



REVIEW ARTICLE

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Mitochondrial dysfunction in obesity: potential benefit and mechanism of Co-enzyme Q10 supplementation in metabolic syndrome

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Abstract

Co-enzyme Q10 (Co-Q10) is an essential component of the mitochondrial electron transport chain. Most cells are sensitive to co-enzyme Q10 (Co-Q10) deficiency. This deficiency has been implicated in several clinical disorders such as heart failure, hypertension, Parkinson's disease and obesity. The lipid lowering drug statin inhibits conversion of HMG-CoA to mevalonate and lowers plasma Co-Q10 concentrations. However, supplementation with Co-Q10 improves the pathophysiological condition of statin therapy. Recent evidence suggests that Co-Q10 supplementation may be useful for the treatment of obesity, oxidative stress and the inflammatory process in metabolic syndrome. The anti-inflammatory response and lipid metabolizing effect of Co-Q10 is probably mediated by transcriptional regulation of inflammation and lipid metabolism. This paper reviews the evidence showing beneficial role of Co-Q10 supplementation and its potential mechanism of action on contributing factors of metabolic and cardiovascular complications.

Keywords: Metabolic syndrome, Co-enzyme Q10, Obesity, Inflammation, Oxidative stress

Introduction

Metabolic syndrome is a cluster of disease symptoms such as dyslipidemia, hyperglycemia and insulin resistance, hypertension and visceral obesity [1]. Oxidative stress and inflammation are pivotal in all stages of atherosclerosis, hypertension, and non-alcoholic fatty liver and in subjects with metabolic syndrome [2,3]. Mitochondrial dysfunction plays a crucial role in the development of diabetes and metabolic disorder [4]. Both, animal and clinical studies revealed that the sources of free radicals would be from mitochondrial origin [4]. The mitochondrial electron transport chain is the generator of free radicals mainly singlet oxygen ($O^{\cdot-}$) while producing the ATP from the substrate molecule. Free radicals may react with other important molecules within cells and enhance lipid peroxidation, oxidize proteins and damage DNA and are thus responsible for oxidative stress [2]. Inflammatory responses are also responsible for most of the organ dysfunction in metabolic disorder. Increased concentration

and expression of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) are evident in adipocyte dysfunction and insulin resistance in obesity and metabolic syndrome [5]. Furthermore, inflammatory cells infiltration are also increased in adipose tissues which is responsible for adipocyte dysfunction [6]. Inflammation in adipose tissues could be a causative factor diminishing mitochondrial biogenesis and energy homeostasis [7-9]. Therefore, supplementation with a dietary antioxidant having anti-inflammatory properties would be beneficial which can scavenge free radicals and restores antioxidant defence as well as suppresses inflammatory responses. Co-enzyme Q10 (Co-Q10), an integral part of the mitochondrial electron transport chain which transports electrons and acts as a natural antioxidant (Figure 1). Co-Q10 can also be found in much of the human diet. Beneficial effects of Co-Q10 supplementation have been noted for most of the symptoms of metabolic syndrome, e.g. hypertension, diabetes, liver diseases, insulin resistance and obesity. This review will thus, focus on the effect of Co-Q10 on various component of metabolic syndrome and elucidate its potential mechanism of action.

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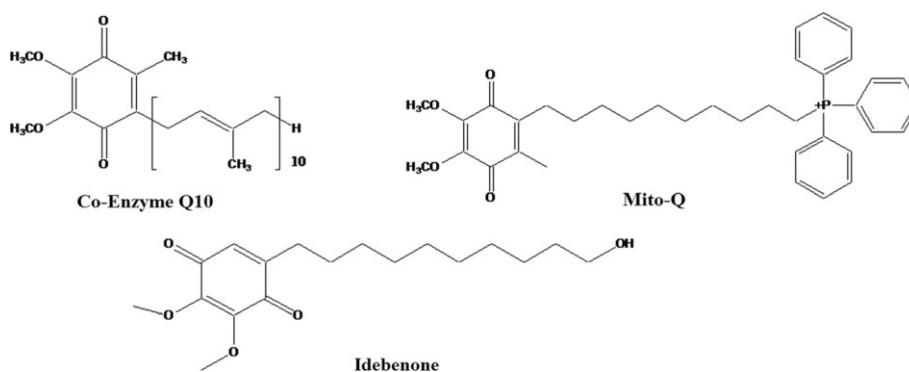


Figure 1 Schematic diagram of Co-Q10, Mito-Q and Idebenone.

Origin, chemistry and absorption of Co-Q10

Chemically Co-Q10 is a quinone molecule found almost in all cells of the body, hence the term ubiquinones [10]. It exists in nature and in the body, ubiquinones, the oxidized form and ubiquinol, the reduced form. Co-Q10 serves as an essential carrier for the electron transfer in the mitochondrial respiratory chain for the synthesis of ATP. Co-Q10 was first isolated in 1957 from beef mitochondria [10]. Folkers et al. revealed the chemical structure of Co-Q10 in 1958 [11]. Meat, poultry and fish are the richest sources of Co-Q10, and the daily intake of these foods provides between 3 to 5 mg of Co-Q10 [12,13]. The absorption of Co-Q10 from the diet occurs mainly in the small intestine and is better absorbed in presence of lipid rich foods [14]. Co-Q10 is then transported to the liver and form lipoprotein complex and deposited in tissues [14]. Tissues with high-energy requirements and metabolic rates such as the heart and the skeletal muscle contain relatively high concentrations of Co-Q10 [15]. About 95% of Co-Q10 in human circulatory system exists in its reduced form as ubiquinol [16]. The safety of high doses of orally-ingested Co-Q10 over long periods is well documented in human [17] and also in animals [18]. Co-Q10 dosages generally range from 100 to 200 mg a day for patients suffering cardiovascular disease [19].

Mitochondrial biogenesis and Co-Q10

Mitochondrial biogenesis means the increased number and function of mitochondria due to the response of increased cellular energy demand and thereby increased ATP production. Generally, mitochondrial electron transport chain consists of several protein complexes, namely, complex I, complex II, complex III and complex IV etc. [20]. NADH which donates electrons to complex I and FADH₂ feed the electron to complex II. Glucose oxidation through glycolysis and pyruvate dehydrogenase to acetyl

CoA generates NADH. In contrast, fatty acid oxidation to acetyl-CoA generates FADH₂ through the process of β -oxidation. Acetyl CoA from both sources feeds the TCA cycle. Electrons coming from NADH and FADH₂ are thus transported via reduced Co-Q10 to Complex III [20]. The proton gradient is generated as a consequence of this sequential process, drives complex V or the ATPase to produce ATP. ATP is thus transported via ANP to its target site. In presence of uncoupling agent, the proton motive force will divert to UCPs and a proton leak occurs. Thus the energy will expend as heat without producing any ATP. Complex I and complex III are the primary sources of O₂ free radicals due to incomplete reduction of the oxygen molecule. The Mitochondrial environment maintains a highly protective defence against this free radical. In normal physiological conditions these free radicals are scavenged by superoxide dismutase of mitochondrial origin and later by catalase in cytosol. Diabetic hyperglycemia and metabolic disorder are responsible for the inactivity of these antioxidant enzyme systems and decreased mitochondrial function. Several evidences suggest that, inhibition of the mitochondrial electron transport chain activity may increase lipid accumulation in adipocyte [21,22].

Mitochondrial biogenesis can be modulated by several transcriptional regulators present in the cell. Peroxisome proliferator activated receptor (PPAR) family is such a regulator of mitochondrial biogenesis [23]. Three types of PPAR proteins have been identified so far, PPAR- α , PPAR- γ and PPAR- δ [24]. PPARs activation is also important for lipid metabolism, adipocyte differentiation and the prevention of inflammation [24]. Moreover, PPARs also regulate mitochondrial biogenesis via an activator called peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-1 α) [25,26]. PGC-1 α is physiologically regulated by exercise [27,28] and calorie restriction [29]. Apart from these exercise and calorie

restriction means, pharmacological agents such as fenofibrates [30] and resveratrol [31] stimulate PGC-1 α and restore mitochondrial function. Co-Q10 mediated activation of PPARs are revealed only recently which would be a possible mechanism of energy homeostasis in failing tissues and obesity [32].

Metabolic disorder due to Co-Q10 deficiency

Ogashara et al. described the first patients (two sisters) with primary Co-Q10 deficiency in 1989 [33]. They had progressive muscle weakness, abnormal fatigue, and central nervous system dysfunction from early childhood characterized by a low Co-Q10 concentration in their muscles. Both patients improved remarkably with oral Co-Q10 [33]. Maintaining adequate Co-Q10 level throughout the body is important for normal function and health. Plasma concentrations of Co-Q10 are high in healthy infant and children and declining with age [34,35]. Metabolic disorder may arise due to Co-Q10 deficiency. Growing bodies of evidences indicate that oxidative stress plays a critical role in the pathogenesis of type 2 diabetes mellitus and its complications [36]. Low plasma Co-Q10 concentrations were found in patients with poor glycaemic control and diabetic complications [37-40].

HMG-CoA reductase inhibitors (statins) reduce Co-Q10 levels in human [41,42]. Alternatively, supplementation with oral Co-Q10 can restore plasma Co-Q10 levels in patients receiving statin therapy [41-43]. Statin mediated Co-Q10 depletion affects muscle function. Patients taking statin to reduce plasma lipids suffered myalgia and myopathic pain [44-46]. Myocardial depletion of Co-Q10 has also been demonstrated in heart failure patients with cardiomyopathy which was improved by Co-Q10 therapy [47]. An important factor contributing to statin related myopathy may be a genetic susceptibility to muscle disorders and underlying metabolic mechanisms [48,49]. Due to the statin therapy, genomic variation has been found in *COQ2* gene which encoding para-hydroxybenzoate-polyprenyl transferase for CoQ10 biosynthesis [48]. Another report suggests that statins may affect energy metabolism (Carnitine palmitoyl-transferase II deficiency) combined with a genetic susceptibility triggering myopathic outcomes in certain high-risk patients [49].

Antioxidant effect of Co-Q10

Benzoquinone group of Co-Q10 is able to accept and donate electrons which is a critical feature for an antioxidant [14]. It scavenges free radicals and inhibits lipid and protein peroxidation. Vitamin E and Co-Q10 prevents lipid peroxidation at nearly the same rate [50]. However, Co-Q10 prevents LDL oxidation more efficiently than α -tocopherol, lycopene, or β -carotene [51]. Co-Q10 also enhances the availability of other

antioxidants such as vitamin C, vitamin E and beta-carotene [52]. Direct elimination of free radical such as lipid peroxy, peroxy and/or alkoxy radicals *in vitro* and *in vivo* as a consequence of Co-Q10 supplementation was reported by several investigators [53,54]. Co-Q10 may also serve as an antioxidant by acting as a cofactor and activator of mitochondrial uncoupling proteins, leading to a reduction in free radical generation *in vivo* [55]. H₂O₂-induced DNA strand breaks in lymphocytes are protected by ubiquinol-10 [56]. In another study, *in vivo* supplementation with Co-Q10 was shown to enhance the recovery of human lymphocytes from oxidative DNA damage [57]. Improved cellular antioxidant enzyme activity was also noted for Co-Q10 supplementation. Co-Q10 treatment increased antioxidant enzyme activity of superoxide dismutase, catalase, and glutathione in the liver homogenates of diabetic rats followed by reduced lipid peroxidation [58]. Antioxidant enzyme, catalase activity and GSH concentration were also improved in liver of acetaminophen induced rats [59]. A recent clinical study also showed that Co-Q10 supplementation at a dose of 150 mg decreased oxidative stress and improved antioxidant enzyme activity in patients with coronary artery disease [60].

Effect of Co-Q10 on inflammation and metabolic syndrome

Inflammation is a response to tissue or organ damage from exogenous and endogenous factors and assists in the restoration of impaired homeostasis. Several inflammatory cytokine are also generated e.g. interleukin-1 (IL-1), interleukin-6 (IL 6), tumour necrosis factor- α (TNF- α) etc. which have both systemic and local effect. Local effects are associated with increased expression of adhesion cell molecules such as intracellular adhesion molecule-1 (ICAM-1), selectins and heat-shock proteins [61]. Macrophage infiltration and fibroblast activation are two inflammatory responses develop chronically in inflamed adipose tissues [6,62]. Systemic chronic inflammatory response is also considered to be a mediator of metabolic syndrome and insulin resistance [62,63]. Pro-inflammatory cytokines and oxidative stress have been shown to be responsible for developing metabolic disturbances, such as insulin resistance and activation of immune response in liver, adipose tissue and in muscle [64-66]. Moreover, activation of inflammatory pathways in hepatocytes is sufficient to cause both local as well as systemic insulin resistance [67,68]. Recent studies have confirmed positive association between obesity indices and inflammatory markers, mainly c-reactive protein (CRP) and other inflammatory cytokines [69-71]. Evidence is also starting to accumulate that inflammatory cytokines are over expressed in adipose tissues of obese rodent models and obese humans [72-75]. Some other studies suggest that systemic administration of the TNF- α also induces insulin resistance in experimental animal [76,77]. In recent years, several inflammatory

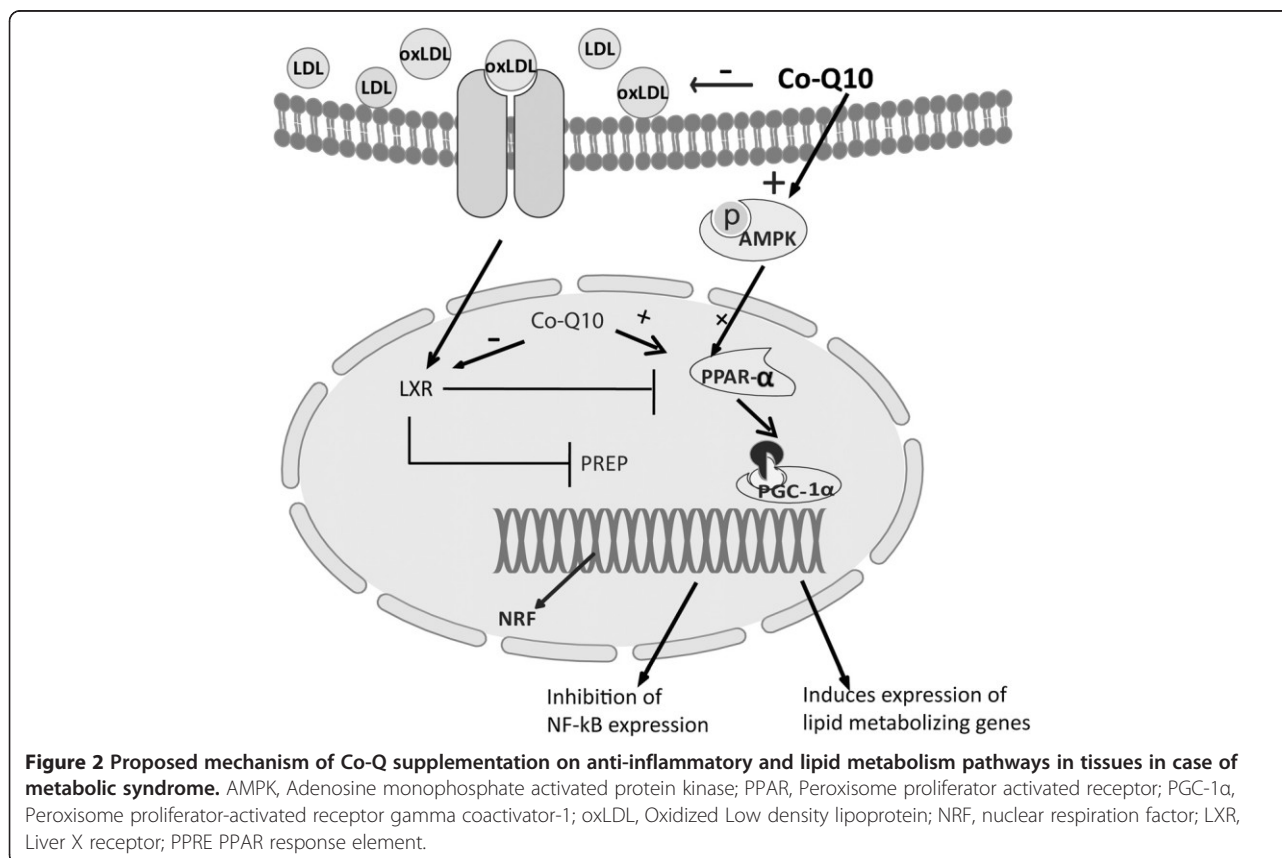
signal mechanisms have been described such as c-JUN kinase (JNK) pathways, protein kinase-C (PKC) and I κ B kinase (IKK) mediated nuclear factor- κ B (NF- κ B) pathways and suppressor of cytokine signaling (SOCS) family mediated pathways [63]. Furthermore, PKC and IKK can be activated by increased fatty acid level in cells [63].

Low density lipoprotein (LDL) cholesterol oxidation is the key regulator for developing inflammation in endothelial cells and other tissues [78]. The LDL receptor plays a vital role in increasing uptake of cholesterol from plasma to cell and increasing clearance of apoB and apoE-containing lipoproteins [79]. In diabetes and obesity, LDL-R populations decrease and increase LDL level in plasma [80]. LDLR $^{-/-}$ mice showed an increased plasma lipid profile and an increase in inflammatory markers in response to high fat diet [79,81,82]. The anti-atherogenic effect of PPAR γ agonist was seen in LDLR $^{-/-}$ male mice which is correlated with improved insulin sensitivity and decreased tissue expression of TNF- α and gelatinase B [83]. However, peroxisome proliferator activated receptor- γ (PPAR- γ) is reported to attenuate inflammation in activated macrophages by interfering with NF- κ B signalling [84]. PPAR- α is another analogue of the PPAR family also regulates anti-inflammatory genes (Figure 2) [85].

The anti-inflammatory activity of Co-Q10 is well documented. Stimulation of cells with LPS resulted in a distinct release of TNF- α , macrophage inflammatory protein-1 alpha (MIP-1 α) and monocyte chemo attractant protein-1 (MCP-1) which were significantly attenuated by pre-incubation of cells with the reduced form of Co-Q10 [86,87]. Treatment with CoQ10 also reduced the elevated plasma lipid profiles and decreased mRNA expression of the pro-inflammatory cytokine TNF- α in adipose tissues of *ob/ob* mice [88]. CoQ10 supplementation also improved the inflammatory state in liver of high fat fructose diet fed rats [89]. Recent evidence suggests that Co-Q10 can serve as an agonist of PPARs and activates the PPAR mediated anti-inflammatory response (Figure 2) [90,91].

Effect of Co-Q10 on endothelial dysfunction and hypertension

Endothelial dysfunction and hypertension are common in metabolic syndrome. Increased glucose intolerance and oxidative stress plays a critical role in the development of endothelial dysfunction in aortas of diabetic rats [36]. Co-Q10 supplementation improved the endothelial dysfunction in the mesenteric arteries in high fat diet fed SHRsp rats [92]. Inflammatory cell infiltration may be a potential



mediator of inflammation and endothelial dysfunction in aortas. Co-Q10 prevented the lymphocytic infiltration in perivascular area of aortas from fructose fed rats [93]. Co-Q10 also improved endothelial dysfunction in statin-treated type II diabetic patients [94]. Considerable evidence indicates that oxLDL-induced endothelial dysfunction is associated with down-regulation of eNOS and up-regulation of inducible nitric oxide synthase (iNOS). A recent study showed that Co-Q10 prevented apoptosis in human umbilical vein endothelial cells (HUVEC) due to oxLDL by preventing the NF- κ B mediated caspase-3 activation [95]. Co-Q10 also attenuated the oxLDL-mediated down-regulation of endothelial nitric oxide synthase (eNOS) and up-regulation of inducible nitric oxide synthase (iNOS) [95]. oxLDL induced inflammatory process and expression of adhesion molecules, release of pro-inflammatory cytokines and the adherence of monocyte were also attenuated by CoQ10 in THP-1 cells [95]. Extracellular superoxide dismutase (ecSOD) activity and endothelium-dependent vasodilatation were also improved remarkably after CoQ10 supplementation which alters local vascular oxidative stress [96].

The antihypertensive effect of Co-Q10 is also well documented in animal and human studies. Co-Q10 supplementation reduced hypertension and cardiac hypertrophy in DOCA-salt hypertensive rats [97,98]. The Co-Q10 analogue decylubiquinone (10 mg/kg) reduced the systolic blood pressure, plasma malondialdehyde, total cholesterol and LDL-cholesterol in the SHRsp rats [99]. A recent meta-analysis of clinical trials investigating the use of Co-Q10 for treatment of hypertension considered 12 trials since 1975 and found beneficial effect of Co-Q10 supplementation [100]. Among these trials, four were prospective randomized trials and eight trials considering the effect of Co-Q10 on final blood pressure compared with previous level [100]. Co-Q10 supplementation has shown to be effective in lowering blood pressure in diabetes, improves the glycaemia control in metabolic syndrome; however, a recent study showed that Co-Q10 treatment failed to reduce blood pressure in patients with uncontrolled hypertension [101]. Another study suggests that treatment with Co-Q10 (50 mg twice a day for ten weeks) in patients with essential hypertension reduced hypertension without affecting the plasma renin activity, serum and urinary sodium and potassium, and urinary aldosterone [102]. These results suggest that treatment with Co-Q10 decreases blood pressure in patients with essential hypertension, possibly because of a reduction in peripheral resistance [102]. However, the exact mechanism is not known, but one theory proposed that it reduces peripheral resistance by preserving nitric oxide bioavailability [103]. Alternatively, coenzyme Q10 may increase the synthesis and sensitivity of prostacyclin (PGI₂), a potent vasodilator and inhibitor of platelet

aggregation, to arterial smooth muscle and does relaxation to arteries [104].

Effect of Co-Q10 on cardiac dysfunction

Clinically, Co-Q10 has potential for the prevention and treatment of cardiovascular diseases such as myocardial infarction, congestive heart failure and other drug-induced/disease induced cardiomyopathies [105]. The heart is highly sensitive to Co-Q10 deficiency. Defective levels of specific oxidative phosphorylation/respiratory enzyme activities and reduced energy reserve in heart failure may be considered as contributing factors for the progression of disease [106]. Low levels of Co-Q10 concentration were found in 70–75% of patients with aortic stenosis or insufficiency, mitral stenosis or insufficiency, diabetic cardiomyopathy, atrial septal defects and ventricular septal defects [107]. Circulating levels of Co-Q10 were also significantly lower in patients with ischemic heart disease and in patients with dilated cardiomyopathy as compared to healthy controls [108]. Pepe et al. have reviewed the meta analysis of clinical trials of Co-Q10 in heart failure, reporting that cardiac output, cardiac index and stroke volumes were improved with the treatment of Co-Q10 [103]. Diastolic dysfunction is one of the earliest identifiable signs of myocardial failure due to severe thickening of the left ventricles, which accounts for 30-49% of heart failure cases. Patients treated with 200 mg/day of Co-Q10 improved interventricular septal thickness significantly with improved symptoms of fatigue and dyspnea with no side effects noted [109]. Studies on isolated rat's heart also demonstrated a protective effect of Co-Q10 against ischemia and reperfusion injuries [110,111]. Pre-treatment with Co-Q10 improved recovery of cardiac function, aerobic efficiency and enzyme levels in young healthy rats compared to untreated controls undergone experimentally induced ischemia-reperfusion in heart [112]. In an another study, mice pre-treated with Co-Q10 for 4 days prior to toxic doses of adriamycin, survival rates were significantly higher (80%) compared to the mice not received the supplements (40%) [113]. This Co-Q10 mediated protection against adriamycin induced cardiac toxicities is probably due to the inhibition of lipid peroxidation and induction antioxidant enzymes in cardiac tissue [114].

Effect of Co-Q10 on diabetes and insulin resistance

Coenzyme Q concentrations appear to be reduced in diabetic states. Diabetic animals showed decreased Co-Q10 concentration in heart, liver and skeletal muscle [115]. Evidence also exists for reduced Co-Q in plasma of humans with diabetes. Lower plasma levels of CoQH₂ have been found in diabetic patients than healthy subjects [37,116]. Supplementation with Co-Q10 would be beneficial for diabetes and insulin resistance. Co-Q10 supplementation (10 mg/kg) improved the elevated

glucose concentration and glucose intolerance in STZ induced diabetic rats without affecting the insulin concentration [58]. However, 200 mg of Co-Q10 daily for 6 months did not improve glycemic control or serum lipid levels of Type-2 diabetics [117]. In another randomized double-blind, placebo-controlled study, Co-Q10 supplementation at a dose 100 mg for three months failed to improve HbA1c, mean daily blood glucose concentrations, mean insulin dose, number of hypoglycemic episodes or cholesterol concentrations compared to the placebo group [118]. Improved glycemic control due to Co-Q10 supplementation could be a protective action against pancreatic beta cell destruction in diabetes. Co-Q10 supplementation did not reduce the pancreatic damage, inflammation and beta cell loss in diabetic rats but decrease glycated HbA1c and pancreatic lipid peroxidation [119]. Further researches are required to evaluate the hypoglycaemic action of Co-Q10 supplementation.

Liver steatosis and effect of Co-Q10 on hepatic dysfunction

Oxidative stress and inflammatory responses are responsible for hepatic damage and fibrosis. The liver X receptors (LXR) constitute a class of nuclear receptors activated by oxidized lipids (Figure 2). Activation of LXR in macrophages induces expression of several genes involved in lipid metabolism and reverse cholesterol transport [120]. Activation of these transcription factors inhibits inflammatory gene expression in macrophages and adipocytes, largely through PPAR- γ mediated suppression of NF- κ B signalling [121,122]. LXR also plays an important role in lipid and cholesterol metabolism. LXR α knockout mice develop enlarged fatty livers, degeneration of liver cells, high cholesterol levels in liver, and impaired liver function when fed a high-cholesterol diet [123]. Generally, oxidized LDL serves as an agonist of LXR and modulates PPAR binding to DNA sequence elements termed peroxisome proliferator response elements (PPRE) [124]. Thus, antioxidants such as Co-Q10 may prevent LDL oxidation and serve as an LXR antagonist. Recent report showed that reduced form of Co-Q10 downregulated genes involved in cholesterol biosynthesis (HMGCS1, HMGCL and HMGCR) which are also deactivated by transcriptional regulators PPAR α and LXR/RXR complex in liver of SAMP1 mice [125]. However, oxidized form of Co-Q10 did not alter the genes expression of HMGCS1, HMGCL and HMGCR [91,125]. A recent report also suggests that LXRs influence CoQ synthesis without directly regulating the process and CO-Q10 concentration was found to be decreased in liver of LXR- α knockout mice and LXR double knockout mice [126].

A high fat diet and fructose feeding can also cause dyslipidemia and hepatic steatosis. Co-Q10 supplementation increases life-span of rats fed a diet enriched with

polyunsaturated fatty acids [127,128]. High fat diet induced hepatic oxidative stress in rats was improved by supplementation with Co-Q10 followed by the improvement of the plasma lipid profile [89]. The lipid lowering effect of Co-Q10 supplementation was also seen in fructose fed rats [93]. A Co-Q10 analogue, Q monomethyl ether, also showed beneficial effect on progressive non-alcoholic fatty liver (NAFL) in rats fed a high fat diet and improved liver architecture by preventing the fat droplet accumulation in hepatocytes [129]. Increased fatty acid beta oxidation would be the potential mechanism of improving lipid profile in metabolic syndrome. Scanty literature was found on any effect of Co-Q10 on mitochondrial fatty acid beta oxidation. However, up regulation of the beta oxidation gene was observed in animal treated with ubiquinol [90]. Recent evidence suggests that this up-regulation of fatty acid oxidation is probably involved PPAR mediated pathways [90]. It is now evident that ubiquinol, a reduced form of Co-Q10, may be an activator of PPAR gene expression and activated a series of lipid metabolizing gene family in mice [90,91]. Alternatively, ubiquinol downregulated a series of genes involved in cholesterol and fatty acid synthesis such as HMGCS1, HMGCL and HMGCR [91]. These genes are also negatively regulated by PPAR mediated pathways.

Co-Q10 supplementation also showed hepatic protection in other model of hepatic dysfunction. Co-Q10 treatment showed hepatic protection against acetaminophen induced liver toxicities in rats [59]. Co-enzyme Q10 treatment improved extensive centrilobular necrosis, cytoplasmic vacuolization and ballooning degeneration of hepatocytes with congested sinusoids in liver of rats [59]. Hepatic protection in these rats depends on the blocking NF- κ B mediated inflammatory signal pathways and inactivation of caspase activity [59]. Co-Q10 supplementation is also effective in preventing the toxin induced hepatic damage [130]. Co-Q10 supplementation in diet also showed hepatic protection in aged rats due to enhanced cellular antioxidant action [131].

Effect of Co-Q10 on obesity and fat metabolism

Generally, obese individuals showed a reduction of fat metabolism and increased fat deposition in the body. Increased fat deposition is responsible for the hyperglycemia, insulin resistance, dyslipidemia and hypertension, most of the common features of metabolic syndrome [132]. Mitochondrial dysfunction and reduced Co-Q10 concentration was found in obese individual [133]. Adipocyte differentiation and fat deposition into adipocytes play important roles in obesity. Co-Q10 prevents adipogenesis in rosiglitazone induced adipogenesis in ob/ob mice [88]. Anti-adipogenic activity of Co-Q10 was also shown in 3 T3-F442A cell line. Inhibition of Co-Q10 synthesis strongly triggered adipocyte differentiation while increment

Table 1 Effect of Co-Q10 supplementation on lipid metabolism in metabolic syndrome

Parameter	Model and dose	Effect and potential mechanism	Reference
Lipid metabolism	3 T3-L1 pre-adipocytes	-Increases fatty acid beta oxidation. - ↑ Ca ⁺⁺ Influx; ↑AMPK; ↑PPAR-α. -Prevents adipocytes differentiation	[32]
	Fructose fed rat	-↓Total cholesterol; ↓LDL-Cholesterol; ↓triglycerides	[93]
	ob/ob mice	- ↓ Total cholesterol; ↓triglycerides; ↓NEFA	[88]
	C57BL6J mice	- ↓ mRNA expression of the lipogenic enzymes such as fatty acid synthase (FAS) and acetyl-CoA carboxylase 1 (ACC1). - Increases fatty acid beta oxidation	[90]

of Co-Q 10 synthesis strongly inhibited adipocyte differentiation [134]. Co-Q10 treatment increases fat oxidation and energy expenditure in inguinal white adipose tissue. Decreased mRNA expression of the lipogenic enzymes fatty acid synthase (FAS) and acetyl-CoA carboxylase 1 (ACC1), and the glycerogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) are responsible for the lipid lowering effect of Co-Q10 [88]. In this study, mRNA expression of proteins involved in mitochondrial biogenesis (peroxisome proliferator-activated receptor-γ coactivator-1 (PGC-1)), oxidative phosphorylation system (OXPHOS) system (cytochrome oxidase subunit IV (COIV)), fatty acid transport into mitochondria (carnitine-palmitoyl transferase 1, muscle isoform (M-CPT1)) and energy expenditure (uncoupling protein-1 (UCP1)) were also increased to promote the fatty acid utilization in high fat diet fed mice [88]. AMPK regulates the expression of lipogenic genes, including fatty acid synthesis (FAS) [135]. Co-Q10 increased the AMPK phosphorylation in 3 T3-L1preadipocytes probably by increasing the cytoplasmic calcium concentrations followed by increased Ca²⁺/calmodulin-dependent protein kinase kinase (CaMKK). Moreover, Co-Q10 increased fatty acid oxidation in 3 T3-L1preadipocytes and increased PPARα in protein and mRNA level [32]. This AMPK-mediated PPARα induction at least in part causes suppression of adipocyte differentiation [32].

Future perspectives and conclusion

Co-Q10 has proven potential as an antioxidant molecule with anti-inflammatory properties. Recent evidence also suggests that Co-Q10 may serve as AMPK and PPARs activators and increases the fat burning capacity of cells (Table 1). Its use is still limited due to poor water solubility and lipophilic nature. Several analogues have so far been synthesized such as mito-Q and idebenone.

Mito-Q10 comprises a lipophilic triphenylphosphonium cation covalently attached to an ubiquinol antioxidant [136]. The lipophilic triphenylphosphonium cation helps this molecule to easily cross the lipid bilayer, be orally bioavailable and accumulate in mitochondria several hundred fold compared with Co-Q10 itself [136]. MitoQ10 has been

shown to be effective against mitochondrial oxidative damage *in vivo* and in rodent models of sepsis and reperfusion injury of heart [137,138]. Administration of MitoQ10 also protects against the development of hypertension, improves endothelial function, and reduces cardiac hypertrophy in young stroke-prone spontaneously hypertensive rats [139]. MitoQ, was shown to completely prevent mitochondrial abnormalities as well as cardiac dysfunction characterized by a diastolic dysfunction [140]. Recent evidence suggests that Mito-Q is effective against ethanol induced micro and macro hepatic steatosis in rats [141]. Metabolic dysfunctions were also improved in mice treated with Mito-Q. Mito-Q supplementation reduced the fat mass and plasma lipid profile in ApoE^{-/-} mice [142]. MitoQ supplementation also improved hyperglycemia, hepatic steatosis and decreased DNA oxidative damage (8-oxo-G) in multiple organs of ApoE^{-/-} mice [142]. Idebenone, a benzoquinone carrying exactly the same quinone moiety as Co-Q0, Co-Q1 and Co-Q10, shows multiple activities *in vitro* and *in vivo*. Idebenone is quickly absorbed and is well tolerated and safe given as single or repeated daily doses [143]. Like Co-Q10, idebenone also prevents lipid peroxidation and ROS production *in vivo* [144-146]. However, to date, no more literature has been found with an idebenone effect on diabetes and metabolic syndrome. In view of the above discussion, Co-Q10 supplementation has proven its efficacy and benefit to treat metabolic syndrome and obesity. Further research is warranted to get benefit in a clinical setup.

Abbreviations

AMPK: Adenosine monophosphate activated protein kinase; ATP: Adenosine triphosphate; CAT: Catalase; ERK: Extracellular receptor kinase; GPx: Glutathione peroxidase; GST: Glutathione S-transferase; HUVEC: Human umbilical vein endothelial cell; IL-6: Interleukin 6; IRS: Insulin receptor substrate; LDL: Low density lipoprotein; LXR: Liver X receptor; MAPK: Mitogen activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; mtTFA: Mitochondrial transcription factor A; NO: Nitric oxide; NRF: Nuclear respiration factor; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator-1α; PPAR: Peroxisome proliferator activated receptor; PPRE: PPAR response element; ROS: Reactive oxygen substrate; SOD: Superoxide dismutase; STZ: Streptozotocine; TNF: Tumour necrosis factor; VSMC: Vascular smooth

muscle cell; oxLDL: Oxidized low density lipoprotein; VCAM-1: Vascular cell adhesion molecule-1; UCP-1: Uncoupling protein-1.

Competing interest

The authors declare that they do not have any competing interests regarding this manuscript.

Authors' contribution

MAA generated the idea, literature search for the review and drafted the manuscript. MMR prepared the drawings, figures and drafted the manuscript. Both authors read and approved the final manuscript.

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References

- Huang PL: A comprehensive definition for metabolic syndrome. *Dis Model Mech* 2009, **2**:231–237.
- Roberts CK, Sindhu KK: Oxidative stress and metabolic syndrome. *Life Sci* 2009, **84**:705–712.
- Hopps E, Noto D, Caimi G, Averna MR: A novel component of the metabolic syndrome: the oxidative stress. *Nutr Metab Cardiovasc Dis* 2010, **20**:72–77.
- Patti M-E, Corvera S: The role of mitochondria in the pathogenesis of type 2 diabetes. *Endocrine Rev* 2010, **31**:364–395.
- Hotamisligil GS, Spiegelman BM: Tumor necrosis factor alpha: a key component of the obesity-diabetes link. *Diabetes* 1994, **43**:1271–1278.
- Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW: Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003, **112**:1796–1808.
- Savage DB, Petersen KF, Shulman GI: Mechanisms of insulin resistance in humans and possible links with inflammation. *Hypertension* 2005, **45**:828–833.
- Nisoli E, Clementi E, Carruba MO, Moncada S: Defective mitochondrial biogenesis. *Circ Res* 2007, **100**:795–806.
- Valerio A, Cardile A, Cozzi V, Bracale R, Tedesco L, Pisconti A, Palomba L, Cantoni O, Clementi E, Moncada S, Carruba MO, Nisoli E: TNF- α downregulates eNOS expression and mitochondrial biogenesis in fat and muscle of obese rodents. *J Clin Invest* 2006, **116**:2791–2798.
- Bonakdar RA, Guarneri E: Coenzyme Q10. *Am Fam Physician* 2005, **72**:1065–1070.
- Littarru GP, Tiano L: Clinical aspects of coenzyme Q-10; in relationship with its bioenergetic and antioxidant properties. In *Mitochondrial Medicine*. Edited by Gvozdzjakova A. Netherlands: Springer; 2008:303–321.
- Pravst I, Žmitek K, Žmitek J: Coenzyme Q10 contents in foods and fortification strategies. *Crit Rev Food Sci Nutr* 2010, **50**:269–280.
- Weber C, Bysted A, Hølmer G: Coenzyme Q10 in the diet-daily intake and relative bioavailability. *Mol Aspects Med* 1997, **18**(Supplement 1):251–254.
- Greenberg S, Frishman WH: Co-enzyme Q10: a new drug for cardiovascular disease. *J Clin Pharmacol* 1990, **30**:596–608.
- Bhagavan HN, Chopra RK: Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic Res* 2006, **40**:445–453.
- Aberg F, Appelkvist EL, Dallner G, Ernster L: Distribution and redox state of ubiquinones in rat and human tissues. *Arch Biochem Biophys* 1992, **295**:230–234.
- Langsjoen PH, Langsjoen PH, Folkers K: Long-term efficacy and safety of coenzyme Q10 therapy for idiopathic dilated cardiomyopathy. *Am J Cardiol* 1990, **65**:521–523.
- Williams KD, Maneke JD, AbdelHameed M, Hall RL, Palmer TE, Kitano M, Hidaka T: 52-Week oral gavage chronic toxicity study with ubiquinone in rats with a 4-week recovery. *J Agric Food Chem* 1999, **47**:3756–3763.
- Langsjoen PH, Langsjoen AM: Coenzyme Q10 in cardiovascular disease with emphasis on heart failure and myocardial ischaemia. *Asia Pacific Heart J* 1998, **7**:160–168.
- Dallner G, Sindelar PJ: Regulation of ubiquinone metabolism. *Free Radic Biol Med* 2000, **29**:285–294.
- Vankoningsloo S, Piens M, Lecocq C, Gilson A, De Pauw A, Renard P, Demazy C, Houbion A, Raes M, Arnould T: Mitochondrial dysfunction induces triglyceride accumulation in 3 T3-L1 cells: role of fatty acid beta-oxidation and glucose. *J Lipid Res* 2005, **46**:1133–1149.
- Choo HJ, Kim JH, Kwon OB, Lee C, Mun J, Han S, Yoon YS, Yoon G, Choi KM, Ko YG: Mitochondria are impaired in the adipocytes of type 2 diabetic mice. *Diabetologia* 2006, **49**:784–791.
- Madrazo JA, Kelly DP: The PPAR trio: regulators of myocardial energy metabolism in health and disease. *J Mol Cell Cardiol* 2008, **44**:968–975.
- Chinetti-Gbaguidi G, Fruchart J-C, Staels B: Role of the PPAR family of nuclear receptors in the regulation of metabolic and cardiovascular homeostasis: new approaches to therapy. *Curr Opin Pharmacol* 2005, **5**:177–183.
- Wenz T: PGC-1 α activation as a therapeutic approach in mitochondrial disease. *Jumb Life* 2009, **61**:1051–1062.
- López-Lluch G, Irujo PM, Navas P, de Cabo R: Mitochondrial biogenesis and healthy aging. *Exp Gerontol* 2008, **43**:813–819.
- Pilegaard H, Saltin B, Neuffer PD: Exercise induces transient transcriptional activation of the PGC-1 α gene in human skeletal muscle. *J Physiol* 2003, **546**:851–858.
- Lira VA, Benton CR, Yan Z, Bonen A: PGC-1 α regulation by exercise training and its influences on muscle function and insulin sensitivity. *Am J Physiol Endocrinol Metab* 2010, **299**:E145–E161.
- Corton JC, Brown-Borg HM: Peroxisome proliferator-activated receptor gamma coactivator 1 in caloric restriction and other models of longevity. *J Gerontol A Biol Sci Med Sci* 2005, **60**:1494–1509.
- Bastin J, Aubey F, Rötig A, Munnich A, Djouadi F: Activation of peroxisome proliferator-activated receptor pathway stimulates the mitochondrial respiratory chain and can correct deficiencies in patients' cells lacking its components. *J Clin Endocrinol Metab* 2008, **93**:1433–1441.
- Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J: Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 α . *Cell* 2006, **127**:1109–1122.
- Lee SK, Lee JO, Kim JH, Kim N, You GY, Moon JW, Sha J, Kim SJ, Lee YW, Kang HJ, Park SH, Kim HS: Coenzyme Q10 increases the fatty acid oxidation through AMPK-mediated PPAR α induction in 3 T3-L1 preadipocytes. *Cell Signal* 2012, **24**:2329–2336.
- Ogasahara S, Engel AG, Frens D, Mack D: Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. *Proc Natl Acad Sci* 1989, **86**:2379–2382.
- Miles MV, Horn PS, Tang PH, Morrison JA, Miles L, DeGrauw T, Pesce AJ: Age-related changes in plasma coenzyme Q10 concentrations and redox state in apparently healthy children and adults. *Clin Chim Acta* 2004, **347**:139–144.
- Menke T, Niklowitz P, de Sousa G, Reinehr T, Andler W: Comparison of coenzyme Q10 plasma levels in obese and normal weight children. *Clin Chim Acta* 2004, **349**:121–127.
- Chew GT, Watts GF: Coenzyme Q10 and diabetic endotheliopathy: oxidative stress and the 'recoupling hypothesis'. *QJM* 2004, **97**:537–548.
- McDonnell MG, Archbold GPR: Plasma ubiquinol/cholesterol ratios in patients with hyperlipidaemia, those with diabetes mellitus and in patients requiring dialysis. *Clin Chim Acta* 1996, **253**:117–126.
- Lim SC, Tan HH, Goh SK, Subramaniam T, Sum CF, Tan IK, Lee BL, Ong CN: Oxidative burden in prediabetic and diabetic individuals: evidence from plasma coenzyme Q10. *Diabetic Med* 2006, **23**:1344–1349.
- El-ghoroury EA, Raslan HM, Badawy EA, El-Saaied GS, Agybi MH, Siam I, Salem SI: Malondialdehyde and coenzyme Q10 in platelets and serum in type 2 diabetes mellitus: correlation with glycemic control. *Blood Coagul Fibrinolysis* 2009, **20**:248–251. 210.
- Menke T, Niklowitz P, Wiesel T, Andler W: Antioxidant level and redox status of coenzyme Q10 in the plasma and blood cells of children with diabetes mellitus type 1. *Pediatr Diabetes* 2008, **9**:540–545.
- Silver MA, Langsjoen PH, Szabo S, Patil H, Zelinger A: Effect of atorvastatin on left ventricular diastolic function and ability of coenzyme Q10 to reverse that dysfunction. *Am J Cardiol* 2004, **94**:1306–1310.
- Folkers K, Langsjoen P, Willis R, Richardson P, Xia LJ, Ye CQ, Tamagawa H: Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci* 1990, **87**:8931–8934.
- Bargossi AM, Battino M, Gaddi A, Fiorella PL, Grossi G, Barozzi G, Di Giulio R, Descovich G, Sassi S, Genova ML, Lenaz G: Exogenous CoQ10 preserves plasma ubiquinone levels in patients treated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Int J Clin Lab Res* 1994, **24**:171–176.

44. Troseid M, Henriksen OA, Lindal S: **Statin-associated myopathy with normal creatine kinase levels. Case report from a Norwegian family.** *APMIS* 2005, **113**:635–637.
45. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, Vladutiu GD, England JD: **Statin-associated myopathy with normal creatine kinase levels.** *Ann Intern Med* 2002, **137**:581–585.
46. Caso G, Kelly P, McNurlan MA, Lawson WE: **Effect of coenzyme q10 on myopathic symptoms in patients treated with statins.** *Am J Cardiol* 2007, **99**:1409–1412.
47. Folkers K, Vadhanavikitt S, Mortensen SA: **Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10.** *Proc Natl Acad Sci* 1985, **82**:901–904.
48. Oh J, Ban MR, Miskie BA, Pollex RL, Hegele RA: **Genetic determinants of statin intolerance.** *Lipids Health Dis* 2007, **6**:7.
49. Vladutiu GD, Simmons Z, Isackson PJ, Tarnopolsky M, Peltier WL, Barboi AC, Sripathi N, Wortmann RL, Phillips PS: **Genetic risk factors associated with lipid-lowering drug-induced myopathies.** *Muscle Nerve* 2006, **34**:153–162.
50. Tappel AL: **Vitamin E and free radical peroxidation of lipids.** *Ann N Y Acad Sci* 1972, **203**:12–28.
51. Stocker R, Bowry VW, Frei B: **Ubiquinol-10 protects human low density lipoprotein more efficiently against lipid peroxidation than does alpha-tocopherol.** *Proc Natl Acad Sci* 1991, **88**:1646–1650.
52. Shekelle P, Hardy ML, Coulter I, Udani J, Spar M, Oda K, Jungvig LK, Tu W, Suttrop MJ, Valentine D, Ramirez L, Shanman R, Newberry SJ: **Effect of the supplemental use of antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cancer. (Prepared by Southern California Evidence-based Practice Center under Contract No. 290-97-0001.) AHRQ Publication No. 04-E003.** Rockville, MD: Agency for Healthcare Research and Quality; 2003.
53. Sohal RS, Forster MJ: **Coenzyme Q, oxidative stress and aging.** *Mitochondrion* 2007, **7**(Suppl):S103–S111.
54. Roginsky VA, Tashlitsky VN, Skulachev VP: **Chain-breaking antioxidant activity of reduced forms of mitochondria-targeted quinones, a novel type of geroprotectors.** *Aging* 2009, **1**:481–489.
55. Abdin AA, Hamouda HE: **Mechanism of the neuroprotective role of coenzyme Q10 with or without L-dopa in rotenone-induced parkinsonism.** *Neuropharmacol* 2008, **55**:1340–1346.
56. Tomasetti M, Littarru GP, Stocker R, Alleva R: **Coenzyme Q10 enrichment decreases oxidative DNA damage in human lymphocytes.** *Free Radic Biol Med* 1999, **27**:1027–1032.
57. Tomasetti M, Alleva R, Borghi B, Collins AR: **In vivo supplementation with coenzyme Q10 enhances the recovery of human lymphocytes from oxidative DNA damage.** *FASEB J* 2001, **15**:1425–1427.
58. Modi K, Santani DD, Goyal RK, Bhatt PA: **Effect of coenzyme Q10 on catalase activity and other antioxidant parameters in streptozotocin-induced diabetic rats.** *Biol Trace Elem Res* 2006, **109**:25–34.
59. Fouad AA, Jresat I: **Hepatoprotective effect of coenzyme Q10 in rats with acetaminophen toxicity.** *Environ Toxicol Pharmacol* 2012, **33**:158–167.
60. Lee B-J, Huang Y-C, Chen S-J, Lin P-T: **Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with coronary artery disease.** *Nutrition* 2012, **28**:250–255.
61. Seitz CS, Kleindienst R, Xu Q, Wick G: **Coexpression of heat-shock protein 60 and intercellular-adhesion molecule-1 is related to increased adhesion of monocytes and T cells to aortic endothelium of rats in response to endotoxin.** *Lab Invest* 1996, **74**:241–252.
62. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H: **Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance.** *J Clin Invest* 2003, **112**:1821–1830.
63. Wellen KE, Hotamisligil GS: **Inflammation, stress, and diabetes.** *J Clin Invest* 2005, **115**:1111–1119.
64. Milagro FI, Campion J, Martinez JA: **Weight gain induced by high-fat feeding involves increased liver oxidative stress.** *Obesity* 2006, **14**:1118–1123.
65. Shoelson SE, Herrero L, Naaz A: **Obesity, inflammation, and insulin resistance.** *Gastroenterol* 2007, **132**:2169–2180.
66. Abedini A, Shoelson SE: **Inflammation and obesity: stamping out insulin resistance?** *Immunol Cell Biol* 2007, **85**:399–400.
67. Arkan MC, Hevener AL, Greten FR, Maeda S, Li ZW, Long JM, Wynshaw-Boris A, Poli G, Olefsky J, Karin M: **IKK-beta links inflammation to obesity-induced insulin resistance.** *Nat Med* 2005, **11**:191–198.
68. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE: **Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB.** *Nat Med* 2005, **11**:183–190.
69. Bochud M, Marquant F, Marques-Vidal P-M, Vollenweider P, Beckmann JS, Mooser V, Paccaud F, Rousson V: **Association between C-reactive protein and adiposity in women.** *J Clin Endocrinol Metab* 2009, **94**:3969–3977.
70. Lapice E, Maione S, Patti L, Cipriano P, Rivellese AA, Riccardi G, Vaccaro O: **Abdominal adiposity is associated with elevated C-reactive protein independent of BMI in healthy nonobese people.** *Diabetes Care* 2009, **32**:1734–1736.
71. Nijhuis J, Rensen SS, Slaats Y, van Dielen FM, Buurman WA, Greve JW: **Neutrophil activation in morbid obesity, chronic activation of acute inflammation.** *Obesity* 2009, **17**:2014–2018.
72. Hotamisligil GS, Shargill NS, Spiegelman BM: **Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance.** *Science* 1993, **259**:87–91.
73. Sethi JK, Hotamisligil GS: **The role of TNF alpha in adipocyte metabolism.** *Semin Cell Dev Biol* 1999, **10**:19–29.
74. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM: **Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance.** *J Clin Invest* 1995, **95**:2409–2415.
75. Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB: **The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase.** *J Clin Invest* 1995, **95**:2111–2119.
76. El-Moselhy MA, Taye A, Sharkawi SS, El-Sisi SFI, Ahmed AF: **The antihyperglycemic effect of curcumin in high fat diet fed rats. Role of TNF-alpha and free fatty acids.** *Food Chem Toxicol* 2011, **49**:1129–1140.
77. Mehta NN, McGillicuddy FC, Anderson PD, Hinkle CC, Shah R, Pruscino L, Tabita-Martinez J, Sellers KF, Rickels MR, Reilly MP: **Experimental Endotoxemia induces adipose inflammation and insulin resistance in humans.** *Diabetes* 2010, **59**:172–181.
78. Matarazzo S, Quitadamo MC, Mango R, Ciccone S, Novelli G, Biocca S: **Cholesterol-lowering drugs inhibit lectin-like oxidized low-density lipoprotein-1 receptor function by membrane raft disruption.** *Mol Pharmacol* 2012, **82**:246–254.
79. Bieghs V, Van Gorp PJ, Wouters K, Hendriks T, Gijbels MJ, van Bilsen M, Bakker J, Binder CJ, Lutjohann D, Staels B, Hofker MH, Shiri-Sverdlow R: **LDL receptor knock-out mice are a physiological model particularly vulnerable to study the onset of inflammation in non-alcoholic fatty liver disease.** *Plos One* 2012, **7**:e30668.
80. Flock MR, Green MH, Kris-Etherton PM: **Effects of adiposity on plasma lipid response to reductions in dietary saturated fatty acids and cholesterol.** *Advances in Nutrition* 2011, **2**:261–274.
81. Henninger DD, Gerritsen ME, Granger DN: **Low-density lipoprotein receptor knockout mice exhibit exaggerated microvascular responses to inflammatory stimuli.** *Cir Res* 1997, **81**:274–281.
82. Zabalawi M, Bhat S, Loughlin T, Thomas MJ, Alexander E, Cline M, Bullock B, Willingham M, Sorci-Thomas MG: **Induction of fatal inflammation in LDL receptor and ApoA-I double-knockout mice fed dietary fat and cholesterol.** *Am J Pathol* 2003, **163**:1201–1213.
83. Li AC, Brown KK, Silvestre MJ, Willson TM, Palinski W, Glass CK: **Peroxisome proliferator-activated receptor gamma ligands inhibit development of atherosclerosis in LDL receptor-deficient mice.** *J Clin Invest* 2000, **106**:523–531.
84. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK: **The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation.** *Nature* 1998, **391**:79–82.
85. Cuzzocrea S, Mazzon E, Di Paola R, Peli A, Bonato A, Britti D, Genovese T, Muia C, Crisafulli C, Caputi AP: **The role of the peroxisome proliferator-activated receptor-alpha (PPAR-alpha) in the regulation of acute inflammation.** *J Leukoc Biol* 2006, **79**:999–1010.
86. Schmelzer C, Lorenz G, Rimbach G, Döring F: **In vitro effects of the reduced form of coenzyme Q10 on secretion levels of TNF-alpha and chemokines in response to LPS in the human monocytic cell line THP-1.** *J Nutr Biochem* 2009, **44**:62–66.
87. Schmelzer C, Lorenz G, Rimbach G, Döring F: **Influence of Coenzyme Q10 on release of pro-inflammatory chemokines in the human monocytic cell line THP-1.** *BioFactors* 2007, **31**:211–217.
88. Carmona MC, Lefebvre P, Lefebvre B, Galinier A, Benani A, Jeanson Y, Louche K, Flajollet S, Ktorza A, Dacquet C, Penicaud L, Casteilla L: **Coadministration of**

- coenzyme Q prevents rosiglitazone-induced adipogenesis in ob/ob mice. *Int J Obes* 2009, **33**:204–211.
89. Sohet FM, Neyrinck AM, Pachikian BD, de Backer FC, Bindels LB, Niklowitz P, Menke T, Cani PD, Delzenne NM: **Coenzyme Q10 supplementation lowers hepatic oxidative stress and inflammation associated with diet-induced obesity in mice.** *Biochem Pharmacol* 2009, **78**:1391–1400.
90. Schmelzer C, Kitano M, Hosoe K, Doring F: **Ubiquinol affects the expression of genes involved in PPARalpha signalling and lipid metabolism without changes in methylation of CpG promoter islands in the liver of mice.** *J Clin Biochem Nutr* 2012, **50**:119–126.
91. Schmelzer C, Kubo H, Mori M, Sawashita J, Kitano M, Hosoe K, Boomgaarden I, Döring F, Higuchi K: **Supplementation with the reduced form of Coenzyme Q10 decelerates phenotypic characteristics of senescence and induces a peroxisome proliferator-activated receptor- α gene expression signature in SAMP1 mice.** *Mol Nutr Food Res* 2010, **54**:805–815.
92. Kunitomo M, Yamaguchi Y, Kagota S, Otsubo K: **Beneficial effect of coenzyme Q10 on increased oxidative and nitrate stress and inflammation and individual metabolic components developing in a rat model of metabolic syndrome.** *J Pharmacol Sci* 2008, **107**:128–137.
93. Ozdogan S, Kaman D, Simsek BC: **Effects of coenzyme Q10 and alpha-lipoic acid supplementation in fructose fed rats.** *J Clin Biochem Nutr* 2012, **50**:145–151.
94. Hamilton SJ, Chew GT, Watts GF: **Coenzyme Q10 improves endothelial dysfunction in statin-treated type 2 diabetic patients.** *Diabetes Care* 2009, **32**:810–812.
95. Tsai KL, Huang YH, Kao CL, Yang DM, Lee HC, Chou HY, Chen YC, Chiou GY, Chen LH, Yang YP, Chiu TH, Tsai CS, Ou HC, Chiou SH: **A novel mechanism of coenzyme Q10 protects against human endothelial cells from oxidative stress-induced injury by modulating NO-related pathways.** *J Nutr Biochem* 2012, **23**:458–468.
96. Tiano L, Belardinelli R, Carnevali P, Principi F, Seddaiu G, Littarru GP: **Effect of coenzyme Q10 administration on endothelial function and extracellular superoxide dismutase in patients with ischaemic heart disease: a double-blind, randomized controlled study.** *Eur Heart J* 2007, **28**:2249–2255.
97. Yamagami T, Iwamoto Y, Folkers K, Blomqvist CG: **Reduction by coenzyme Q10 of hypertension induced by deoxycorticosterone and saline in rats.** *Int J Vitam Nutr Res* 1974, **44**:487–496.
98. Iwamoto Y, Yamagami T, Folkers K, Blomqvist CG: **Deficiency of coenzyme Q10 in hypertensive rats and reduction of deficiency by treatment with coenzyme Q10.** *Biochem Biophys Res Commun* 1974, **58**:743–748.
99. Murad LB, Guimaraes MR, Vianna LM: **Effects of decylubiquinone (coenzyme Q10 analog) supplementation on SHRSP.** *BioFactors* 2007, **30**:13–18.
100. Rosenfeldt FL, Haas SJ, Krum H, Hadj A, Ng K, Leong JY, Watts GF: **Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials.** *J Hum Hypertens* 2007, **21**:297–306.
101. Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, Nicholls MG, Scott RS, George PM: **A randomized, double-blind, placebo-controlled crossover study of coenzyme q10 therapy in hypertensive patients with the metabolic syndrome.** *Am J Hypertens* 2012, **25**:261–270.
102. Digiesi V, Cantini F, Oradei A, Bisi G, Guarino GC, Brocchi A, Bellandi F, Mancini M, Littarru GP: **Coenzyme Q10 in essential hypertension.** *Mol Aspects Med* 1994, **15**(Suppl):s257–s263.
103. Pepe S, Marasco SF, Haas SJ, Sheeran FL, Krum H, Rosenfeldt FL: **Coenzyme Q10 in cardiovascular disease.** *Mitochondrion* 2007, **7**(Suppl):S154–S167.
104. Lonnrot K, Porsti I, Alho H, Wu X, Hervonen A, Tolvanen JP: **Control of arterial tone after long-term coenzyme Q10 supplementation in senescent rats.** *Br J Pharmacol* 1998, **124**:1500–1506.
105. Kumar A, Kaur H, Devi P, Mohan V: **Role of coenzyme Q10 (CoQ10) in cardiac disease, hypertension and Meniere-like syndrome.** *Pharmacol Ther* 2009, **124**:259–268.
106. Vogt AM, Kübler W: **Heart failure: is there an energy deficit contributing to contractile dysfunction?** *Basic Res Cardiol* 1998, **93**:1–10.
107. Folkers K, Littarru GP, Ho L, Ruong TM, Havanonda S, Cooley D: **Evidence for a deficiency of coenzyme Q10 in human heart disease.** *Int Z Vitaminforsch* 1970, **40**:380–390.
108. Langsjoen PH, Folkers K: **A six-year clinical study of therapy of cardiomyopathy with coenzyme Q10.** *Int J Tissue React* 1990, **12**:169–171.
109. Langsjoen PH, Langsjoen A, Willis R, Folkers K: **Treatment of hypertrophic cardiomyopathy with coenzyme Q10.** *Mol Aspects Med* 1997, **18**(Suppl):S145–S151.
110. Ohhara H, Kanaide H, Yoshimura R, Okada M, Nakamura M: **A protective effect of coenzyme Q10 on ischemia and reperfusion of the isolated perfused rat heart.** *J Mol Cell Cardiol* 1981, **13**:65–74.
111. Hano O, Thompson-Gorman SL, Zweier JL, Lakatta EG: **Coenzyme Q10 enhances cardiac functional and metabolic recovery and reduces Ca²⁺ overload during postischemic reperfusion.** *Am J Physiol* 1994, **266**:H2174–H2181.
112. Niibori K, Wroblewski KP, Yokoyama H, Crestanello JA, Whitman GJ: **Bioenergetic effect of liposomal coenzyme Q10 on myocardial ischemia reperfusion injury.** *BioFactors* 1999, **9**:307–313.
113. Combs AB, Choe JY, Truong DH, Folkers K: **Reduction by coenzyme Q10 of the acute toxicity of adriamycin in mice.** *Res Commun Chem Pathol Pharmacol* 1977, **18**:565–568.
114. Shinozawa S, Etowo K, Araki Y, Oda T: **Effect of coenzyme Q10 on the survival time and lipid peroxidation of adriamycin (doxorubicin) treated mice.** *Acta Med Okayama* 1984, **38**:57–63.
115. Kucharska J, Braunova Z, Ulicna O, Zlatos L, Gvozdzjakova A: **Deficit of coenzyme Q in heart and liver mitochondria of rats with streptozotocin-induced diabetes.** *Physiol Res* 2000, **49**:411–418.
116. Gvozdzjakova A, Kucharska J, Mizera S, Braunova Z, Schreinerova Z, Schramekova E, Pechan I, Fabian J: **Coenzyme Q10 depletion and mitochondrial energy disturbances in rejection development in patients after heart transplantation.** *BioFactors* 1999, **9**:301–306.
117. Eriksson JG, Forsen TJ, Mortensen SA, Rohde M: **The effect of coenzyme Q10 administration on metabolic control in patients with type 2 diabetes mellitus.** *BioFactors* 1999, **9**:315–318.
118. Henriksen JE, Andersen CB, Hother-Nielsen O, Vaag A, Mortensen SA, Beck-Nielsen H: **Impact of ubiquinone (coenzyme Q10) treatment on glycaemic control, insulin requirement and well-being in patients with Type 1 diabetes mellitus.** *Diabet Med* 1999, **16**:312–318.
119. Sena CM, Nunes E, Gomes A, Santos MS, Proença T, Martins MI, Seça RM: **Supplementation of coenzyme Q10 and α -tocopherol lowers glycated hemoglobin level and lipid peroxidation in pancreas of diabetic rats.** *Nutr Res* 2008, **28**:113–121.
120. Repa JJ, Mangelsdorf DJ: **The liver X receptor gene team: potential new players in atherosclerosis.** *Nat Med* 2002, **8**:1243–1248.
121. Seo JB, Moon HM, Kim WS, Lee YS, Jeong HW, Yoo EJ, Ham J, Kang H, Park M-G, Steffensen KR, Stulnig TM, Gustafsson JÅ, Park SD, Kim JB: **Activated liver X receptors stimulate adipocyte differentiation through induction of peroxisome proliferator-activated receptor γ expression.** *Mol Cell Biol* 2004, **24**:3430–3444.
122. Joseph SB, Castrillo A, Laffitte BA, Mangelsdorf DJ, Tontonoz P: **Reciprocal regulation of inflammation and lipid metabolism by liver X receptors.** *Nat Med* 2003, **9**:213–219.
123. Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE, Mangelsdorf DJ: **Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha.** *Cell* 1998, **93**:693–704.
124. Ide T, Shimano H, Yoshikawa T, Yahagi N, Amemiya-Kudo M, Matsuzaka T, Nakakuki M, Yatoh S, Iizuka Y, Tomita S, Ohashi K, Takahashi A, Sone H, Gotoda T, Osuga J-I, Ishibashi S, Yamada N: **Cross-talk between peroxisome proliferator-activated receptor (PPAR) α and liver X receptor (LXR) in nutritional regulation of fatty acid metabolism. II. LXRs suppress lipid degradation gene promoters through inhibition of PPAR signaling.** *Mol Endocrinol* 2003, **17**:1255–1267.
125. Schmelzer C, Okun JG, Haas D, Higuchi K, Sawashita J, Mori M, Doring F: **The reduced form of coenzyme Q10 mediates distinct effects on cholesterol metabolism at the transcriptional and metabolite level in SAMP1 mice.** *lubb Life* 2010, **62**:812–818.
126. Bentinger M, Tekle M, Dallner G, Brismar K, Gustafsson J, Steffensen K, Catrina SB: **Influence of liver-X-receptor on tissue cholesterol, coenzyme Q and dolichol content.** *Molec Membrane Biol* 2012, **29**:299–308.
127. Quiles JL, Ochoa JJ, Battino M, Gutierrez-Rios P, Nepomuceno EA, Frias ML, Huertas JR, Mataix J: **Life-long supplementation with a low dosage of coenzyme Q10 in the rat: effects on antioxidant status and DNA damage.** *BioFactors* 2005, **25**:73–86.
128. Quiles JL, Ochoa JJ, Huertas JR, Mataix J: **Coenzyme Q supplementation protects from age-related DNA double-strand breaks and increases lifespan in rats fed on a PUFA-rich diet.** *Exp Gerontol* 2004, **39**:189–194.

129. Safwat GM, Pisano S, D'Amore E, Borioni G, Napolitano M, Kamal AA, Ballanti P, Botham KM, Bravo E: **Induction of non-alcoholic fatty liver disease and insulin resistance by feeding a high-fat diet in rats: does coenzyme Q monomethyl ether have a modulatory effect?** *Nutrition* 2009, **25**:1157–1168.
130. Sutken E, Aral E, Ozdemir F, Uslu S, Alatas O, Colak O: **Protective role of melatonin and coenzyme Q10 in ochratoxin A toxicity in rat liver and kidney.** *Int J Toxicol* 2007, **26**:81–87.
131. Bello RI, Gomez-Diaz C, Buron MI, Alcain FJ, Navas P, Villalba JM: **Enhanced anti-oxidant protection of liver membranes in long-lived rats fed on a coenzyme Q10-supplemented diet.** *Exp Gerontol* 2005, **40**:694–706.
132. Cornier M-A, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH: **The metabolic syndrome.** *Endocrine Rev* 2008, **29**:777–822.
133. Mehmetoglu I, Yerlikaya FH, Kurban S: **Correlation between vitamin A, E, coenzyme Q-10 and degree of insulin resistance in obese and non-obese subjects.** *J Clin Biochem Nutr* 2011, **49**:159–163.
134. Bour S, Carmona MC, Galinier A, Caspar-Bauguil S, Van Gaal L, Staels B, Penicaud L, Casteilla L: **Coenzyme Q as an antiadipogenic factor.** *Antioxid Redox Signal* 2011, **14**:403–413.
135. Foretz M, Pacot C, Dugail I, Lemarchand P, Guichard C, le Lièvre X, Berthelmer-Lubrano C, Spiegelman B, Kim JB, Ferré P, Foufelle F: **ADD1/SREBP-1c is required in the activation of hepatic lipogenic gene expression by glucose.** *Mol Cell Biol* 1999, **19**:3760–3768.
136. Murphy MP, Smith RA: **Drug delivery to mitochondria: the key to mitochondrial medicine.** *Adv Drug Deliv Rev* 2000, **41**:235–250.
137. Adlam VJ, Harrison JC, Porteous CM, James AM, Smith RA, Murphy MP, Sammut IA: **Targeting an antioxidant to mitochondria decreases cardiac ischemia-reperfusion injury.** *FASEB J* 2005, **19**:1088–1095.
138. Lowes DA, Thottakam BM, Webster NR, Murphy MP, Galley HF: **The mitochondria-targeted antioxidant MitoQ protects against organ damage in a lipopolysaccharide-peptidoglycan model of sepsis.** *Free Radic Biol Med* 2008, **45**:1559–1565.
139. Graham D, Huynh NN, Hamilton CA, Beattie E, Smith RAJ, Cochemé HM, Murphy MP, Dominiczak AF: **Mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy.** *Hypertension* 2009, **54**:322–328.
140. Vergeade A, Mulder P, Vendeville-Dehaudt C, Estour F, Fortin D, Ventura-Clapier R, Thuillez C, Monteil C: **Mitochondrial impairment contributes to cocaine-induced cardiac dysfunction: prevention by the targeted antioxidant MitoQ.** *Free Radical Biol Med* 2010, **49**:748–756.
141. Chacko BK, Srivastava A, Johnson MS, Benavides GA, Chang MJ, Ye Y, Jhala N, Murphy MP, Kalyanaraman B, Darley-Usmar VM: **Mitochondria-targeted ubiquinone (MitoQ) decreases ethanol-dependent micro and macro hepatosteatosis.** *J Hepatol* 2011, **54**:153–163.
142. Mercer JR, Yu E, Figg N, Cheng K-K, Prime TA, Griffin JL, Masoodi M, Vidal-Puig A, Murphy MP, Bennett MR: **The mitochondria-targeted antioxidant MitoQ decreases features of the metabolic syndrome in ATM+/-/ApoE-/- mice.** *Free Radical Biol Med* 2012, **52**:841–849.
143. Kutz K, Drewe J, Vankan P: **Pharmacokinetic properties and metabolism of idebenone.** *J Neurol* 2009, **256**(Suppl 1):31–35.
144. Sugiyama Y, Fujita T, Matsumoto M, Okamoto K, Imada I: **Effects of idebenone (CV-2619) and its metabolites on respiratory activity and lipid peroxidation in brain mitochondria from rats and dogs.** *J Pharmacobiodyn* 1985, **8**:1006–1017.
145. Suno M, Nagaoka A: **Inhibition of lipid peroxidation by idebenone in brain mitochondria in the presence of succinate.** *Arch Gerontol Geriatr* 1989, **8**:291–297.
146. Suno M, Shibota M, Nagaoka A: **Effects of idebenone on lipid peroxidation and hemolysis in erythrocytes of stroke-prone spontaneously hypertensive rats.** *Arch Gerontol Geriatr* 1989, **8**:307–311.

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