

Periodontal Diseases & Coenzyme Q10 : A Review

Abstract

Reactive oxygen species (ROS) not only play an important role in cell signaling and metabolic processes but are also thought to be implicated in the pathogenesis of a variety of inflammatory disorders. Indeed, novel therapies are being developed, specifically aimed at reducing oxidative stress at the tissue and cellular level. Oxidative stress arises within tissues when the normal balance between ROS generation and antioxidant defence shifts in favour of the former, a situation arising from either an excess of ROS and/or a depletion of antioxidants. Periodontitis is a term used to describe an inflammatory process, initiated by the plaque biofilm, that leads to loss of periodontal attachment to the root surface and adjacent alveolar bone and which ultimately results in tooth loss. Periodontal pathogens can induce ROS overproduction and thus may cause collagen and periodontal cell breakdown. When ROS are scavenged by antioxidants, there can be a reduction of collagen degradation. Coenzyme Q10 serves as an endogenous antioxidant which increases the concentration of CoQ10 in the diseased gingiva and effectively suppresses advanced periodontal inflammation.

Key Words

Antioxidant, bioscavenger, coenzyme Q10, periodontal disease

Introduction

Coenzyme Q10 (CoQ10) is a compound found naturally in the energy-producing center of the cell known as the mitochondria. Because of its ubiquitous presence in the nature and its quinone structure (similar to that of vitamin K), CoQ10 is also known as ubiquinone.^[1,2] The primary biochemical action of CoQ10 is a cofactor in the electron-transport chain, the series of redox reactions that are involved in the biosynthesis of adenosine triphosphate (ATP). ATP serves as the cell's major energy source and drives a number of biological processes, including muscle contraction and the production of protein. CoQ10 also works as an antioxidant, so the CoQ10 is essential for the health of virtually all human tissue and organs.^[1,2] Antioxidants are substances that scavenge free radicals, damaging compounds in the body that alter cell membranes, tamper with DNA, and even cause cell death. Free radicals occur naturally in the body, but environmental toxins (including ultraviolet light, radiation, cigarette smoking, and air pollution) can also increase the number of these damaging particles. Scientists believe free radicals contribute to the aging process, as well as the development of a number of health problems, including heart disease and cancer.

Antioxidants, such as CoQ10, can neutralize free radicals and may reduce or even help prevent some of the damage they cause.^[3,4]

Although CoQ10 can be synthesized in the body, a situation may arise in which the body's synthetic capacity is insufficient to meet CoQ10 requirements. Susceptibility to CoQ10 deficiency appears to be greatest in cells that are metabolically active (such as heart, immune system, gingiva and gastric mucosa), since these cells presumably have the highest requirements for CoQ10.^[3] Tissue deficiencies of CoQ10 have been observed in the wide range of medical and dental conditions, including cardiovascular diseases, periodontal diseases, gastric ulcer, cancer and acquired immunodeficiency syndrome (AIDS). A deficiency may result from: i) impaired synthesis due to nutritional deficiencies ii) genetic or acquired defect in synthesis or utilization iii) increased tissue needs resulting from illness iv) CoQ10 levels decline with advancing age.^[5]

Historical context

Coenzyme Q-10 (CoQ-10 or Ubiquinone) is a naturally occurring quinone that is found in most aerobic organisms from bacteria to mammals. It was first identified in 1940 and isolated

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from the mitochondria of beef heart in 1957.^[6] In 1961 Peter Mitchell proposed the electron transport chain (which includes the vital proton-motive role of CoQ10). In 1972, Gian Paolo Littarru and Karl Folkers separately demonstrated a deficiency of CoQ10 in human heart disease. The antioxidant role of the molecule as a free radical scavenger was widely studied by Lars Ernster.^[1]

Common Names

Coenzyme Q10 is also known as Coenzyme Q, CoQ, CoQ10, Ubiquinone, Ubiquinone-Q10, Ubidecarenone, and Vitamin Q10.

Biochemistry

Normal blood levels of CoQ10 are 0.7 - 1 mcg/ml^[7]. CoQ10 is another name for 2,3-dimethoxy-5-methylbenzoquinone to which a terpenoid side chain (consisting of ten monounsaturated trans-isoprenoid units) is attached. It is a fat soluble quinone, structurally similar to vitamin K2.^[8] Quinones with six to 10 side chains (CoQ6 -CoQ10) are found in mammals. Human cells synthesize CoQ10 in an eight-step cascade starting

from the amino acid, tyrosine. The synthetic chain requires adequate levels of folic acid, niacin, and vitamins B2, B6, and C3. CoQ10 is slowly absorbed after oral administration.^[9]

It is taken up by chylomicron, distributed to the liver and incorporated into very low density lipoproteins.^[8] Peak blood levels occur 5 - 10 hours after ingestion; the elimination half life is 34 hours, and it is primarily excreted through the biliary tract. Typical adult daily doses of 100 - 150 milligrams double normal serum levels.^[8] Absorption of the substance largely depends on its physiochemical characters in the preparation and hence coenzyme Q10 in powder, suspension, oil solution, or solubilized form exhibits different bioavailability. Study has shown that solubilized coenzyme Q10 is obviously preferred due to its better absorption, higher plasma concentration, and consequently better bioavailability^[10] indicating that plasma concentrations of coenzyme Q10 are 2-2.5 times higher during long-term oral therapy with solubilized forms^[11] and the bioavailability is 3-6 times higher in comparison with powder.^[12]

Functions of CoQ10:

Physiologically, CoQ10 plays four major roles. It has an essential role in mitochondrial energy (ATP) production through redox activity in the respiratory chain, transporting electrons between enzymes. Second, it plays a role in extra mitochondrial redox activity in the cell membrane and endomembranes. CoQ10 also functions as an antioxidant, inhibiting lipid peroxidation and scavenging free radicals. Finally, it plays an important role in membrane stabilization and fluidity.^[8,13]

Ubiquinone molecules are classified based on the length (n) of their isoprenoid side chain (Ubiquinone -n). For example, the main species in humans is Ubiquinone -10, in rodents it is Ubiquinone-9, in *Escherichia coli* it is Ubiquinone -8 and, in *Saccharomyces cerevisiae*, it is Ubiquinone -6 in varying amounts.^[14] CoQ9 is the predominant form in relatively short-lived species such as rats and mice whereas in humans and other long-lived mammals the major homologue is CoQ10. Among blood cells, lymphocytes and platelets contain significant amounts of CoQ10 whereas red blood cells which lack mitochondria contain only a tiny amount that is likely to be associated with membranes. Lymphocyte CoQ10 content can be

increased by CoQ10 supplementation with concomitant functional improvement as evidenced by enhanced reversal of oxidative DNA damage.^[15]

Antioxidant function of CoQ10:

The antioxidant nature of CoQ10 derives from its energy carrier function. As an energy carrier, the CoQ10 molecule is continuously going through an oxidation-reduction cycle. As it accepts electrons, it becomes reduced. As it gives up electrons, it becomes oxidized. In its reduced form, the CoQ10 molecule holds electrons rather loosely, so this CoQ molecule will quite easily give up one or both electrons and, thus, act as an antioxidant. CoQ10 inhibits lipid peroxidation by preventing the production of lipid peroxy radicals (LOO).^[16] In addition, the reduced form of CoQ effectively regenerates vitamin E from the α -tocopheroxyl radical and, thereby interfering with the propagation step. Furthermore, during oxidative stress, interaction of H₂O₂ with metal ions bound to DNA generates hydroxyl radicals and CoQ efficiently prevents the oxidation of bases, in particular, in mitochondrial DNA. In contrast to other antioxidants, this compound inhibits both the initiation and the propagation of lipid and protein oxidation.^[15]

Immune function:

Cells and tissues that play a role in immune function are highly energy-dependent and therefore require an adequate supply of CoQ10 for optimal function. Several studies have been demonstrated immune-enhancing effects of CoQ10 or its analogues.^[17,18] These effects included increase in phagocytic activities of macrophages, increase in proliferation of granulocytes in response to infection and treatment of infected animals with CoQ10 increased the survival rate. In a study of eight chronically ill patients, administration of 60mg/day of CoQ10 was associated with significant increase in serum level of immunoglobulin G (IgG) in 27 - 98 days of treatment. These studies suggest that CoQ10 may help prevent or reverse the immunosuppression that is associated with aging and chronic diseases.^[19]

CoQ10 and Periodontal diseases:

Periodontitis is a term used to describe an inflammatory process, initiated by the plaque biofilm, that leads to loss of periodontal attachment to the root surface and adjacent alveolar bone and which ultimately results in tooth loss. The inflammatory and immune responses to the bacteria and also viruses^[20] that

colonize the periodontal and associated tissues involve the systemic circulation and ultimately the peripheral systems of the body. This creates a complex bidirectional series of host-microbial interactions involving cellular and humoral factors and networks of cytokines, chemokines, and growth factors. The majority of periodontal tissue destruction is caused by an inappropriate host response to periopathogens and their products^[21]. Whether acute or chronic, inflammation is dependent upon regulated humoral and cellular responses, and the molecules considered to mediate inflammation at one time or another are legion.^[22] However, an event characteristic of mammalian inflammation, tissue infiltration by polymorphonuclear leukocytes and monocytes and subsequent phagocytosis features non-mitochondrial O₂ consumption, which may be 10 or 20 times that of resting consumption ultimately ends in generating free radicals (FRs) and reactive oxygen species (ROS), such as superoxide anion radicals, hydrogen peroxide, hydroxyl radicals, and hypochlorous acid, all capable of damaging either cell membranes or associated biomolecules.^[23] Because of their high reactivity, several FRs and ROS can rapidly modify either small, free biomolecules (i.e., vitamins, amino acids, carbohydrates, and lipids) or macromolecules (i.e., proteins, nucleic acids) or even supramolecular structure (i.e., cell membranes, circulating lipoproteins).

Usually, the oxidative damage is perfectly controlled by the anti-oxidant defense mechanisms of the surrounding tissues but plaque microorganisms promoting periodontitis can unbalance this equilibrium. A massive neutrophil migration to the gingiva and gingival fluid leads to abnormal spreading of FR/ROS produced. Consequently, this led to a search for appropriate "antioxidant therapy" in inflammatory periodontal disease.^[23]

Periodontal disease (gum disease) affects 60% of young adults and 90% of individuals over age 65. Healing and repair of periodontal tissue requires efficient energy production. A metabolic function dependent on an adequate supply of CoQ10. CoQ10 deficiency has been reported in gingival tissue of patients with periodontal disease. Gingival biopsies revealed subnormal tissue level of CoQ10 in 60% to 96%

patients with periodontal disease and low level of CoQ10 in leukocytes in 86% of cases.^[24,25] These finding indicated that periodontal disease is frequently associated with CoQ10 deficiency.

Patients with periodontal disease have low concentrations of CoQ10 in gingival tissue and blood.^[20,21,22] This has led some clinical investigators and dentists to recommend CoQ10 supplementation, particularly for diabetic patients and others at risk for periodontal disease. A case report of one patient with severe periodontal disease who had a dramatic improvement with CoQ10 therapy prompted several open label trials.^[24]

In one case series, eight patients with periodontal disease were treated with CoQ10 (50 mg daily); symptoms were significantly reduced over 21 days of treatment^[26,27]. In an open label study of ten adult patients with periodontal disease, topical therapy with CoQ10 was associated with significant improvement in disease^[28].

In an open trial, administration of CoQ10 produced " extraordinary post surgical healing (2 to 3 time faster than normal) in 7 patients in advanced periodontal disease. The beneficial effect of CoQ10 has also been confirm in dogs, where it reduced the severity of experimentally induced periodontal disease.^[29]

The specific activity of succinic dehydrogenase-coenzyme Q10 reductase in gingival tissues from patients with periodontal disease against normal periodontal tissues has been evaluated using biopsies, which showed a deficiency of CoQ10 in patients with periodontal disease. On exogenous CoQ10 administration, an increase in the specific activity of this mitochondrial enzyme was found in deficient patients.^[24,26,29] The periodontal score was also decreased concluding that CoQ10 should be considered as an adjunct for the treatment of periodontitis in current dental practice.^[27]

Many clinical trials with oral administration of CoQ10 to patients with periodontal disease have been conducted. The results have shown that oral administration of CoQ10 increases the concentration of CoQ10 in the diseased gingiva and effectively suppresses advanced periodontal inflammation^[26,30,31] and periodontal microorganisms.

Topical application of CoQ10 to the periodontal pocket was evaluated with and without subgingival mechanical debridement. In the first three-week

period, significant reduction in gingival crevicular fluid flow, probing depth and attachment loss were found and significant improvements in modified gingival index, bleeding on probing and peptidase activity derived from periodontopathic bacteria.

A study evaluated the periodontium condition after oral applications of coenzyme Q10 with vitamin E. The total antioxidant status in the mixed saliva by the colorimetric method was determined twice. The average value of plaque index decreased from 1.0 to 0.36, average value of interdental hygiene index was reduced from 39.51-6.97%, gingival index values decreased from 0.68 to 0.18, and the values of sulcus bleeding index decreased from 7.26 to 0.87. Periodontal pockets also shallowed by 30%. The laboratory examination result improved by 20%. It concluded that coenzyme Q10 with vitamin E had a beneficial effect on the periodontal tissue.^[32]

Because it is an antioxidant, coenzyme Q10 has received much research attention in the medical literature in the last several years. Although coenzyme Q10 may have been viewed as an alternative medication, it is used routinely, both topically and systemically.

Preliminary clinical studies also suggest that CoQ10 use as a therapeutic agent in:

- Researchers believe that the beneficial effect of CoQ10 in the prevention and treatment of heart disease^[33]
- High blood pressure and high cholesterol^[33]
- CoQ10 supplements may improve heart health and blood sugar and help manage high cholesterol and high blood pressure in individuals with diabetes.^[33]
- Malignancies^[33]
- Improve immune function in individuals with immune deficiencies (such as acquired immunodeficiency syndrome or AIDS) and chronic infections (such as yeast, bacteria, and viral infections)^[33]
- Be used as part of the treatment for Alzheimer's disease and Parkinson's disease^[34]
- Reduce damage from stroke^[33]
- Enhance physical activity in people with fatigue syndromes^[34]
- Improve exercise tolerance in individuals with muscular dystrophy^[34]
- Improve symptoms of tinnitus, or

ringing in the ears^[35]

- Delay the aging process and increase longevity^[33]

Side effects of CoQ10:

No serious side effects have been reported from the use of CoQ10. Some patients using CoQ10 have experienced mild insomnia, elevated level of enzymes, rashes, nausea and upper abdominal pain.^[36]

Conclusion:

The major use for CoQ10 is the prevention and treatment of cardiovascular diseases including chronic heart failure, atherosclerotic and ischemic heart disease, ischemia associated with cardiac surgery, toxin-induced cardiomyopathies and hypertension. Other popular uses include adjunctive therapy for periodontal disease, cancer and diabetes and to enhance athletic performance. CoQ10 is a natural human ubiquinone, but it can be chemically synthesized. It has an important role in mitochondrial metabolism, and it functions as an antioxidant. Data from animal studies, case series, open-label trials and comparison studies support its use in treating ischemic heart disease, ischemia associated with cardiac surgery, chronic heart failure, hypertension, and ventricular arrhythmias. Additional studies are needed to define its precise role in the treatment of these conditions and to evaluate its use as an adjunctive therapy for cancer and periodontal disease.

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