Coenzyme Q_{10}
March 2011

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

• BIOLAB • The Stone House • 9 Weymouth Street • London • W1W 6DB • U.K. •
• Tel: (+44) 020 7636 5959/5905 • Fax (+44) 020 7580 3910 • E-mail: info@biolab.co.uk •

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 Biolab 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 and needles can be supplied by Biolab. Postal samples should reach Biolab within 24 hours of collection.

Turn around time: 7 working days.

References:

1. Pepping J. Coenzyme Q10. Am J Health Syst Pharm 1999;56:519-521.
2. Overvad K, Diamant B, Holm L, et al.: Coenzyme Q10 in health and disease. Eur J Clin Nutr 53 (10): 764-70, 1999.
3. Folkers K, Osterborg A, Nylander M, et al. Activities of vitamin Q10 in animal models and a serious deficiency in patients with cancer. Biochem Biophys Res Commun 1997;234: 296-299.
4. Bliznakov E, Casey A, Premuzic E: Coenzymes Q: stimulants of the phagocytic activity in rats and immune response in mice. Experientia 1970;26: 953-954.
5. Kawase I, Niitani H, Saijo N, et al.: Enhancing effect of coenzyme, Q10 on immunorestoration with Mycobacterium bovis BCG in tumor-bearing mice. Gann 1978;69:493-497.
6. Folkers K, Shizukuishi S, Takemura K, et al. Increase in levels of IgG in serum of patients treated with coenzyme Q10. Res Commun Chem Pathol Pharmacol 1982;38:335-338.
7. Folkers K, Hanioka T, Xia LJ, et al.: Coenzyme Q10 increases T4/T8 ratios of lymphocytes in ordinary subjects and relevance to patients having the AIDS related complex. Biochem Biophys Res Commun 1991;176:786-791.
8. Barbieri B, Lund B, Lundström B, et al. Coenzyme Q10 administration increases antibody titre in hepatitis B vaccinated volunteers--a single blind placebo-controlled and randomized clinical study. Biofactors 1999;9: 351-357.
9. Rosendfeldt FL, Haas SJ, Krum H et al. Coenzyme Q_{10} in the treatment of hypertension: a meta-analysis of the clinical trials. J Human Hypertension 2007;21:297-306.
10. Bernini F, Poli A, Paoletti R. Safety of HMG-CoA reductase inhibitors: focus on atorvastatin. Cardiovasc Drugs Ther 2001; 15 (3): 211-218.
11. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994 Nov 19; 344 (8934): 1383-9.
12. Criqui MH, Golomb BA. Low and lowered cholesterol and total mortality. J Am Coll Cardiol 2004 Sep 1; 44 (5): 1009-1010.
13. Buhaescu I, Izzedine H. Mevalonate pathway: a review of clinical and therapeutical implications. Clin Biochem 2007; 40 (9-10): 575-84.
14. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature 1990 Feb 1; 343 (6257): 425-430.
15. Mol MJ, Stalenhoef AF, Stuyt PM, et al. Effects of inhibition of cholesterol synthesis by simvastatin on the production of adrenocortical steroid hormones and ACTH. Clin Endocrinol (Oxf) 1989; 31 (6): 679-689.
16. Hyyppa MT, Kronholm E, Virtanen A, et al. Does simvastatin affect mood and steroid hormone levels in hypercholesterolemic men? A randomized double-blind trial. Psychoneuroendocrinology 2003; 28 (2): 181-194.
17. Cimino M, Gelosa P, Gianella A, et al. Statins: multiple mechanisms of action in the ischemic brain. Neuroscientist 2007; 13 (3): 208-213.

18. Harris JI, Hibbeln JR, Mackey RH, et al. Statin treatment alters serum n-3 and n-6 fatty acids in hypercholesterolemic patients. Prostaglandins Leukot Essent Fatty Acids 2004; 71 (4): 263-269.
19. De Pinieux G, Chariot P, Ammi-Said M, et al. Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. Br J Clin Pharmacol 1996; 42: 333-337.
20. Rundek T, Naini A, Sacco R, et al. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Arch Neurol 2004; 61: 889-892.
21. Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovascular Drugs 2008;8:373-418.
22. Vladutiu GD, Simmons Z, Isackson PJ, et al. Genetic risk factors associated with lipid-lowering drug-induced myopathies. Muscle Nerve 2006;34:153-162.
23. Tsivgoulis G, Spengos K, Karandreas N, et al. Presymptomatic neuromuscular disorders disclosed following statin treatment. Arch Intern Med 2006 24; 166 (14): 1519-24.
24. Livingstone C, Al Riyami S, Wilkins P, et al. McArdle's disease diagnosed following statin-induced myositis. Ann Clin Biochem 2004; 41: 338-340.
25. Voermans NC, Lammens M, Wevers RA, et al. Statin-disclosed acid maltase deficiency. J Intern Med 2005; 258: 196-197.
26. Barbiroli B, Frassineti C, Martinelli P, et al. Coenzyme Q10 improves mitochondrial respiration in patients with mitochondrial cytopathies: an in vivo study on brain and skeletal muscle by phosphorous magnetic resonance spectroscopy. Cell Mol Biol 1997; 43: 741-749.
27. Niklowitz P, Menke T, Wiesel T, et al. Coenzyme Q10 in plasma and erythrocytes: comparison of antioxidant levels in healthy probands after oral supplementation and in patients suffering from sickle cell anemia. Clin Chim Acta 2002; 326 (1-2): 155-161.
28. Wolters M, Hahn A. Plasma ubiquinone status and response to six-month supplementation combined with multivitamins in healthy elderly women: results of a randomized, double-blind, placebo-controlled study. Int J Vitam Nutr Res 2003; 73:207-214.
29. Golomb BA, McGraw JJ, Evans MA, et al. Physician response to patient reports of adverse drug effects: implications for patient-targeted adverse effect surveillance. Drug Saf 2007; 30 (8): 669-675.
30. Ogasahara S, Engel AG, Frens D, et al. Muscle coenzyme Q deficiency in familial mitochondrial encephalomyopathy. Proc Natl Acad Sci U S A 1989;86 : 2379-2382.
31. Langsjoen PH, Langsjoen JO, Langsjoen AM, et al. Treatment of statin adverse effects with supplemental coenzyme Q10 and statin drug discontinuation. Biofactors 2005; 25 (1-4): 147-152.
32. Caso G, Kelly P, McNurlan MA, et al. Effect of coenzyme q10 on myopathic symptoms in patients treated with statins. Am J Cardiol 2007; 99: 1409-1412.
33. Silver MA, Langsjoen PH, Szabo S, et al. Statin cardiomyopathy? A potential role for co-enzyme Q10 therapy for statin-induced changes in diastolic LV performance: description of a clinical protocol. Biofactors 2003; 18: 125-127.
34. Graves S, Sikorska M, Borowy-Borowski H et al. Analysis of co-enzyme Q10 content in human plasma and other biological samples. In: Free Radical and Antioxidant Protocols, Methods in Molecular Biology, 108. Ed. Armstrong DA. Humana Press Inc, publishers, Totowa NJ 1998 :pp 353-365.