Coenzyme Q10 and ubiquinol as adjunctive therapy for heart failure

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ABSTRACT: Coenzyme Q10 (also known as Ubiquinone) and its active form, Ubiquinol, are essential for the body's energy production processes, including those which take place in the heart. Thus, a deficiency of heart and blood CoQ10 could be a risk factor for the development of cardiovascular diseases.
The latest advance in supplemental Coenzyme Q10 is the reduced, active form Ubiquinol. While traditional, oxidized CoQ10 has to be converted into Ubiquinol before it works in the body, Ubiquinol can work quickly and directly without such conversion. It is effective at lower dosages. Ubiquinol daily doses range from 100 to 600 mg and can increase blood plasma levels of CoQ10 to more than 3.5 mg/l, which is the level required by patients with severe heart problems for improving heart function. Clinical studies support the safety of Ubiquinol in CHF patients and demonstrate that Ubiquinol is more effective than oxidized Coenzyme Q10.

INTRODUCTION

In today's industrialised countries, cardiovascular diseases are the most common cause of death, with congestive heart failure (CHF) being the third most common cause in this category. In 2009, one in nine death certificates (274,601 deaths) in the United States mentioned heart failure, and heart failure was the underlying cause in 56,410 of those deaths. The number of deaths attributable to heart failure was approximately as high in 1995 (287,000) as it was in 2009 (275,000) (1).
As a constantly active organ, the heart muscle has to be supplied on a permanent basis with enough energy for optimal function. CoQ10 and its reduced form, Ubiquinol, play important roles in the body's energy production processes, including those which take place in the heart. In fact, Coenzyme Q10 occurs in every cell of the body and is an essential cofactor in the mitochondrial electron transport system. It interacts with at least three mitochondrial enzyme complexes involved in oxidative phosphorylation during ATP production (2). A deficiency of Coenzyme Q10 causes reduced energy delivery in the cardiac myocyte, despite an optimal mitochondrial substrate level for energy production. This effect is considered to be important in the clinical application of CoQ10. Cardiac myocytes are cells with very high energy requirements. The body's highest concentration of Coenzyme Q10 is found in the heart. Necessary for approximately 95 per cent of cellular ATP production, Coenzyme Q10 is important in heart muscle function.
Another fundamental property is the coenzyme's antioxidant function (3). Through its molecular properties as a potent lipid-soluble antioxidant residing in the mitochondrial membrane, CoQ10, in its antioxidant form Ubiquinol, can effectively counteract oxidative damage there. Increased levels of oxidative stress markers have been confirmed in animal models and in human CHF.
The fundamental role of CoQ10 for the functioning of heart muscle makes it obvious that any deficiency could lead to serious clinical consequences, and should hopefully be corrected. Observational studies have reported that the plasma CoQ10 concentration was an independent predictor of mortality in patients with CHF (4). Indeed, it has been found that people suffering from CHF have a lowered CoQ10 content in both the blood and in the heart muscle (5). The severity of heart failure seems to correlate directly with the severity of Coenzyme Q10 deficiency (6, 7). Even though CoQ10 deficiency is not in many cases the primary cause of the cardiopathy, it could further impair the metabolic status of the heart muscle.
Therefore, supplementation with Coenzyme Q10 and Ubiquinol could act as an adjunctive therapy for this disease at all stages.
In healthy individuals, blood plasma levels of Coenzyme Q10 are about 1.0 +/- 0.2 mg/l, whereas in certain diseases levels of close to 0.6 mg/l or even lower are found (8). CoQ10 is naturally synthesized in all human tissues, and in healthy young people, normal levels are maintained by biosynthesis combined with Coenzyme Q10 intake from the diet. However, it is known that CoQ10 levels in the body start to decrease after the age of 20 in all tissues (9, 10).

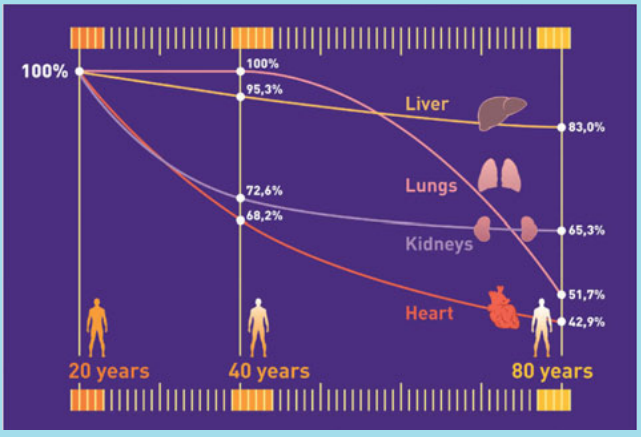

Figure 1. Age related decrease of CoQ10 in the human body.

Structure

Coenzyme Q10 is a fat-soluble vitamin-like nutrient with a quinone structure similar to Vitamin E and Vitamin K. There are three methods used for the manufacturing of CoQ10: yeast fermentation, bacteria fermentation and chemical synthesis. The yeast fermentation process results in CoQ10 with the so-called "all-trans configuration", which means that it is identical to naturally occurring CoQ10 found in meat, fish and other products. CoQ10 produced by chemical synthesis also generates the cis-isomer (a configuration of the molecular structure not found in naturally occurring CoQ10).

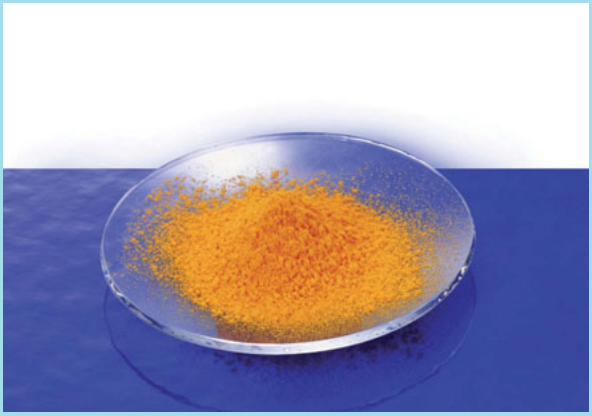

Figure 2. Traditional CoQ10: the oxidized form is recognised by its yellow colour.

Figure 3. Ubiquinol, the reduced form of CoQ10 is recognised by its white colour. The most common application form is softcapsules.

MECHANISMS OF ACTION

Coenzyme Q10 can act in different ways to support heart health in congestive heart failure. First of all, it has direct short-term effects on the heart's energy production: Supplementation increases the amount of CoQ10 and ATP production in the heart (11). In addition, CoQ10 supplementation has indirect effects on other cardiovascular risk factors, such as increasing CoQ10/ Ubiquinol content in LDL lipoproteins and thus reducing LDL oxidation (12).

There are two potential pathways that influence heart metabolism in CHF. On the one hand it affects ATP production. On the other hand, due to the coenzyme's location in the inner mitochondrial membrane, a higher CoQ10 content could offer protection against reactive oxygen species, necessarily generated in the ATP production process. This effect could slow down the loss of mitochondria number and function in the heart cells of CHF patients as well as the progression of the disease itself (13). More recent data indicate that another possible mechanism could be related to the effect of CoQ10 in counteracting endothelial dysfunction. Under this respect the improvement in myocardial contractility might also be due to a more efficient coronary blood supply (14-16).

CLINICAL STUDY RESULTS

International clinical data on the effectiveness of CoQ10 supplementation in the treatment of congestive heart failure patients has accumulated over the past three decades. Initial studies were carried out in Japan, and the Japanese Government approved CoQ10 supplementation for the treatment of heart failure in 1974. However, controversial results have been reported about Coenzyme Q10's beneficial effects in this field (17, 18). The design of these controversial trials has been criticized because most of them were open label studies. Moreover other causes of criticism were low CoQ10 dosages, short-term study periods and supplementation in late stages of CHF. While the optimal dose of Coenzyme Q10 in CHF treatment has not yet been established, a daily amount of 100 mg is suboptimal for the majority of patients. This has led researchers to start using higher CoQ10 doses over a longer period of time, resulting in many clinical observations where heart function in CHF patients improved dramatically (19).

A study led by Khatta found that blood plasma CoQ10 levels in patients with congestive heart failure rose upon receiving 200 mg conventional CoQ10 daily for six months. But there was no positive effect on the heart ejection fraction. The study showed that a dosage of 200 mg CoQ10 daily created a wide range of different blood plasma levels of CoQ10 (1.0 to 3.4 mg/l), and that an average blood plasma level of 2.2 mg/l is too low to be effective in this field (20).

Due to individual variation in patient ability to absorb CoQ10, it was found to be better to use a flexible dosing schedule whereby higher doses and long-term application were able to attain plasma levels of > 2.5 mg/l or in some cases even > 3.5 mg/l. In many cases, this required supplementation of very high doses of traditional, oxidized CoQ10 per day. In this respect, 34 controlled trials and several open-label and long-term studies have been reviewed (21). Of a total of 23 randomized controlled trials of CoQ10 supplementation in congestive heart failure from 1972 to 2009, 20 found significant benefit and three trials showed no benefit. These three trials were found to have CoQ10 treatment levels that were too low (resulting in CoQ10 plasma levels of less than 2.5 mg/l) (19). A recent meta-analysis on conventional CoQ10, where more strict selection criteria were adopted, showed an average of 3.7 per cent increase in ejection fraction, and some significant improvements in the NYHA class. In most of those studies a dose of CoQ10 close to 100 mg/day was used (18).

In a study with 109 hypertensive patients, 51 per cent were able to stop taking between one and three antihypertensive drugs an average of 4.4 months after starting Coenzyme Q10 supplementation, while the overall NYHA (New York Heart Association) classification improved significantly, from a mean value of 2.40 to 1.36 (23). A recent review also highlights the hypotensive effects of CoQ10 (24).

NYHA III and IV patients appear to have extremely low levels of CoQ10 in the heart and suffer from a decrease in ejection fraction. Treatment therefore has to reach much higher plasma levels of CoQ10 than those achieved in

most studies in the past. To attain higher plasma levels, it is important to optimize the bioavailability of Coenzyme Q10 from supplements, which is normally quite low. The latest advance in supplemental Coenzyme Q10 is the stabilized reduced form, Ubiquinol, developed in Japan. As outlined below, studies based on supplementation of Ubiquinol attained higher plasma levels, while traditional CoQ10 failed to achieve the same levels even at dosage of 650mg. (22, 25).

Langsjoen selected NYHA III and NYHA IV patients with extremely low heart pumping volume of around 10 to 35 per cent. These patients were on full medication and also received 150 to 600 mg daily supplementation of conventional CoQ10. However, their blood plasma CoQ10 levels did not exceed 2.0 mg/l and there was no increase in heart pumping volume either. These patients then received Ubiquinol instead of conventional CoQ10. As a result, CoQ10 blood plasma levels increased in all patients three to five-fold compared with normal Coenzyme Q10 supplementation. In five out of seven patients, the pumping volume increased and NYHA classes improved by one, two or even three classes in each case (22).

In a follow up study, Langsjoen gave 23 NYHA II and III patients Ubiquinol instead of oxidized CoQ10. Although the patients received 50 mg less Ubiquinol per day than the previously used amount of CoQ10 (334 mg instead of 384 mg), their mean CoQ10 blood plasma level was almost doubled (from 2.9 mg/l to 5.3 mg/l) and the mean NYHA class decreased from 2.5 to 1.6 (22).

Safety and dosage

Sold as food supplements, yeast fermented CoQ10 and Ubiquinol are recognized in many published studies as being completely safe and without any known toxicity or drug interactions. The highest doses used in human trials have been 1200 mg CoQ10 per day in patients with Morbus Parkinson (26) and up to 3000 mg CoQ10 per day in patients with familial cerebellar ataxia: In both cases, no adverse reactions were noted (27). At least 39 open trials with CoQ10 supplementation in heart failure have been published, involving 4498 patients, again with a remarkably good tolerability. Rarely, mild nausea was reported as a side-effect. The long-term safety of CoQ10 was documented by Langsjoen in a six-year study of 126 heart failure patients (28).

Since 2007, Ubiquinol has become available worldwide for use in food supplements. Because it is taken up by the body more quickly and efficiently than CoQ10, Ubiquinol works more effectively. Effective dosages of Ubiquinol range from 100 to 600 mg per day, which can increase blood plasma levels of CoQ10 to > 3.5 mg/l, the level that is necessary for CHF as well as NYHA III and IV patients.

SUMMARY

Congestive heart failure is a major cause of death in the industrialized world. Coenzyme Q10 deficiency contributes to the severity of this situation. The majority of the clinical studies that have examined the treatment of heart diseases have been consistent in their conclusions: Supplementation with Coenzyme Q10 in the form of Ubiquinol significantly improves heart muscle function while causing no adverse effects or drug interactions. Ubiquinol, the reduced form of Coenzyme Q10, is more bioavailable than conventional CoQ10. Indeed, conventional CoQ10 can be considered as precursor that needs to be reduced to Ubiquinol during the absorption process, whereas Ubiquinol is directly absorbed without the need for conversion. In the past, there have been a greater number of clinical studies with CoQ10 and fewer investigations into the effects of treating CHF with Ubiquinol. However, recent studies show that Ubiquinol is a very promising food supplement in CHF and is much more effective than conventional CoQ10. Thus, Ubiquinol could become the nutrient of first choice for adjunctive therapy in congestive heart failure.

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