



## **Coenzyme Q10 may be effective in the treatment of non alcoholic fatty liver disease (NAFLD)**

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### **Abstract**

Nonalcoholic fatty liver disease (NAFLD) represents a spectrum of disorders characterized by predominantly macrovesicular hepatic steatosis that occur in individuals even in the absence of consumption of alcohol in amounts considered harmful to the liver. At present, there is no standard recommended treatment for NAFLD. Treatment currently focuses on gradual weight loss through diet and regular exercise. Insulin sensitizers such as thiazolidinediones and metformin show promise, and several studies have explored the role of lipid lowering agents and antioxidants. Coenzyme Q10 (CoQ) is a powerful antioxidant and has an important role in respiratory metabolism, as a mobile electron and proton carrier in the mitochondrial electron transport chain. However, to date, there is no published clinical trial on CoQ in NAFLD. We postulate the hypothesis that CoQ might be effective in the treatment of NAFLD.

### **Keywords**

*Coenzyme Q10, Nonalcoholic fatty liver disease (NAFLD)*

### ***Nonalcoholic fatty liver disease (NAFLD)***

Nonalcoholic fatty liver disease (NAFLD) is a significant health problem worldwide. It affects 70 million adults in the United States (30% of the adult population) (1). NAFLD is a clinicopathologic syndrome ranging from simple steatosis, which is relatively benign, to the more severe form known as nonalcoholic steatohepatitis (NASH), which may progress to cirrhosis, liver failure, and

hepatocellular carcinoma (2,3). The pathogenesis of NAFLD has not been fully elucidated. The initial insult is the accumulation of hepatic fat secondary to insulin resistance (4). In the setting of hepatic steatosis, the second hit can be caused by reactive oxygen species, inflammatory cytokines, and adipokines such as TNF- $\alpha$ , leptin, and adiponectin (5).

Several therapeutic modalities that target these mechanisms are under investigation, but no

proven treatment has yet emerged. Insulin sensitizers such as thiazolidinediones and metformin show promise, and several studies have explored the role of lipid lowering agents, antioxidants, and cytoprotective agents. Novel agents such as anti-obesity drugs, selective cannabinoid-1 receptor blockers, and dual PPAR alpha and gamma agonists are also under investigation. NAFLD treatment currently focuses on reducing metabolic risk factors, with the mainstay of therapy focusing on life-style modifications such as gradual weight loss through diet and regular exercise (6).

Insulin resistance has a key role in the development of hepatic steatosis and potentially steatohepatitis (7). The two main mechanisms of insulin resistance are lipolysis and hyperinsulinemia. Lipolysis increases circulating fatty acids. Increased uptake of fatty acids by hepatocytes leads to mitochondrial  $\beta$ -oxidation overload, with the consequent accumulation of fatty acids within hepatocytes. FFAs are inducers of several cytochrome p-450 microsomal lipoxigenases, capable of producing hepatotoxic free oxygen radical species. It has been reported that mitochondrial dysfunction and increase production of ROS occurs during hyperglycemia which leads to the oxidative stress (8). Free radicals and lipid peroxidation can deplete antioxidants system, thus rendering the liver susceptible to oxidative injury (9).

Hyperinsulinemia resulting from insulin resistance increases the synthesis of fatty acids in hepatocytes by increasing glycolysis and favors the accumulation of triglycerides within hepatocytes by decreasing hepatic production of apolipoprotein B-100 (10). Hepatic fatty acids are normally esterified into triglycerides, some of which are exported out of hepatocytes as very-low-density lipoproteins (VLDL). The increased level of lipids, mostly in the form of triglycerides, within hepatocytes in patients with nonalcoholic fatty liver disease results from an imbalance between the enzyme systems that promote the uptake and synthesis of fatty acids and those promote the oxidation and export of fatty acids (10).

Resistance to the action of insulin results in important changes in lipid metabolism. These include enhanced peripheral lipolysis, increased triglyceride synthesis, and increased hepatic uptake of fatty acids. Each of these may contribute to the accumulation of hepatocellular triglyceride (11).

Impaired VLDL synthesis and secretion can result from abetalipoproteinemia, protein malnutrition, or choline deficiency. Patients with NASH may have a defect in postprandial Apo B secretion, leading to triglyceride accumulation (12). Impaired  $\beta$ -oxidation of FFA to ATP may be seen with vitamin B5 (pantothenic acid) deficiency, excessive alcohol consumption, or coenzyme A

deficiency (as can occur with valproic acid or chronic aspirin use). Activation of peroxisome proliferator-activated receptor alpha appears to have a central role in stimulating  $\beta$ -oxidation and disposing hepatic fatty acids in NASH (13). The ability to recover from hepatic ATP depletion is severely impaired in patients with obesity-related NASH (14).

### *Coenzyme Q10 and our hypothesis*

Coenzyme Q10 (CoQ) or ubiquinone, a lipid-soluble component of virtually all cell membranes, is an isoprenylated benzoquinone. CoQ has an important role in respiratory metabolism, as a mobile electron and proton carrier in the mitochondrial electron transport chain (15). In eukaryotes, CoQ shuttles electrons from complexes I and II to complex III in the mitochondrial electron transfer system. Recently, it has been demonstrated that CoQ also functions as an antioxidant, which protects the cells both directly by preventing lipid peroxidation and indirectly by regenerating other antioxidants such as ascorbate and  $\alpha$ -tocopherol. In the plasma membrane, CoQ functions in the transmembrane electron transport to stabilize extracellular ascorbate (16). Approximately half of the body's CoQ is obtained through dietary fat ingestion, whereas the remainder results from endogenous synthesis (17). It has been reported that CoQ supplementation increases life-span of rats fed on a diet enriched with polyunsaturated fatty acids (18, 19). Sutken et al reported that CoQ protects liver tissue against ochratoxin A toxicity (20). Bello et al showed that CoQ-supplemented diet enhanced antioxidant protection of liver membranes in long-lived rats (21). It has been reported that CoQ provides some protection against cardiotoxicity or liver toxicity during cancer treatment (22). Grudzinski et al have found that CoQ has a promising antioxidant agent in sodium nitrite-induced lipid peroxidation (23). Yesilova et al showed the increased systemic levels of malondialdehyde and depletion of antioxidants such as CoQ, CuZn-superoxide dismutase, and catalase activity in NAFLD. They concluded that disturbances in lipid metabolism may contribute to altered oxidative status in NAFLD, and insulin resistance may be related to decreased antioxidants in NAFLD as well as products of lipid peroxidation (24).

With the potential role of CoQ in the  $\beta$ -oxidation of fatty acid that is also implicated in the cell defense against reactive oxygen species (ROS) and free radical damage, we propose that CoQ might be effective in NAFLD as shown in figure 1. To our knowledge there is not any report showing the benefit CoQ in NAFLD.

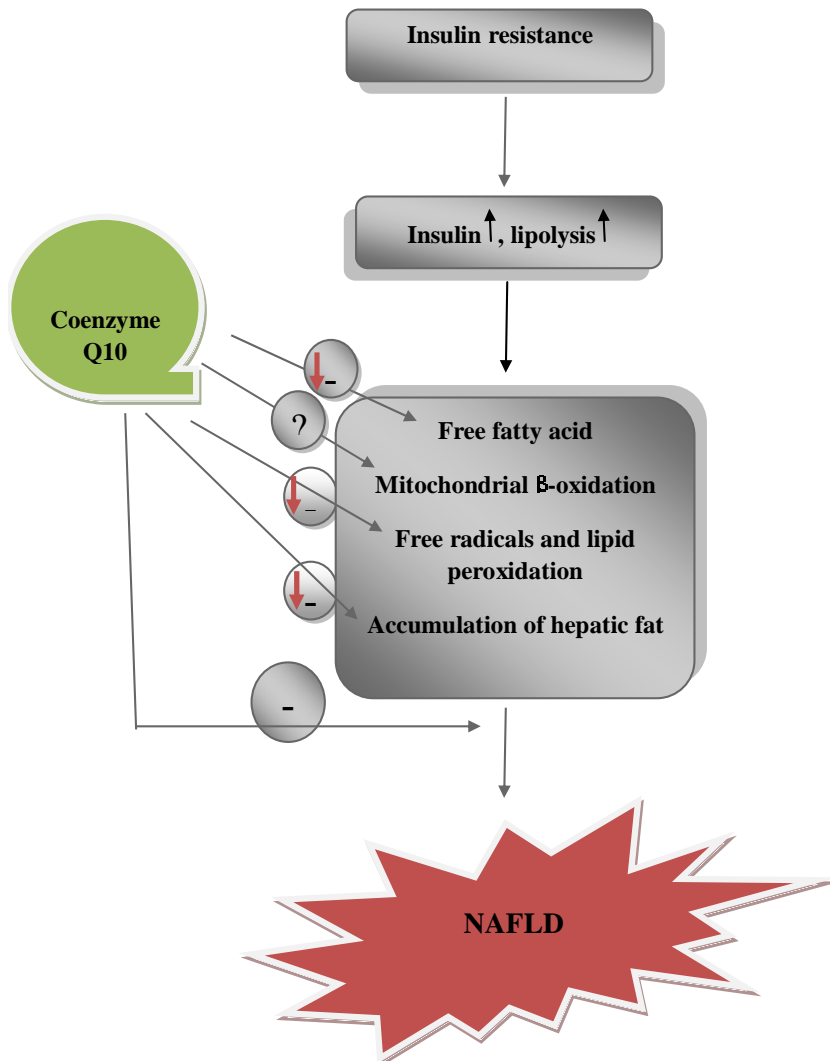
### *Evaluation of the hypothesis*

Our hypothesis might provide a novel therapeutic strategy for patients with NAFLD which currently the only effective treatment is caloric restriction. With the aid of animal model, (for instance, experimental NAFLD), this hypothesis could be partially or fully confirmed.

To test the hypothesis, NAFLD can be induced in rats fed by methionine choline-deficient diet for 9 weeks as described previously (25-27). Then the rats can be divided randomly into different groups and treated with CoQ and other drugs to evaluate the liver steatosis, MDA and other biochemical factors. By this experiment, we could evaluate the effect of CoQ in NAFLD.

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**Figure 1.** Schematic representative the pathogenesis of NAFLD and the potential site of Coenzyme Q10 action in the treatment of disease