Coenzyme Q_{10}

Introduction

Coenzyme Q_{10} is a "semi-vitamin": a nutrient which can be synthesised in the body - but in amounts that are insufficient for metabolic needs - and which is also present in food. First isolated in 1957 [1], it acts as a cofactor in the electron transport system, carrying electrons from Complex I and Complex II to Complex III; CoQ_{10} also an important antioxidant component of the membranes and tissues within which it is located [2]. Research into this compound's role in electron transport was the subject for the Nobel Prize in Chemistry in 1978.

The dietary requirement for CoQ_{10} is not known and is presumed to be variable, depending on the condition of the individual. Inhibition of HMG CoA reductase by statin drugs to reduce serum cholesterol has the effect of reducing endogenous coenzyme Q_{10} synthesis, thus increasing the dietary requirement. Various medical conditions, including renal and ischaemic heart disease, cardiac failure, neurological disease (such as Parkinson's) and muscular degenerative disorders (such as mitochondrial myopathies) have been reported as lowering CoQ_{10} levels. As such, knowledge of CoQ_{10} physiology is progressing into the description of the long latency effects of CoQ_{10} deficiency, in which energy production requirements may be satisfied, but nevertheless there are deficiency effects that may be observed around the body.

The short-term effect of a marked deficiency of CoQ_{10} is thus malfunctioning of mitochondrial energy production. There has been interest in a therapeutic role for CoQ_{10} in a variety of medical conditions. In 1961 it was first examined as an agent for the treatment of cancer [3], when low levels were noted in the blood of breast cancer patients. Coenzyme Q_{10} has been shown, in animal models, to stimulate the immune system, enhancing antibody production as well as the activities of macrophages and T cell lymphocytes [4,5]. Coenzyme Q_{10} has also been reported to increase IgG antibody levels and to increase the CD4 to CD8 T-cell ratio in humans [6,7,8].

A number of clinical trials have been done testing the effects of CoQ_{10} in hypertension, which has been the subject of a meta-analysis [9]. This suggested that CoQ_{10} supplementation has the potential to lower systolic blood pressure by up to 17 mm of Hg and diastolic blood pressure by up to 10 mm of Hg, without significant side effects. This finding, as well as providing an interesting insight into the effect of a deficiency of Q_{10}, underlines the dictum that nutrients are required by all tissues and organ systems, and that nutritional treatments have a role to play in a wide variety of human diseases and disorders beyond the condition that was originally associated with the deficiency of a particular nutrient.

Coenzyme Q_{10} and HMG-CoA reductase inhibitors (statins)

HMG-CoA reductase inhibitors (statins) are reported to have a very favorable safety profile [10], with well documented cardiovascular benefits [11,12]. These drugs have their effect by partial enzyme inhibition at an stage early in the mevalonate pathway, which is responsible for the synthesis of cholesterol, as well as coenzyme Q_{10}, haem A and isoprenylated proteins [13,14]. Cholesterol itself is an intermediate to the synthesis of steroid hormones, bile acids and vitamin D, and these compounds have been shown to be affected by statin therapy [15,16]. Thus the biochemical influence of statins extends well beyond effects on plasma low-density lipoprotein, high-density lipoprotein and triglycerides, and even beyond the direct products of the mevalonate pathway, to include a range of other metabolic products, such as nitric oxide [17] and polyunsaturated fatty acids [18].

Statin therapy leads to a dose-dependent reduction in the synthesis of coenzyme Q_{10} [19,20], which is an antioxidant as well as a component of the mitochondrial electron transport chain. Haem A also has a central function in mitochondrial respiration. The muscular and hepatic side effects of statins can thus be

related to the metabolic role of these compounds via a statin-induced mitochondrial dysfunction in affected tissues [21].

Side effects of statin therapy

The most commonly reported side effects of statins are on muscle, and include muscle pain, fatigue, and weakness, as well as rhabdomyolysis. These effects are dose-dependent and can be amplified by drug interactions, for example through inhibition of cytochrome P-450 (several statins - atorvastatin, simvastatin, and lovastatin - are metabolized by the cytochrome P450 pathway). Co-existent disease (such as thyroid disease) and genetic mutations associated with mitochondrial dysfunction can also have the same effect. This evidence supports a mitochondrial foundation for statin-induced muscle side-effects and suggests that mitochondrial dysfunction may also underlie non-muscle statin side effects [22]. Muscle effects arising from statins do not uniformly resolve fully with statin discontinuation [23]. A range of cases have now been reported in which statin use has 'uncovered' previously clinically silent conditions, including McArdle disease, myotonic dystrophy, acid maltase deficiency, and possible Kennedy disease [24,25].

The risk factors for these effects appear to share one or both of two mediating pathways: either increased statin exposure (e.g. dose, drug interactions, genetic variants or other factors that affect clearance or hepatic uptake) or promotion of mitochondrial dysfunction. Reduced concentrations of coenzyme Q_{10} are particularly a problem in the setting of existing mitochondrial dysfunction; it is known that an excess of available coenzyme Q_{10} can over-ride a range of respiratory chain defects [26], improving both ATP production and the redox state of vulnerable cells.

While a variety of causes may contribute to statin side effects, mitochondrial mechanisms have been repeatedly implicated in muscle side effects. Dose-dependent reductions in coenzyme Q_{10} [18,19] can reduce cell energy, promote oxidative stress and apoptosis and unmask silent mitochondrial defects. Conversely, oral coenzyme Q_{10} supplementation increases serum coenzyme Q_{10} levels [27,28] and is presumed to reverse such adverse effects.

Cognitive problems are second only to muscle problems among patient reports of statin side effects [29]. Muscle and brain are the dominant organs clinically affected by pure mitochondrial defects (mitochondrial myopathy and encephalomyopathy are the classical manifestations of respiratory chain disease). For instance, mitochondrial encephalomyopathy resulting from heritable coenzyme Q_{10} deficiency classically produces fatigue, muscle symptoms, and cognitive problems [30].

Prevention of statin-associated side effects

Observational and limited randomized data variably suggest benefits to muscle symptoms and to other side effects of statins from coenzyme Q_{10} supplementation [31,32,33]. Additional studies are required to better understand coenzyme Q_{10} supplementation. One issue is that preparations of coenzyme Q_{10} vary widely in their bioavailability, which makes recommendations as to dosage dependent on the particular form in which the coenzyme Q_{10} is administered (for example, as the –quinone or the –quinol).

Coenzyme Q_{10} in clinical samples

The reference interval for serum coenzyme Q_{10} is from 0.55 – 2.00 µmol/L [34].

Patient preparation:

No special preparation is required other than that the patient should cease taking nutritional supplements containing coenzyme Q_{10} for three days before the collection of the sample.

Specimen requirements

For serum coenzyme Q_{10} measurement, the sample should be collected into an 8 ml serum separator (SST) tube. Collection tubes are available on request. Postal samples should reach the laboratory within 24 hours of collection.

Turn around time: **14** working days.

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