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Invited critical review

Coenzyme Q10 treatment of cardiovascular disorders of ageing including heart failure, hypertension and endothelial dysfunction

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ABSTRACT

Advancing age is a major risk factor for the development of cardiovascular diseases. The aetiology of several cardiovascular disorders is thought to involve impaired mitochondrial function and oxidative stress. Coenzyme Q10 (CoQ10) acts as both an antioxidant and as an electron acceptor at the level of the mitochondria. Furthermore, in cardiac patients, plasma CoQ10 has been found to be an independent predictor of mortality. Based on the fundamental role of CoQ10 in mitochondrial bioenergetics and its well-acknowledged antioxidant properties, several clinical trials evaluating CoQ10 have been undertaken in cardiovascular disorders of ageing including chronic heart failure, hypertension, and endothelial dysfunction. CoQ10 as a therapy appears to be safe and well tolerated.

Contents

Abbreviations: CoQ10, Coenzyme Q10; CVD, cardiovascular disease; CHF, chronic heart failure.

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1. Introduction

Cardiovascular disease (CVD) remains the principal cause of death in both developed and developing countries, accounting for approximately 20% of all worldwide deaths per year [1]. There are several lines of evidence implicating oxidative stress and impaired mitochondrial function in CVD [2,3]. Coenzyme Q10 (CoQ10) or ubiquinone or 2-methyl-5, 6-dimethoxy-1, 4-benzoquinone is a vitamin-like compound widely distributed in the body in two forms: reduced (ubiquinol), and oxidised (ubiquinone) form [4]. CoQ10 is an essential component for electron transport in oxidative phosphorylation of mitochondria. It is a potent antioxidant, a membrane stabiliser, and cofactor in the production of adenosine triphosphate by oxidative phosphorylation, inhibition of the oxidation of proteins and DNA [5]. Based on these properties, clinical trials investigating the ability of CoQ10 to slow disease progression have been considered for many CVDs. The clinical trials evaluating CoQ10 in chronic heart failure (CHF), hypertension and endothelial dysfunction are reviewed (Table 1) and critical issues inherent to these trials are discussed.

2. Physiology of CoQ10

CoQ10 is an obligatory member of the respiratory chain in the mitochondria of all cells (Fig. 1). Therefore, it is an essential ingredient in the formation of adenosine triphosphate (ATP), the source of energy in most cellular processes. CoQ10 is located in the mitochondria, lysosomes, and Golgi and plasma membranes, and provides an antioxidant action either by direct reaction with free radicals or by regeneration of

Table 1
Clinical trials of CoQ10 in heart failure, hypertension and endothelial dysfunction.

Reference number	Author	Study design	No. of patients	Diagnosis	CoQ10 daily oral dose	Significant finding
CHF						
[63]	Langsjoen (1985)	Crossover	19	CHF	100 mg	Increased EF
[64]	Judy (1986)	Parallel	14	CHF	100 mg	Improved CO and EF
[65]	Poggesi (1991)	Crossover	20	ICM	100 mg	Improved EF
[66]	Permanetter (1992)	Parallel	25	IDCM	100 mg	No benefit
[67]	Rengo (1993)	–	60	CHF	100 mg	Improved EF
[23]	Morisco (1993)	Randomised double-blind placebo-controlled	641	CHF	100 mg	Fewer hospitalizations; for CHF at 1 year
[68]	Morisco (1994)	Crossover	6	CHF	2 mg/kg	Improved EF, VS, CO
[69]	Hofman-Bang (1995)	Crossover	79	CHF	150 mg	Improved EF
[70]	Watson (1999)	Crossover	30	CHF	100 mg	EF and VS unaltered, left ventricular systolic and diastolic volume ↓
[71]	Munkholm (1999)	RandomizedRandomised double-blind placebo-controlled	22	CHF	200 mg	Improved SV and exercise tolerance
[72]	Khatta (2000)	Two parallel groups	55	CHF	200 mg	Improved Exercise tolerance, EF unaltered, oxygen consumption ↑
[73]	Keogh (2003)	Randomised double-blind, placebo-controlled	39	CHF	150 mg	Improved exercise tolerance
[51]	Belardinelli (2006)	Double-blind, placebo-controlled crossover design	23	CHF	150 mg	Improved exercise tolerance.
[26]	Hosseini (2008)	Randomised placebo-controlled	50	CHF	150 mg	Improved EF
[74]	Langsjoen (2008)	–	7	CHF	450–900 mg	Improved EF and NYHA class
[29]	Mortensen (2014)	Randomised, placebo-controlled, trial	420	CHF	300 mg	Improved symptoms and survival
Hypertension						
[75]	Yamagami (1986)	Randomised, placebo-controlled, double-blind trial.	52	EH	100 mg	Reduction in SBP (6.6 ± 7.09 mm Hg) and DBP (2.2 ± 4.1 mm Hg)
[76]	Digiesi (1990)	Randomised, placebo-controlled, crossover trial.	18	EH	100 mg	Reduction in SBP (10.3 ± 2.31 mm Hg) and DBP (8.1 ± 1 mm Hg)
[77]	Singh (1999)	Randomised, double-blind trial	59	EH, CAD	120 mg	Reduction in SBP (11.5 ± 2.2 mm Hg) and DBP (5 ± 1.17 mm Hg)
[40]	Burke (2001)	Randomised, double-blind, placebo-controlled trial	83	Isolated systolic hypertension	120 mg	Reduction in SBP of the CoQ-treated group (17.8 ± 7.3 mm Hg)
ED						
[57]	Raitakari (2000)	Double-blind crossover study	12	Moderate hypercholesterolemia.	150 mg	Not associated with improvement in arterial ED
[55]	Watts (2002)	Case–control study	40	Type 2 diabetes	200 mg	Improvement in arterial ED
[54]	Kuettner (2005)	Prospective, randomised, cross-over study	25	ED	150 mg	Improvement in arterial ED
[50]	Tiano (2007)	Randomised controlled study	19	CAD	300 mg/d	Improvements in ED and endothelium-bound ecSOD activity
[45]	Hamilton (2009)	Double-blind crossover study	23	Type 2 diabetes, ED	200 mg/d	Improvement in arterial ED
[56]	Dai (2011)	Randomised, double-blind, placebo-controlled study	28	CAD	300 mg/d	Improvement in arterial ED

CO, cardiac output; CoQ10, coenzyme Q10; CAD, coronary artery disease; CHF, chronic heart failure; DBP, dilated blood pressure; ED, endothelial dysfunction; EF, ejection fraction; EH, essential hypertension; ICM, ischaemic cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; NYHA, New York Heart Association; SBP, systolic blood pressure; SV, systolic volume.

tocopherol and ascorbate from their oxidised state [6]. It efficiently protects membrane phospholipids from peroxidation and also mitochondrial DNA and membrane proteins from free-radical-induced oxidative damage. More recently, expression profiling revealed that CoQ10 affects the expression of several hundred genes and may exert many of its effects via the induction of gene transcription [7], and it exerts anti-inflammatory properties via NFκB1-dependent gene expression; therefore it acts as a potent gene regulator [8]. Interest in CoQ10 has increased during recent years, mainly because of its antioxidant function and its use as a dietary supplement. Positive clinical and haemodynamic effects of oral CoQ10 supplementation have been observed in double-blind trials, especially in chronic heart failure, hypertension and endothelial dysfunction.

3. CoQ10 and heart failure (HF)

3.1. Clinical background

Energy metabolism and mitochondrial biogenesis disorders appear to play an important role in cardiac dysfunction and progression to HF. Experimental and clinical studies have suggested an increased production of reactive oxygen species (ROS) in both animals and patients with acute and chronic HF [9]. Mitochondrial function is dramatically altered in failing hearts in dog, rodent and human [10]. Therefore, heart failure is a state of chronic deterioration of oxidative mechanisms due to enhanced oxidative stress and a state of being unable to maintain normal mitochondrial function. The antioxidant properties of CoQ10 and its location within the mitochondria make it an obvious candidate as a therapeutic agent in these situations. Multiple underlying mechanisms are likely to be involved in the antioxidant effects of CoQ10 (Fig. 2).

3.2. Role and possible mechanisms of action of CoQ10 in HF

3.2.1. Improvement of heart bioenergetics

Derangement of cardiac energy substrate metabolism plays a key role in the pathogenesis of HF. CoQ10 plays a pivotal role in the bioenergetics of heart muscle. It is an obligatory and a rate-limiting cofactor in mitochondrial ATP production and is a crucial component of the electron transport chain in the mitochondria where energy is generated as ATP [11].

3.2.2. Antioxidant activity

Oxidative stress has been implicated in most processes thought to have a significant effect on cardiac function. When the local levels of ROS are high, they tend to react with numerous protein centers, DNA, cell membranes, and other molecules, causing considerable cellular damage [12]. The renin–angiotensin–aldosterone system (RAAS) has been shown to play a significant role in the development of myocardial structural and functional abnormalities. In the presence of an increased production of ROS, AngII induces the activation of c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) via apoptosis signal-regulating kinase-1 (ASK-1) [13]. Moreover, increased oxidative stress products and cytokines directly stimulate the growth of myocytes with the subsequent development of hypertrophy [14,15].

Excess interstitial fibrosis and cardiac stiffness are important detrimental aspects of CHF. The increased burden of oxidative stress has also been shown to lead to cardiac perivascular and tissue fibrosis, myocyte hypertrophy and, subsequently, diastolic dysfunction [16].

The reduced form of CoQ10 acts by affecting the initiation process and preventing the formation of lipid peroxyl radicals. Lipid solubility, efficient continuous regeneration and involvement in the initiation and propagation steps of lipid peroxidation can explain why CoQ is considered as a highly efficient antioxidant against radicals produced in biological membranes [17].

Oxidative stress may also be critical in the activation of apoptosis, which is thought to be an important contributor to the progression of HF, especially in its advanced stages. Because of neurohormonal and inflammatory activation with an increase in oxidative stress, cardiac cells could initiate a programmed death with progressive functional tissue decrease. Seven genes that are regulated by CoQ10 are known to participate in the apoptosis processes [18].

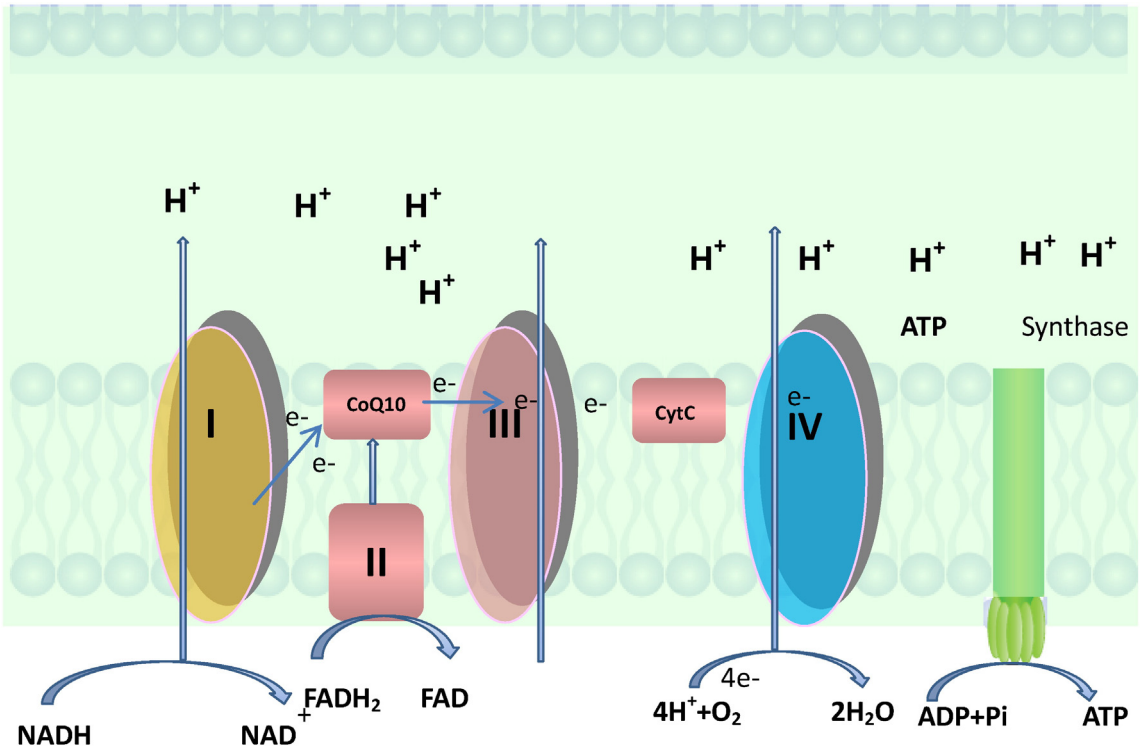

Fig. 1. CoQ10 acts as an electron acceptor at the level of mitochondria. ADP, adenosine diphosphate; Cyt c, cytochrome c; Pi, inorganic phosphate.

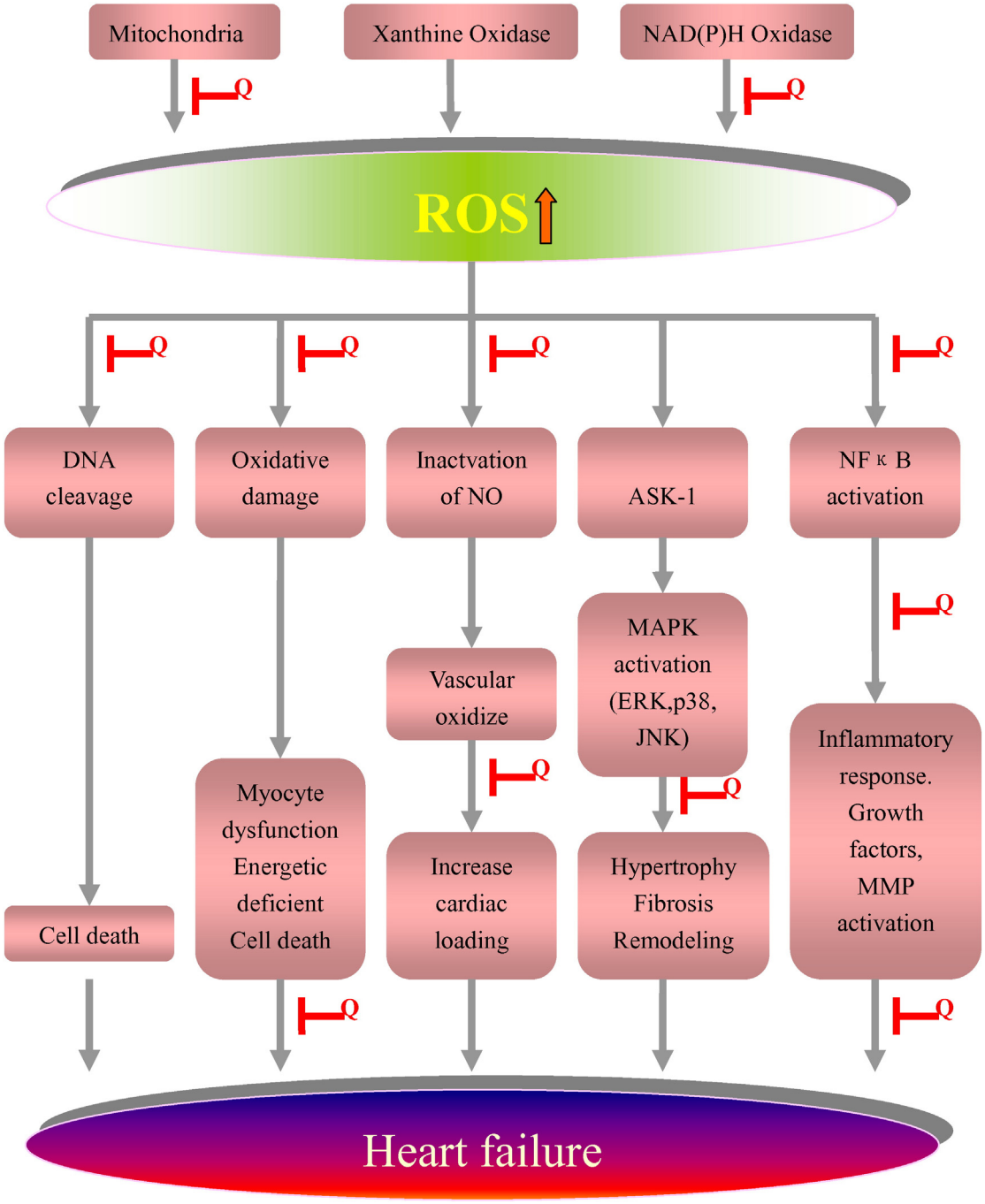

Fig. 2. Main pathophysiological effects of oxidative stress and the role of CoQ10 in heart failure. Co Q10 and its putative sites of action are illustrated in red. ROS, reactive oxygen species; NO, nitric oxide; ASK-1, apoptosis signal-regulating kinase-1; ERK, extracellular-signal regulated kinase; JNK, Jun kinase; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NFκB, nuclear factor κB.

3.2.3. Anti-inflammatory activity

Chronic heart failure is associated with chronic inflammation, as suggested by findings of elevated levels of circulating cytokines, their soluble receptors, and soluble adhesion molecules [12]. Chronically activated inflammatory processes through the activation of different cell types and the secretion of cytokines and chemokines lead to myocardial fibrosis and changes in left ventricular structure and geometry, thus contributing to the development of HF [19]. Recent studies have demonstrated that CoQ10 possesses a considerable anti-inflammatory effect, possibly via down-regulating the level of nitric oxide (NO) [20,21].

3.3. Clinical trials

Pioneering studies on the role of CoQ10 in improving heart function in adult patients with HF were first carried out in Japan in the 1960s [22]. Since then, evidence has been accumulating regarding the use of CoQ10 as an adjunct to conventional therapy in adults with HF. In 1997, Soja and Morensten [23] published a meta-analysis showing that CoQ10 has a well-documented basis as an adjunctive treatment of CHF. Sander et al. [24] concluded from their meta-analysis that there was a significant 3.7% (95% CI 1.59–5.77) net improvement in ejection fraction in patients receiving CoQ10 treatment [24]. However, the largest

controlled CoQ10 trial on chronic congestive heart failure was reported by Morisco et al. [25] in 1993 and was not included in the reported meta-analyses. This study involved a total of 641 patients and the results demonstrate that the addition of CoQ10 to conventional therapy significantly reduces hospitalisations for worsening of HF and the incidence of serious complications in patients with chronic congestive HF.

Two large multi-centre, open-label studies investigated safety and clinical efficacy of CoQ10 adjunctive treatment in CHF [26,27]. These two studies evaluated a total of more than 4000 patients with varying severity of CHF who experienced clinical improvement in signs and symptoms such as cyanosis, oedema, pulmonary rales, dyspnoea, palpitations and subjective arrhythmia. Baggio et al. [27] published the largest open trial in HF involving 2664 patients treated with up to 150 mg of CoQ10 per day, demonstrating a significant benefit and lack of toxicity. One recent randomised placebo-controlled clinical trial conducted by Hosseini [28] also examined the effect of CoQ10 on signs and symptoms and ejection fraction in patients with CHF. They concluded that CoQ10 therapy can be recommended as an adjuvant therapy. The preliminary results of the Q-SYMBIO study were presented at the 7th European Society of Cardiology Meeting, Heart Failure 2013 [29]. The study, a randomised, double-blind, multicentre trial, showed that CoQ10 supplementation with 100 mg three times daily vs. placebo in 420 patients receiving standard therapy improved symptoms and survival.

Although randomised placebo-controlled clinical trials show some benefit for symptoms of HF, there has been no clear effect on cardiac structure or function. Further work will be necessary to determine whether CoQ10 has a therapeutic effect in human HF.

4. CoQ10 and hypertension

4.1. Clinical background

NO and ROS play important roles in blood pressure regulation via the modulation of the autonomic nervous system, particularly in the central nervous system (CNS) [30]. In general, accumulating evidence suggests that NO inhibits, but ROS activates [31], the sympathetic nervous system. An imbalance between NO bioavailability and ROS generation in the CNS activates the sympathetic nervous system and this mechanism is involved in the pathogenesis of neurogenic aspects of hypertension.

4.2. Role of CoQ10

4.2.1. Antioxidant properties

Oxidative stress has an important role in various aspects of hypertension [32] and excessive ROS have emerged as a central common pathway by which disparate influences may induce and exacerbate hypertension [33]. These findings are based, in general, on increased levels of plasma thiobarbituric acid reactive substances and 8-epi-isoprostanes, biomarkers of lipid peroxidation and oxidative stress [34]. Superoxides can oxidise proteins and lipids, or react with endothelium-derived NO to create the reactive nitrogen species peroxynitrite. Peroxynitrite and other reactive nitrogen species can subsequently oxidise proteins, lipids, and critical enzymatic cofactors that may further increase oxidative stress and cause DNA damage. In addition to excess ROS generation, decreased antioxidant defence mechanisms contribute to oxidative stress in patients with hypertension. CoQ10 levels have been shown to be lower in older adults known to have a greater prevalence of hypertension [35]. CoQ10 may reduce mitochondrial superoxide production by increasing the efficiency of electron transfer from Complexes I and II down the mitochondrial electron transport chain [36]. CoQ10 may also exert an antioxidant effect by scavenging free radicals and reducing lipid peroxidation at the level of the plasma membrane [37–39].

4.2.2. Preserving NO

NO plays an important role in the development and progression of arterial hypertension and its complications [40]. ROS generated by oxidatively modified low-density lipoprotein (oxLDL) directly reacts with NO to form peroxynitrite, thus reducing NO availability [6].

CoQ10 attenuates the oxLDL-mediated down-regulation of endothelial nitric oxide synthase (eNOS) and up-regulation of inducible nitric oxide synthase (iNOS). CoQ10 reduces peripheral resistance by preserving NO. In some forms of hypertension, superoxide radicals that inactivate NO are overproduced; CoQ10, with its antioxidant effects, may prevent the inactivation of NO by these free radicals [41].

4.2.3. Boosting the production of the prostaglandin prostacyclin

CoQ10 may boost the production of the prostaglandin prostacyclin (PGI_2), a potent vasodilator, or it may enhance the sensitivity of arterial smooth muscle to PGI_2 [42].

4.3. Clinical trials

A number of trials provide clinical evidence that some patients with high blood pressure may benefit from CoQ10 supplementation. Burke et al. [43] found that CoQ10 decreased systolic blood pressure after 12 weeks of treatment in a randomised, double-blind, placebo-controlled trial. A non-Cochrane review [44] concluded that CoQ10 has the potential in hypertensive patients to lower systolic blood pressure by up to 17 mm Hg and diastolic blood pressure by up to 10 mm Hg without significant side effects. One recent systematic review [45] concluded that CoQ10 is a remarkably effective antihypertensive agent with a mean blood pressure lowering capacity of 11/7 mm Hg. However, in patients with ischaemic left ventricular systolic dysfunction or with type 2 diabetes mellitus, whose blood pressure was normal, supplementation of CoQ10 did not alter blood pressure [46–48]. A recent double-blind, randomised controlled study demonstrated that oral administration of CoQ10 did not significantly affect the blood pressure of obese subjects [49].

As an alternative to drug therapy, it is desirable to use CoQ10 as an adjunct or alternative anti-hypertensive to conventional agents such as diuretics and ACE inhibitors in the treatment of hypertension. It should be noted, however, that in healthy animals or humans, CoQ10 has no direct vasodilatory or hypotensive effect. This suggests that the hypotensive effect of CoQ10 is specific to the state of enhanced oxidative stress occurring in hypertensive patients.

5. CoQ10 and endothelial dysfunction

5.1. Clinical background

Endothelial dysfunction refers to different alterations in endothelial phenotype and can be regarded as a syndrome that exhibits systemic manifestations associated with significant morbidity and mortality. The reduced endothelial availability of NO, in part due to increased vascular oxidant stress, has been shown to promote a pro-inflammatory and prothrombotic phenotype of the endothelium [50,51].

CoQ10 may reduce the rate of inactivation of NO and may also affect vascular function indirectly via inhibition of oxidative damage to LDL [52]. Recently, CoQ10 has also been shown to improve endothelial function in patients with coronary artery disease [53], heart failure [54], and diabetes mellitus [48].

5.2. Role and possible mechanisms of action of CoQ10

Oxidative stress plays a critical role in the pathogenesis of endothelial dysfunction [55]. Circulating oxLDL is consistently associated with the pro-inflammatory cytokine tumour necrosis factor-α and CRP. Considerable evidence indicates that oxLDL-induced endothelial dysfunction is associated with down-regulation of eNOS and up-regulation of iNOS. Another reliable marker for the assessment of oxidative DNA damage and vascular oxidative stress is 8-OHdG. NADPH oxidase-derived superoxide reacts with NO to form peroxynitrite, which decreases active NO

and damages endothelial cells, leading to attenuation of endothelium dependent relaxation [56]. The antioxidant activity confers protection against lipid peroxidation and lipid membrane damage.

Endothelial dysfunction is also considered to be a chronic inflammation status. The level of TNF-α and the changed levels of TNF-α and IL-6 were significantly decreased after coenzyme Q10 supplementation The level of coenzyme Q10 was significantly negatively correlated with inflammatory markers (TNF-α and IL-6) [57]. Schmelzer et al. [8,58] demonstrated that coenzyme Q10 could exert anti-inflammation effects via the reduction of nuclear factor-κB (NF-κB) dependent gene expression.

CoQ10 can help prevent the development of endothelial dysfunction by preventing oxidative and inflammation and nitrative stress.

5.3. Clinical trials

There is increasing evidence that CoQ10 supplementation improves endothelial function. One prospective study indicated a positive effect of CoQ10 supplementation on human endothelial dysfunction, which appears to be independent of lipid lowering [59]. In a double-blind crossover study, CoQ10 supplementation demonstrated a benefit on endothelial function in type 2 diabetic patients [48]. Watts et al. [60] randomly assigned 40 patients to receive 200 mg of CoQ10 or placebo daily for 12 weeks. After 12 weeks of therapy, flow-mediated dilation (FMD) increased by 1.6% with CoQ10 and decreased by −0.4% with placebo. Dai et al. [61] performed a randomised, double-blind, placebo-controlled trial and concluded that CoQ10 supplementation improves mitochondrial function and brachial FMD in patients with ischaemic left ventricular systolic dysfunction. However, Raitakari et al. [62] concluded that dietary supplementation with CoQ10 had no significant effect on arterial endothelial function in patients with moderate hypercholesterolemia.

6. Conclusions

CoQ10 deficiency has been observed in patients with congestive heart failure, angina pectoris, coronary artery disease, cardiomyopathy, and hypertension. The clinical benefits of CoQ10 supplementation in prevention and treatment of cardiovascular diseases have been observed in many trials. CoQ10 may be recommended to patients at risk for or diagnosed with cardiovascular disease as an adjunct to conventional treatment. Hopefully this article will contribute to the scientific knowledge base for complementary adjuncts in the practice of cardiovascular nursing.

Conflict of interest statement

The authors have no conflict of interest with respect to this work.

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