure is one of the earliest pathological events during vitamin E depletion;
(iii) dietary vitamin E dose dependently attenuated hydrogen peroxide production in mitochondria isolated from liver and skeletal muscle of male and female rats;
(iv) female rats, however, were more profoundly affected by dietary vitamin E than male rats in the suppression of mitochondrial hydrogen peroxide production in both organs studied.

Besides its role in oxidative phosphorylation, another mechanism where ubiquinol exerts its antioxidant properties is that reduced coenzyme Q regenerates α-tocopherol, the active form of vitamin E, by reducing the α-tocopheryl radical. In these reactions ubisemiquinone radical is formed [90]. The fact should be kept in mind that coenzyme Q is the only lipid soluble antioxidant that animal cells can biosynthesize "de novo" and for which appropriate enzymatic mechanisms exist to regenerate the reduced form. This mechanism is of particular importance as also outside of the mitochondria several mechanisms have been identified for reducing ubiquinone to the active form, i.e. CoQ10 [91, 92]. Specifically the cytosolic NADH-CoQ reductase, DT-diaphorase and NADH-CoQ reductase of the Golgi apparatus and plasma membranes are responsible for the cytosolic reduction of ubiquinone, i.e. a mechanism which regenerates the active form of CoQ10 [93]. However, recent studies indicate that the oxidized form of CoQ10 is also endowed with antioxidant activity [94].

After supplementation with CoQ10 and vitamin E a significant increase occurred in all lipoprotein classes: CoQ10 was primarily incorporated into low-density lipoprotein (LDL). Vitamin E and omega-3 fatty acids had similar patterns [95]. These studies revealed that lipoprotein distribution of CoQ10 is markedly different from that of vitamin E, suggesting that they may be metabolized by distinct routes. Furthermore, vitamin E is distributed similarly to omega-3 fatty acids and n-3 fatty acids, thus providing protection on location for the oxidatively labile polyunsaturated fatty acids (PUFAs).

CoQ10 administration also elevated the vitamin E concentration in tissue homogenates and their mitochondria, thereby providing an in vivo indication of the "sparing" effect of CoQ10 on α-tocopherol. Moreover, CoQ10 intake enhances antioxidant potential of tissues by elevating the endogenous amounts of vitamin E [96]. In an animal model of atherosclerosis, Vitamin E+CoQ10 supplements are more anti-atherogenic than CoQ10 or Vitamin E supplements alone and disease inhibition is associated with a decrease in aortic lipid hydroperoxides but not in 7-ketocholesterol [97-99].

In conclusions in the pathogenesis of cardiovascular diseases, malignant tumours and toxic hepatic lesions (of alcoholic origin), oxidative stress developing in the organism plays a significant role. The amount of free radicals accumulating in the body to a pathological degree can be reduced by proper nutrition containing many natural antioxidants (a diet poor in fat and rich in vitamins and minerals, i.e. containing plenty of fruit and vegetables). We can contribute effectively to the improvement of the quality of our diet with food supplements containing coenzyme Q, vitamins, minerals, trace elements (selenium) and omega-3 fatty acids. However, considering that interactions can also occur in vivo between the individual vitamins and antioxidants, we consider it necessary to formulate our advice individually in the case of each patient.

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