Is there a place for coenzyme Q in the management of metabolic disorders associated with obesity?

Florence M Sohet and Nathalie M Delzenne

Coenzyme Q (CoQ), a lipophilic cofactor of the electron transport chain in the mitochondria, can be synthesized endogenously or provided by food. The aim of this review is to summarize the in vitro cell culture studies, the in vivo animal studies, and the human studies investigating the impact of CoQ supplementation on the occurrence of obesity and related disorders (diabetes, hypertension, lipemia, and atherosclerosis). The antioxidative properties of CoQ have been observed in different experimental models of atherosclerosis, obesity, and diabetes. The recent discovery of the anti-inflammatory effect of CoQ, mostly described in vitro, has generated increased interest in CoQ supplementation, but it needs to be confirmed in vivo in pathological situations. CoQ intervention studies in humans failed to show reproducible effects on body weight, fat mass, or glycemia, but CoQ supplementation does seem to have an antihypertensive effect. The molecular mechanism to explain this effect has only recently been discovered.

INTRODUCTION

Obesity, particularly central obesity, has been associated with metabolic disorders that include raised fasting glucose levels, increased blood pressure, and dyslipidemia characterized by increased triglycerides and decreased high-density lipoprotein cholesterol. This pattern of metabolic disorders leads to an increased risk of cardiovascular disease and type 2 diabetes. Subjects with three of the following five abnormalities are diagnosed with metabolic syndrome: abdominal obesity, hypertension, high triglycerides, low high-density lipoprotein cholesterol, and high fasting glucose. Over the past decade, chronic low-grade inflammation and oxidative stress have also been associated with diabetes and obesity. Since coenzyme Q10 (CoQ10) exhibits well-described antioxidant properties and has been recently described as an anti-inflammatory compound, this review will focus on the potential usefulness of CoQ10 in metabolic disorders associated with obesity.

This introductory section will review the main functions of CoQ, with special attention placed on the potential anti-inflammatory properties of CoQ. The alteration of the CoQ level or the CoQ redox state, as related to pathological states (mainly diabetes and obesity), will also be examined.

Biological functions of coenzyme Q

CoQ is an effective lipid-soluble antioxidant, acting through prevention of lipid peroxidation (chain-breaking), through restoration of vitamin E, or through interaction with superoxide or other reactive oxygen species. Moreover, CoQ is a key component of the electron transport chain in the mitochondria and thereby participates in the regulation of energy homeostasis. Furthermore, CoQ is involved in cell signaling, in the control of gene expression, and in the control of cellular redox balance. The length of the isoprenoid side chain varies between species, consisting of 9 isoprenoid units in...
Role of coenzyme Q in inflammation

The effect of CoQ10 supplementation on inflammation has largely been studied in cells by the team of Schmelzer et al. followed by Doring. Their initial observations were based on in silico experiments, which helped them to discover that a panel of genes involved in inflammation (interleukin 5, thrombin, vitronectin, vitronectin receptor, and C-reactive protein) were regulated by CoQ10. They also showed, in various studies on monocytic cell lines (human monocytic cell line THP1 and murine monocytic cell line RAW 264.7) incubated with lipopolysaccharide (LPS), that CoQ10 or CoQ10H2 has no effect on cell viability but decreases the release of cytokines in the medium (tumor necrosis factor α [TNFα], regulated on activation, normal T cell expressed and secreted [RANTES]), and macrophage inflammatory protein 1α [MIP1α]). Those results are in accordance with the results obtained by Fuller et al. on inflamed dermal fibroblasts isolated from human neonatal foreskin. They showed that CoQ10 reduces the production of proinflammatory mediators (interleukin 6 and prostaglandin E2) and protects the skin’s dermal extracellular matrix from degradation by matrix metalloproteinase 1.

Several studies performed in animals with acute inflammation induced by LPS suggest beneficial effects due to CoQ10 supplementation (i.e., decreased mortality and decreased oxidative stress). Decreased oxidative stress was observed by Abd El-Gawad and Khalifa, who found lower glutathione peroxidase activity, lipid peroxidation, and nitric oxide production in endotoxemic rat brain when the animals received CoQ10 treatment. Lelli et al. found a protective effect of CoQ supplementation on free-radical-mediated lipid peroxidation assessed by fluorescent products during septic shock in dogs. Suzuki et al. described the decreased superoxide anion and liver thiobarbituric-acid-reactive substances (2 h after intravenous injection of LPS) in polymorphonuclear leukocytes of rats treated with endotoxin. Sugino et al. showed that CoQ10 supplementation could reduce the LPS-induced lipid peroxidation in mice, which might have been associated with the enhanced survival of CoQ10-supplemented mice. Studies in mice, rats, and broiler chickens described a decreased mortality from endotoxemic shock in animals pretreated with CoQ10.

Interestingly, a new possible effect of CoQ10 supplementation on microRNA was recently described by Schmelzer et al. MicroRNAs are a class of endogenous, approximately 22-nucleotide, noncoding RNAs that suppress gene expression at the post-transcriptional level. They have a critical function in cell proliferation, cell death during development, fat metabolism, insulin secretion, innate immunity, and inflammation. Specifically, miR-146a seems to be involved in inflammation, with nuclear factor-κB playing a role in the upregulation of miR-146a by LPS.

Most of the studies presented here described a protective effect of CoQ10 supplementation on mortality and oxidative stress in animal models of inflammation. Disappointing results, however, were obtained when immune parameters were analyzed in mice treated with an electromagnetic field and supplemented with CoQ10, with no effect of CoQ10 supplementation observed in that model.

The anti-inflammatory effect of CoQ10 could be enhanced when CoQ10 is combined with antioxidant nutrients. To illustrate this concept, cosupplementation of CoQ10 with vitamin E in baboons fed a high-fat/high-cholesterol diet reduced serum C-reactive protein levels. Reduced cytokine levels in the circulation, in peritoneal macrophages, and in spleen lymphocytes, as well as reduced activation of nuclear factor-κB and of stress-activated protein kinase/c-Jun NH2-terminal kinase (SAPK/JNK) by lymphocytes, occurred in mice that received a mix of vitamin E, β-carotene, and CoQ9 during the 2 weeks before an LPS challenge.
Evolution of coenzyme Q levels with pathological states

Certain pathological states have been associated with CoQ10 deficiency. For example, the myocardial tissue of patients presenting with cardiovascular disease is deficient in CoQ10. Moreover, although 95% of CoQ10 is in its reduced form in healthy subjects, this proportion decreases in patients with coronary artery disease (for review, see Singh et al.30). Pituitary diseases are also associated with CoQ10 deficiency, since thyroid hormones play a role in modulating CoQ10 levels and in regulating metabolism.31 Upon observation of decreased total CoQ10 levels and/or a decreased ratio of the reduced form of CoQ10 (CoQH2/total CoQ10) in pathological states, several authors postulated that the circulating levels of CoQ10 could constitute a potential biomarker of several diseases.

Aging has also been associated with lower CoQ10 levels. The human CoQ10 levels increase from birth to 20–30 years and then decrease to reach the initial birth level at 80 years.32 A study by Miles et al.33 also shows that the ratio of reduced CoQ10 versus oxidized CoQ10 decreases with age in healthy humans, indicating a reduction in antioxidant capacity. Statins are inhibitors of a limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase. Since CoQ10 and cholesterol share a common biosynthesis pathway, the idea that statins not only reduce cholesterol but also affect CoQ10 levels merits attention.34 A specific section will be devoted to describing the impact of CoQ10 on statin side effects.

The following sections will focus on the description of CoQ10 status in obesity and diabetes.

Coenzyme Q status in obese individuals

Several authors have studied CoQ and CoQH2 levels in obese animals and humans, publishing controversial results. They observed similar, increased, or decreased CoQ levels in obese versus nonobese individuals.

Human studies. In a small pre- and post-surgery study, Mancini et al.35 found no difference in plasma CoQ10 levels between obese patients before biliopancreatic diversion and aged-matched controls. A significant decrease in plasma CoQ10 levels was observed in obese patients after bariatric surgery when results were expressed as the ratio of total CoQ10 to total cholesterol, and after normalization to plasma cholesterol levels. This decrease could be due to reduced lipid absorption after the surgery. Increased plasma CoQ10 levels were found in obese versus nonobese children,36 but this effect was not significant when expressed as a ratio of total CoQ10 to total cholesterol. Miles et al.33 also found increased plasma CoQH2 and total CoQ10 levels, as well as an increased ratio of total CoQ10 to total cholesterol in patients with metabolic syndrome (n = 133), although plasma CoQ10 (ubiquinone) levels were unchanged. Butler et al.37 showed a tendency of decreased plasma CoQ10 in obese patients. In another study, lower levels of CoQ10 were shown in adipose tissue from obese humans.38

Animal studies. In animals, CoQ status was mainly assessed in blood, in the liver, and in adipose tissue. Galinier et al.39 found decreased CoQ levels in the blood of Zucker rats, while Kohli et al.40 found a significant increase in plasma CoQ levels in obese C57Bl6/J mice with nonalcoholic steatohepatitis. Ciapaite et al.41 found no change in CoQ levels in liver mitochondria of Wistar rats fed a high-fat diet for 7 weeks, while Galinier et al.42 found decreased CoQ levels in the liver of obese Zucker rats. CoQ levels were decreased in the inguinal adipose tissue of obese mice38 and Zucker rats.39,42 Galinier et al.39,42 also found increased ratio of total CoQ10 to total cholesterol in pathological states, several authors postulated that the circulating levels of CoQ10 could constitute a potential biomarker of several diseases.

Coenzyme Q status in diabetic individuals

Human studies. In humans, conflicting results have been obtained in diabetic patients, with plasma CoQ levels being decreased, increased, or unchanged compared with findings in nondiabetic individuals. Decreased CoQ10 levels were detected in the serum of 97 non-insulin-dependent diabetic patients with normal cholesterol,43 in the plasma of 28 patients with type 2 diabetes, indicating increased oxidative stress,44 and in the plasma of 50 patients with type 2 diabetes.45 Among the 50 patients with type 2 diabetes, plasma CoQ levels were significantly decreased in the 33 insulin-dependent diabetic patients but not in the 17 non-insulin-dependent diabetic patients.46 Lower plasma total CoQ levels and a lower ratio of CoQ10H2 to total CoQ characterized patients with impaired fasting glucose versus controls, and this level was even lower in patients with type 2 diabetes.45 Asano et al.47 observed a tendency of decreased CoQ10 levels and increased CoQ10H2 levels in the plasma of 18 patients with hyperlipidemia and type 2 diabetes treated with fenofibrate. Hasegawa et al.48 observed modifications of the plasma antioxidant ratio in patients with type 2 diabetes, possibly associated with increased oxidative stress in diabetes and characterized
by an increased ratio of oxidized CoQ10 to reduced CoQ10 and a decreased vitamin E level. Menke et al. reported a significant increase in CoQ10 levels in the plasma of children with type 1 diabetes, with no change in the ratio of plasma CoQ10 to cholesterol, an observation suggesting that the type of diabetes could modulate the CoQ10 status differently.

Animal studies. Data obtained in different models of diabetes in animals report either increased or decreased levels of CoQ in blood and tissues.

Sena et al. observed a significant decrease in plasma total CoQ10 in Goto-Kakizaki rats, while two other studies in rats with streptozotocin-induced diabetes showed increased CoQ levels, with the first study showing increased CoQ9 and CoQ10 levels in blood and the second study showing increased plasma CoQ9 levels in diabetic rats fed a high-cholesterol diet.

In the liver, CoQ10 levels were significantly increased in the mitochondria of rats with severe hyperglycemia (diabetes induced with streptozotocin) and mild hyperglycemia (Goto-Kakizaki rats) but, in another study, were significantly decreased in the mitochondria of rats with streptozotocin-induced diabetes. Liver CoQ9 levels were increased in another study of rats with streptozotocin-induced diabetes fed a high-cholesterol diet.

CoQ levels in animals were also assessed in several other tissues (pancreas, heart, kidney, skeletal muscle). Sena et al. observed a trend of decreased CoQ10 levels in pancreatic mitochondrial preparations of Goto-Kakizaki rats. Kucharska et al. observed decreased CoQ levels in heart mitochondria and increased CoQ9 levels in heart, kidney, and skeletal muscle in rats with streptozotocin-induced diabetes. Kuselova et al. also observed an increased CoQ10 concentration in the myocardium of rats with streptozotocin-induced diabetes fed a high-cholesterol diet.

The specific effect of CoQ supplementation in diabetes will be further discussed in another section (Table 2).

### COENZYME Q SUPPLEMENTATION AND OBESITY

**Human studies**

One study in obese individuals showed a promising effect of CoQ10 supplementation on body weight. Van Gaal et al. reported a greater weight loss in morbidly obese patients with CoQ10 deficiency upon caloric restriction and CoQ10 supplementation during 2 months compared with morbidly obese patients under caloric restriction without CoQ10 supplementation. This study was conducted almost 20 years ago in a small intervention group of patients and has never been confirmed by a larger intervention study.

**Animal and cell studies**

In animals, supplementation with CoQ has been associated with the improvement of different parameters associated with obesity but is not associated with any change in body weight. In a genetic model of obese mice, the

---

**Table 1 CoQ10 supplementation in obesity in human and animals studies.**

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Reference</th>
<th>Target population</th>
<th>Treatment</th>
<th>Significant effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Van Gaal et al. (1984)&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Morbidly obese patients on caloric restriction</td>
<td>2 months</td>
<td>Larger weight loss</td>
</tr>
<tr>
<td></td>
<td>Carmona et al. (2009)&lt;sup&gt;56&lt;/sup&gt;</td>
<td>ob/ob mice</td>
<td>10 mg/kg/day, ip administration, for 13 days</td>
<td>Decreased TNFα mRNA expression in adipose tissue</td>
</tr>
<tr>
<td></td>
<td>Kunitomo et al. (2008)&lt;sup&gt;57&lt;/sup&gt;</td>
<td>SHR/Ndmcrcp/cp rats fed a high-fat diet</td>
<td>0.07%, 0.2%, and 0.7% in the diet, for 26 weeks</td>
<td>Decreased oxidative stress, nitrosative stress, inflammation, hypertension, and hyperinsulinemia</td>
</tr>
<tr>
<td></td>
<td>Sohet et al. (2009)&lt;sup&gt;58&lt;/sup&gt;</td>
<td>C57Bl6J mice fed a high-fat diet and 21% fructose in the water</td>
<td>1% in the diet, for 60 days</td>
<td>Tendency or significant increase of the expression of genes involved in inflammation following high-fat diet supplemented with fructose</td>
</tr>
<tr>
<td></td>
<td>Ratnam et al. (2009)&lt;sup&gt;59&lt;/sup&gt;</td>
<td>Sprague-Dawley rats fed a high-fat diet</td>
<td>Coadministration of CoQ10 and ellagic acid in suspension or in nanoCAPs</td>
<td>CoQ10 tended to blunt this effect</td>
</tr>
</tbody>
</table>

**Abbreviations**: ip, intraperitoneal; nanoCAPs, nano-co-encapsulated antioxidant particles; TNFα, tumor necrosis factor alpha.
### Table 2  CoQ10 supplementation in diabetes in in vivo, animal, and human studies.

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Reference</th>
<th>Population studied</th>
<th>Dosage</th>
<th>Effects observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>Cong et al. (1996)</td>
<td>Rat pancreatic islets</td>
<td>CoQ10 (0 to 8 μM; 90 min)</td>
<td>No significant modification of insulin release (but a 25% increase in insulin secretion at 8 μM CoQ)</td>
</tr>
<tr>
<td></td>
<td>Schroeder et al. (2005)</td>
<td>Mouse pancreatic islets incubated with IL1B (1,000 U/3 mL)</td>
<td>CoQ10 (10^{-12} to 10^{-6} M), lipoic acid (10^{-12} to 10^{-6} M), 48 h</td>
<td>The antioxidant CoQ and lipoic acids blocked IL1B-mediated inhibition of glucose-stimulated insulin secretion from islet cells</td>
</tr>
<tr>
<td></td>
<td>Tsunek et al. (2007)</td>
<td>Human umbilical vein endothelial cells, high glucose (30 mM)</td>
<td>CoQ10 10 μM, 24 h</td>
<td>Inhibition of reactive oxygen species induced apoptosis</td>
</tr>
<tr>
<td>Animal</td>
<td>Ayaz et al. (2008)</td>
<td>Sprague-Dawley rats, ip injection of 50 mg/kg BW of STZ</td>
<td>CoQ10 10 mg/kg/day, 2 weeks</td>
<td>Improvement of high-glucose-induced endothelial dysfunction</td>
</tr>
<tr>
<td></td>
<td>Sena et al. (2008)</td>
<td>Goto-Kakizaki rats</td>
<td>3 times a week ip injection of CoQ10 (20 mg/kg BW) and/or vitamin E (200 mg/kg BW), 8 weeks</td>
<td>Neuroprotective effect of CoQ10 supplementation related to changes in nerve velocities associated with diabetes</td>
</tr>
<tr>
<td></td>
<td>Moreira et al. (2005)</td>
<td>Goto-Kakizaki aged diabetic rats</td>
<td>CoQ10 ip injection 20 mg/kg/ every 2 days, 7 weeks</td>
<td>No change in CoQ10 in the plasma, but CoQ10 increased in pancreatic mitochondrial preparation following CoQ10 supplementation</td>
</tr>
<tr>
<td></td>
<td>Al-Thakafy et al. (2004)</td>
<td>Wistar rats, ip injection of 55 mg/kg BW of STZ</td>
<td>CoQ10 10 mg/kg/day, 4 weeks (1 to 5 months after STZ injection)</td>
<td>Following CoQ10 + vitamin E supplementation, level of HbA1c decreased; no change in the development of pancreatic lesions</td>
</tr>
<tr>
<td></td>
<td>Modi et al. (2006)</td>
<td>STZ-induced diabetic rat (40 mg/kg, iv)</td>
<td>CoQ10 ip injection 10 mg/kg/day, 4 weeks</td>
<td>CoQ10 attenuated the decreased in oxidative phosphorylation efficiency and avoided the increase in H_{2}O_{2} production in brain-isolated mitochondria treated with a neurotoxic peptide</td>
</tr>
<tr>
<td></td>
<td>Ratnam et al. (2008)</td>
<td>Sprague-Dawley rats treated with STZ (ip 55 mg/kg), selection of rats with blood glucose level &gt;250 mg/dL, treatment started 6 weeks after injection</td>
<td>Oral administration of ellagic acid + CoQ10 in nanoCAPS (50 mg/kg alone or 25 mg/kg together) each day or every 3 day, 2 weeks</td>
<td>Significant decrease in elevated levels of glucose, cholesterol, TG, VLDL, LDL, and atherogenic index, and significant increase in HDL</td>
</tr>
<tr>
<td></td>
<td>Rauscher et al. (2001)</td>
<td>Sprague-Dawley rats, 30 days after 100 mg/kg ip induction of diabetes with STZ</td>
<td>CoQ10 10 mg/kg/day, 14 days</td>
<td>Significant decrease in AUC 120 min for glucose, without a change in plasma insulin level and the AUC 120 min for insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased lipid peroxidation and increased antioxidant parameters in the liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased the elevated blood pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diminution of lipid peroxidation and dyslipidemia and prevention of organ damage by the combination of ellagic acid and CoQ10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased oxidized glutathione in the liver of CoQ10-treated mice compared with control mice</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased oxidized glutathione in the brain of CoQ10-treated mice compared with STZ mice</td>
</tr>
<tr>
<td>Type of study</td>
<td>Reference</td>
<td>Population studied</td>
<td>Dosage</td>
<td>Effects observed</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td>--------------------</td>
<td>--------</td>
<td>-----------------</td>
</tr>
</tbody>
</table>
| Human        | Andersen et al. (1997)⁶⁴ | Patients with insulin-dependent diabetes | CoQ10 100 mg/day, 12 weeks | Two-fold increased serum concentration of CoQ10 with no improvement in glycemic control. 
No change in cholesterol level or blood pressure. 
Serum concentration of CoQ10 significantly increased with no difference in glycemic control or total insulin doses, nor in hypoglycemic episodes, during the entire intervention period. |
|              | Henriksen et al. (1999)⁶³ | Patients with T1DM requiring insulin 4 times a day | CoQ10 100 mg/day, 3 months | No improvement in glycemic control. 
No change in cholesterol levels or blood pressure. |
|              | Lim et al. (2008)⁶⁴ | Patients with T2DM | CoQ10 200 mg/day, 12 weeks | Stable metabolic control. 
Increased plasma CoQ10 cholesterol increased, with no change in ubiquinol/total CoQ10 in the CoQ10-supplemented patients. |
|              | Hodgson et al. (2002)⁶¹ | Patients with T2DM and dyslipidemia | Fenofibrate (200 mg/day) and/or CoQ10 (200 mg/day), 12 weeks | CoQ10: increased CoQ10 serum concentration, lowered systolic BP and diastolic BP, and lowered HbA1c, with no change in fasting plasma glucose, fasting serum insulin, or plasma F2-isoprostanes. |
|              | Playford et al. (2003)⁶⁰ | Diabetic and dyslipidemic patients | CoQ10 (200 mg/day) and/or fenofibrate (200 mg/day), 12 weeks | No reduction in plasma F2-isoprostanes, but systolic BP and HbA1c were lower following CoQ10 supplementation. |
|              | Chew et al. (2008)⁶⁰ | Patients with T2DM and mild left ventricular diastolic dysfunction and good control of BP, lipids, and glycemia | 160 mg/day fenofibrate and/or 200 mg/day CoQ10, 6 months | Improved endothelial and nonendothelial vasodilative function of the forearm microcirculation following fenofibrate and CoQ10 supplementation. |
|              | Watts et al. (2002)⁶² | Patients with T2DM and dyslipidemia | 200 mg/day, 12 weeks | Increased flow-mediated dilatation. 
Increased plasma CoQ10 level, with no modification of plasma F2-isoprostanes, oxygen radical absorbance capacity, lipids concentrations, glycemic control, or BP. |
|              | Hamilton et al. (2009)⁶⁵ | Patients with T2DM treated with statins | 200 mg/day, 12 weeks | CoQ10 supplementation improved endothelial dysfunction. 
CoQ10 supplementation did not change oxidative stress parameters. |
|              | Suzuki et al. (1998)⁶⁵ | Patients with MIDD | 150 mg/day, 3 years | Prevention of progressive insulin secretory defect, exercise intolerance, and hearing loss in MIDD patients. |
|              | Bergamin et al. (2008)⁶⁶ | Case report of a patient with MIDD | 100 mg/day, 3 years | Disappearance of gastrointestinal symptoms. |
|              | Suzuki et al. (1995)⁶⁶ | Case report of a patient with diabetic amyotrophy associated with 3243 mitochondrial DNA mutation | CoQ10 30–210 mg/day, 3 to 5 months | Improvement of fatigue, paresthesia in legs, palpitations and chest discomfort, constipation, and sleep disturbances. |
|              | Suzuki et al. (1997)⁶⁶ | Patients with diabetic amyotrophy associated with 3243 mitochondrial DNA mutation | CoQ10 150 mg/day, 6 months | Gradual improvement of left ventricular function, with increase in fractional shortening and ejection fraction; improved systolic function. |
|              | Salles et al. (2006)⁶⁷ | Case report of a patient with MIDD and congestive heart failure (3243 mutation) | CoQ10 30–210 mg/day, 3 to 5 months | Improvement of fatigue, paresthesia in legs, palpitations and chest discomfort, constipation, and sleep disturbances. |

Abbreviations: AUC, area under the curve; BP, blood pressure; BW, body weight; CoQ10, coenzyme Q10; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IL1β, interleukin 1 beta; ip, intraperitoneal; LDL, low-density lipoprotein; MIDD, maternally inherited diabetes and deafness; nanoCAPs, nano-co-encapsulated antioxidant particles; STZ, streptozotocin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TG, triglycerides; VLDL, very-low-density lipoprotein.
ob/ob mice, intraperitoneal CoQ10 supplementation had no effect on body weight gain, on fat mass development, or on glucose tolerance but tended to normalize insulin and glucose levels. Moreover, CoQ10 supplementation decreased TNFα mRNA expression and increased lipid oxidation in the white adipose tissue and decreased lipid levels in blood (triglycerides and nonesterified fatty acids). In SHR/NDmcr-cp rats fed a high-fat diet and presenting several characteristics of the metabolic syndrome (hypertension, obesity, glucose intolerance, and hyperlipidemia), CoQ10 supplementation during 26 weeks suppressed oxidative stress, nitrosative stress, inflammation, hypertension, and hyperinsulinemia. In a model of mice fed a high-fat diet plus fructose, CoQ10 supplementation during 8 weeks tended to blunt the induction of a panel of inflammatory genes (i.e., NADPH oxidase, cyclooxygenase 2, 6 transmembrane proteins of prostate 2, C-reactive protein, interleukin 6, TNFα, cluster of differentiation 68), with no effect on glucose tolerance and body weight. In a model of Sprague-Dawley rats fed a high-fat diet, cosupplementation with CoQ10 and ellagic acid during 2 weeks was associated with decreases in glucose, total cholesterol, low-density lipoprotein cholesterol level, and plasma triglycerides and with an improved protection of endothelium.

Based on the experimental data suggesting that CoQ may act as antiadipogenic factor, administered, to obese mice, CoQ together with rosiglitazone, a ligand of peroxisome proliferator-activated receptor γ (PPARγ), which is a lead regulator of adipocyte differentiation and function. Rosiglitazone, which increases insulin sensitivity, has been proposed for the treatment of type 2 diabetes, but its use is limited due to its adverse side effects on cardiovascular events and on adiposity (increased storage in adipose tissue and increased free fatty acids). Interestingly, in both nutritional (mice fed a high-fat diet) and genetic (ob/ob mice) models of obesity, the coadministration of CoQ and rosiglitazone prevents the increase in body weight and adiposity that occurs with rosiglitazone treatment. The decreases in body weight and adiposity are associated with increased lipid oxidation in inguinal adipose tissue of CoQ-treated animals. These results highlight the potential role of CoQ in adiposity, which was recently confirmed in an in vitro study conducted by Bour et al. They showed that the inhibition of CoQ synthesis by a pharmacological approach leads to increased adipocyte differentiation, triglyceride accumulation, and a higher expression of PPARγ and fatty acid synthase (two markers of adipocyte differentiation) in 3T3-F442A cells. On the contrary, the enhancement of CoQ synthesis by overexpression of the COQ2 gene (4-hydroxy benzoate acid polypropenyl transferase, a key enzyme of CoQ biosynthesis) leads to decreased adipocyte differentiation, as assessed by decreased accumulation of triglycerides and decreased expression of adipocyte fatty acid binding protein (aP2) and PPARγ mRNA. The decreased adipocyte differentiation is associated with decreased production of reactive oxygen species. Altogether, these results obtained in animal and cell models highlight a new function for CoQ in the control of adiposity.

COENZYM E Q SUPPLEMENTATION AND DIABETES

Human studies

An improvement in glycemia, as assessed by HbA1c measurements, was reported in two intervention studies performed in dyslipidemic type 2 diabetic patients, while three other studies reported no change in glycemic control upon CoQ10 supplementation. The lack of improvement in oxidative stress, mainly assessed by serum F2-isoprostanes (a marker of lipid peroxidation), has been reported a few times. CoQ supplementation also showed beneficial effects in particular diabetic conditions such as maternal inherited diabetes and deafness and diabetic amyotrophy associated with the 3243 mutation in the mitochondrial DNA. A clinical intervention study in diabetic patients with this mutation (n = 15) showed that CoQ10 supplementation could improve fatigue, paresthesia in the legs, palpitation and chest discomfort, constipation, and sleep disturbances. Three other case studies reported that CoQ supplementation in patients with this same condition prevented exercise intolerance, hearing loss, and the progressive defect of insulin secretion, improved gastrointestinal symptoms, and improved the symptoms of fatigue, paresthesia in the legs, and residual urine in bladder, associated with an improvement in neurological parameters. Finally, another case study of patients with mitochondrial diabetes and congestive heart failure reported the gradual improvement of left ventricular function, associated with increases in fractional shortening and improvement of systolic function upon CoQ10 supplementation.

Animal studies

CoQ10 supplementation in diabetic animals has shown various effects, such as improvement in oxidative stress (decreased lipid peroxidation or modulation of antioxidant enzyme activity), improvement in lipidemia (decreased triglycerides, total cholesterol, low-density lipoprotein cholesterol, and very-low-density lipoprotein cholesterol), and increased high-density lipoprotein cholesterol, and improvement in blood pressure. There are conflicting reports about the effect of CoQ10...
supplementation on glucose homeostasis: some authors observed no change in glucose\textsuperscript{3,74} or insulin levels,\textsuperscript{74} while Modi et al.\textsuperscript{75} observed an improvement in the area under the curve of glycemia upon intraperitoneal CoQ10 supplementation in rats with streptozotocin-induced diabetes. CoQ10 supplementation could also be associated with an improvement in complications of diabetes, such as modification of nerve fiber velocity associated with diabetic neuropathies.\textsuperscript{73} Another study in aged Goto-Kakizaki rats showed a slight effect of CoQ10 supplementation that prevented the decrease of ATP levels and the increase of H$_2$O$_2$ production induced by amyloid β-peptide, a neurotoxic agent that mimics the mitochondrial dysfunction in diabetes.\textsuperscript{76}

**In vitro studies**

In vitro, the incubation of isolated rat and mice pancreatic islets with CoQ10 did not modify\textsuperscript{77} (or even increased) the release of insulin.\textsuperscript{78} Incubation of human umbilical vein endothelial cells under high-glucose conditions with CoQ10 was associated with an inhibitory effect against endothelial dysfunction.\textsuperscript{79}

**COENZYME Q AND HYPERTENSION**

CoQ10 supplementation has been shown to exert hypotensive effects in diabetic patients\textsuperscript{60,61,80} and in animals with streptozotocin-induced diabetes.\textsuperscript{72}

The effect of CoQ10 on blood pressure has also been assessed in nondiabetic patients. During the last few years, three meta-analyses supported the effect of CoQ10 as an antihypertensive compound\textsuperscript{81–83} even though they all concluded that further larger studies are needed to prove this effect. The first meta-analysis was conducted by Rosenfeldt et al.\textsuperscript{82} and showed a decrease of 16 mmHg systolic and 10 mmHg diastolic blood pressure after 8 to 12 weeks of treatment and included eight studies (4 with placebo, 4 without placebo). The second meta-analysis was also conducted by Rosenfeldt et al.\textsuperscript{83} but included 12 studies: three randomized controlled trials (RCT, n = 120), one crossover study (CS, n = 18), and eight open-label observational studies (OPOS, n = 214). The RCT, CS, and OPOS were analyzed separately, but all showed reduced systolic (RCT, −16.5 mmHg; CS, −11 mmHg; OPOS, −13.5 mmHg) and diastolic (RCT, −8 mmHg; CS, −8 mmHg; OPOS, −10 mmHg) blood pressure after CoQ10 treatment. The third meta-analysis was conducted by Ho et al.\textsuperscript{81} Following the Cochrane methodology, only three trials were included in the study. Conclusive antihypertensive effects were observed, with decreases in systolic blood pressure (−11 mmHg), diastolic blood pressure (−7 mmHg), and heart rate (−12%) (data for this last parameter were available from only 1 of the 3 trials included) in patients with systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. Further studies are needed, however, because only 96 patients were included in that meta-analysis, which is not sufficient to prove an antihypertensive effect of CoQ10. Other clinical small-scale CoQ10 supplementation studies also show interesting tendencies with, e.g., decreased systolic blood pressure and diastolic blood pressure, and decreased levels of high-sensitivity C-reactive protein and creatinine in patients with massive hypertriglyceridemia.\textsuperscript{84}

CoQ10 is not a typical hypotensive compound but might reverse some metabolic alterations involved in hypertension. Its primary action is vasodilatation, via a direct effect on the endothelium and vascular smooth muscle, resulting in decreased peripheral resistance accompanying lowered blood pressure. The free radicals (superoxide anion) overproduced in the hypertensive state could be quenched by CoQ10, thus preventing the reaction between nitric oxide and superoxide, which in turn preserves nitric oxide availability and its vasodilator effect.\textsuperscript{82,83,85,86} Besides the potential effect on vascular endothelium via its antioxidative properties, the hypotensive effect of CoQ10 could also influence other mechanisms (i.e., decreased blood viscosity, improved diastolic function, decreased aldosterone secretion, and altered angiotensin effect on sodium retention), as reviewed by Kumar et al.\textsuperscript{85}

**COENZYME Q, LIPEMIA, AND ATHEROSCLEROSIS**

Oxidized low-density lipoprotein cholesterol exhibits potential proatherogenic activities, leading to impairment of endothelial function, attraction to and retention of blood monocytes in the intimal space, promotion of foam cell formation, inducement of cytotoxicity, and cell proliferation. Oxidized phospholipids play a central role in the development of atherosclerosis.\textsuperscript{87} CoQH$_2$ has been proposed as an antioxidant with potential usefulness in controlling the oxidation of low-density lipoprotein cholesterol, namely because of its capacity to avoid the accumulation of tocopheryl radicals that would compromise vitamin E efficacy.\textsuperscript{86,88}

When given at a low dose (4.3 mg CoQ10/kg body weight), CoQ10 failed to control atherosclerosis in Watanabe heritable hyperlipidemic rabbits\textsuperscript{89} as well as in hyperlipidemic and atherosclerotic mice issued by crossing Mclk1+/− mice (with CLK1/MCLK1 being a mitochondrial hydroxylase required for CoQ10 synthesis) with apolipoprotein E−/− and low-density lipoprotein receptor−/− mice.\textsuperscript{90} CoQ10 supplementation was, however, able to inhibit atherosclerosis in rabbits without
modifying cholesterol or triglyceride levels. In apolipo-
protein E knockout mice fed a high-fat diet, CoQ10 reduced athero-
sclerosis – especially in the aortic root, the proximal and distal aortic arches, the descending thoracic aorta, and the abdominal aorta – particularly when combined with vitamin E. However, based on a human study, Tomasetti et al. hypothesized that the ratio of lipids to CoQ10 could be a marker of increased risk for atherosclerosis in healthy individuals.

COENZYME Q AS AN ADJUVANT IN DRUG TREATMENT: THE EXAMPLE OF THE STATINS

Statins are hydroxymethylglutaryl coenzyme A reductase inhibitors, used to lower cholesterol levels by inhibition of the cholesterol biosynthetic pathway. Blood CoQ10 levels have been shown to decrease in statin-treated patients due to the inhibition of the CoQ10 synthesis, which shares part of cholesterol biosynthetic pathway. As reviewed by Littarru and Langsjoen, varying degrees of CoQ10 depletion in blood and tissue have been described in animals treated with statins. In those animal studies, CoQ10 deficiency can be prevented by CoQ10 supplementation. In human studies, the depletion in blood levels of CoQ10 after treatment with statins is associated with muscle CoQ10 deficiency. Muscular CoQ10 deficiency is one of effects of statin treatment, which has been related to muscle pain, rhabdomyolysis, muscle weakness, and neuropathy. Mitochondrial dysfunction due to reduced CoQ10 levels could be part of the syndrome.

It has been proposed by several authors that CoQ10 supplementation could counteract the side effects of statins. Several studies assessed the potential beneficial role of CoQ10 supplementation in statin-treated patients with myopathic symptoms, with promising or less promising results. In particular, Langsjoen et al. describe a decrease in fatigue (from 84% to 16%), in myalgia (from 64% to 6%), in dyspnea (from 58% to 12%), in memory loss (from 8% to 4%), and in peripheral neuropathy (from 10% to 2%) in patients with continuous statin treatment who were supplemented with CoQ10. To date, there are not enough studies to demonstrate a definitive role of CoQ10 for treating the side effects of statin therapy. In light of several studies that reported beneficial effects of CoQ10 supplementation in statin-treated patients, some patients could likely benefit from CoQ10 supplementation, but it is still unknown if the resulting effect is attributable to CoQ10 or to a placebo-like effect. In any case, the classical way to avoid statin-induced myopathy is to use the lowest possible dosage of statins to achieve the targeted decrease in cholesterol.

CONCLUSION

A number of authors have suggested that a decrease in serum CoQ levels could be a good marker of pathologies associated with oxidative stress. From the articles reviewed here, it seems difficult to generalize this conclusion to the pathologies associated with obesity. Nevertheless, CoQ supplementation might play a protective role in the control of metabolic disorders such as hypertension, for example. Although the antioxidant properties of CoQ often receive the most attention, CoQ is also involved in the following: electron transport chain in the mitochondria, activation of mitochondrial uncoupling proteins, and regulation of mitochondrial permeability transition pores. This review reveals two areas of research that seem particularly interesting for investigating the potential usefulness of CoQ in the management of metabolic disorders associated with obesity. The first is the potential usefulness of CoQ as an anti-inflammatory compound, which must still be proven in vivo, namely, in human studies. The second is the contribution of CoQ to the regulation of adipose tissue metabolism, studies of which could help assess the physiological relevance of the endogenous synthesis of CoQ in adipose cells. CoQ thus appears to be a novel molecular target and not solely a dietary supplement with antioxidant properties.

Acknowledgment

Funding. The funding for experimental data obtained for the PhD thesis of Florence Sohet – not presented in this manuscript – was provided by Kaneka, Inc., a company that produces chemical products, including food supplements (e.g., coenzyme Q10). The funding source had no impact on the collection, analysis, or interpretation of the data, on the writing of this review, or on the decision to submit this review for publication.

Declaration of interest. The authors have no relevant interests to declare.

REFERENCES


