LEADING ARTICLE

Drug Safety 2005; 28 (8): 659-676
0114-5916/05/0008-0659/$34.95/0

The Effect of HMG-CoA Reductase Inhibitors on Coenzyme Q_{10}

Possible Biochemical/Clinical Implications

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Abstract

The HMG-CoA reductase inhibitors, also known as statins, have an enviable safety profile; however, myotoxicity and to a lesser extent hepatotoxicity have been noted in some patients following treatment. Statins target several tissues, depending upon their lipophilicity, where they competitively inhibit HMG-CoA reductase, the rate-limiting enzyme for mevalonic acid synthesis and subsequently cholesterol biosynthesis. HMG-CoA reductase is also the first committed rate-limiting step for the synthesis of a range of other compounds including steroid hormones and ubidecarenone (ubiquinone), otherwise known as coenzyme Q_{10} (CoQ_{10}). Recent interest has focused on the possible role CoQ_{10} deficiency may have in the pathophysiology of the rare adverse effects of statin treatment. Currently, there is insufficient evidence from human studies to link statin therapy unequivocally to pathologically significantly decreased tissue CoQ_{10} levels. Although statin treatment has been reported to lower plasma/serum CoQ_{10} status, few human studies have assessed tissue CoQ_{10} status. The plasma/serum CoQ_{10} level is influenced by a number of physiological factors and, therefore, has limited value as a means of assessing intracellular CoQ_{10} status. In those limited studies that have assessed the effect of statin treatment upon tissue CoQ_{10} levels, none have shown evidence of a fall in CoQ_{10} levels. This may reflect the doses of statins used, since many appear to have been used at doses below those recommended for their maximum therapeutic effects. Moreover, the poor bioavailability in those peripheral tissues tested may not reflect the effects the agents are having in liver and muscle, the tissues commonly affected in those patients who do not tolerate statins. This article reviews the biochemistry of CoQ_{10}, its role in cellular metabolism and the available evidence linking possible CoQ_{10} deficiency to statin therapy.

HMG-CoA reductase inhibitors, also known as statins, were first introduced in 1987 for the treatment of hypercholesterolaemia, a major risk factor for developing strokes and coronary heart disease.[1,2] Since that time, statins have become the most widely prescribed of the lipid-lowering drugs, exhibiting excellent efficacy and safety profiles.[3,4] In addition, it has recently been shown that some statins have other effects, including the ability to inhibit P-glycoprotein-mediated transport.[5] Thus, further large potential therapeutic areas including the treatment of tumours and dementias may be recognised and the number of patients treated with statins may be huge. As with all pharmaceutical therapies, the administration of statins is not without clinical risk, and adverse effects associated with

these treatments have been reported.[6] The most serious adverse effects appear to occur in liver and muscle cells (see section 3), although it could be predicted that because of their lipophilicity, cerebral effects might also be seen in some patients. However, the statins are well tolerated at low doses and have recently been made available as 'over-the-counter' medications in the UK.[7] At higher doses and often in combination with other hypolipidaemic agents some potentially severe adverse effects such as raised serum enzyme levels or muscle problems may occur that require the patient to stop taking the agents.[8]

The precise mechanism(s) by which statins induce adverse effects remains unclear. The HMG-CoA reductase step in cholesterol biosynthesis is a very early reaction for a range of other important molecules including steroid hormones and ubidecarenone (ubiquinone), otherwise known as coenzyme Q_{10} (CoQ_{10}). CoQ_{10} is a compound whose biochemistry has been largely ignored in recent years. However, it is now recognised that it acts as an important cellular antioxidant and possibly an intracellular signalling compound in addition to its classically described role as an integral component of the mitochondrial respiratory chain. Thus, it has been hypothesised that, in susceptible individuals, statins may interfere with key cellular metabolic pathways by rendering cells relatively CoQ_{10} deficient and a number of studies have sought to investigate the effect of statin treatment on CoQ_{10} status. The purpose of this article is to review our current understanding of the biochemistry of CoQ_{10} and its role in cellular metabolism and to critically examine the available evidence linking possible CoQ_{10} deficiency to statin therapy.

1. Coenzyme Q_{10} (CoQ_{10})

CoQ_{10} was first isolated from beef heart mitochondria in 1957 by Crane et al.[9] In the following year, the structure of CoQ_{10} was determined by Wolf et al.[10] and shown to be 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone (illustrated in figure 1). CoQ_{10} is a member of a family of naturally occurring quinones, which are known as ubiquinones because of their ubiquity in nature. They have a common benzoquinone nucleus, but differ in the length of their isoprenoid side chains,

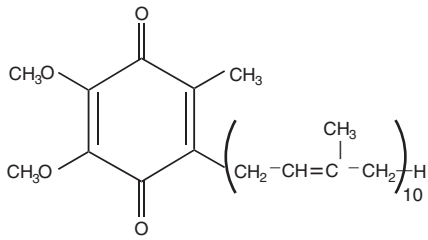

Fig. 1. The structure of coenzyme Q_{10}.

which can range from 6 to 12 isoprenoid units.[11-13] In humans, CoQ_{10} is the major quinone species present,[13] whereas in the rat and legumes a 9-isoprenoid side chain is the most commonly observed quinone.

1.1 Functions of CoQ_{10}

In common with other polyisoprenoid compounds such as dolichol and dolichyl phosphate, CoQ_{10} is localised within the central hydrophobic portion of membranes throughout the cell.[14-16] Within the inner mitochondrial membrane CoQ_{10} functions as a redox compound in the electron transport chain (ETC) [illustrated in figure 2]. It accepts electrons from complex I (nicotinamide adenine dinucleotide [NADH] ubiquinone reductase) and complex II (succinate ubiquinone reductase) and subsequently reduces complex III (ubiquinol cytochrome c reductase).[17] CoQ_{10} also accepts electrons generated by the β-oxidation of fatty acids, which again reduces complex III of the ETC.[18] CoQ_{10} participates in the transfer of protons from the matrix to the intermitochondrial membrane space. This is referred to as the proton motive Q cycle and is generally accepted as an underlying mechanism for mitochondrial proton transport.[19] The resultant proton gradient across the inner mitochondrial membrane, known as the proton motive force, can then be utilised by the reversible mitochondrial adenosine triphosphate (ATP) synthetase to catalyse ATP production (oxidative phosphorylation).[20] CoQ_{10} is also reported to be an 'essential cofactor' for the mitochondrial uncoupling proteins. In brown adipose tissue, regulated dissipation of the transmembrane proton motive force is used for thermogenesis rather than ATP production.[21]

The reduced ubiquinol form of CoQ_{10}, $CoQ_{10}H_2$, has an important cellular antioxidant function,

which is to protect membranes and plasma lipoproteins against free radical-induced oxidation.[22,23] Ubiquinone formed from ubiquinol in preventing oxidative cellular damage is reduced back to ubiquinol by the ETC.[24] However, this does not occur in all cell types. Those lacking mitochondria, red blood cells and Hep G2 cells, although able to reduce oxidised CoQ_1 are unable to efficiently reduce the natural ubiquinone, CoQ_{10}.[25] These observations highlight the difficulty of using unnatural ubiquinol derivatives in experimental systems.

Ubiquinol has an essential role in the maintenance of two other powerful antioxidants: ascorbic acid and tocopherol (vitamin E). In the case of the former molecule, ubiquinol in the plasma membrane is able to reduce the ascorbate radical, monodehydroascorbate, and thereby regenerate extracellular ascorbate.[26] Ubiquinol can also reduce tocopherol to generate the reduced (active) α-tocopherol form of the vitamin.[27]

Ubiquinones are essentially insoluble in aqueous media; thus, in common with α-tocopherol, CoQ_{10} is transported in the plasma by the lipoproteins. The approximate relative distribution among the lipoproteins is: low-density lipoproteins (LDL) 60%; high-density lipoproteins (HDL) 25%; and other lipoproteins 15%.[28] *In vitro* studies have indicated that ubiquinol is the first antioxidant to be depleted when LDL is subjected to oxidative stress. Therefore, it has been suggested that the plasma ratio of ubiquinol to total CoQ_{10} level may be a possible sensitive marker of oxidative stress.[29]

CoQ_{10} is present in most tissues of the body as the reduced ubiquinol species. However, in the brain and lung the oxidised forms predominate, representing approximately two-thirds of the total tissue level.[30] This observation may reflect the higher relative oxidative stress noted in these tissues.

CoQ_{10} may also play a central role in cell signalling and gene expression. These potential functions are outside the scope of this article but are reviewed and discussed in detail by Crane.[31]

1.2 The Biosynthesis of CoQ_{10}

The biosynthesis of CoQ_{10} is a multistage process that can be divided into three major steps: (i) synthesis of the benzoquinone nucleus from tyrosine; (ii) formation of the isoprenoid side chain from acetyl-CoA via the mevalonate pathway; and (iii) the condensation of these two structures catalysed by the enzyme *trans*-prenyl transferase.[32] CoQ_{10} synthesis appears to be initiated in the rough endoplasmic reticulum and the final condensation reaction takes place in the Golgi apparatus.[33] The major regulatory step of CoQ_{10} synthesis is HMG-CoA reductase, an enzyme common to the cholesterol biosynthetic pathway that it also regulates.[34]

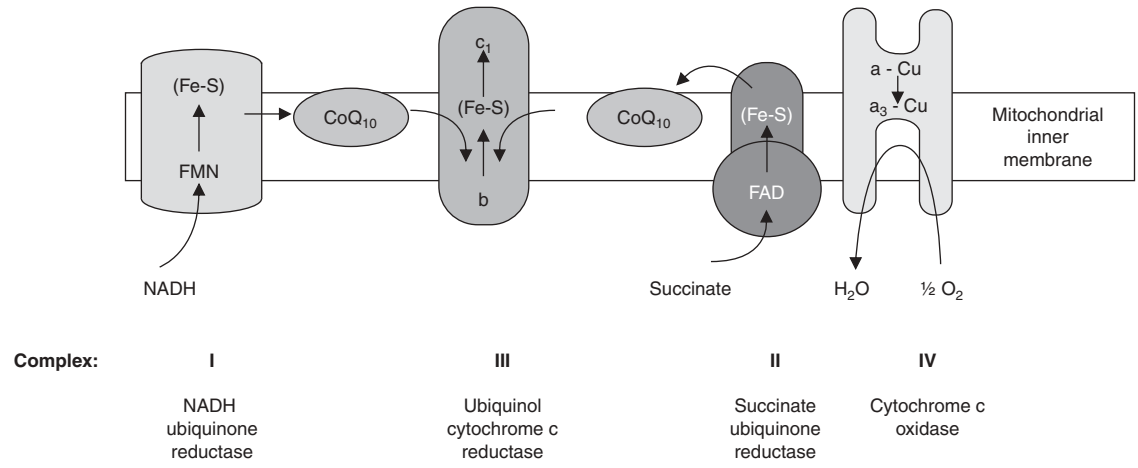

Fig. 2. The structure of the electron transfer chain showing the electron carrier function of coenzyme Q_{10} (CoQ_{10}). **a** = haem groups; **b** = cytochrome b; **c** = cytochrome c; **Cu** = copper; **FAD** = flavin adenine dinucleotide; **Fe-S** = iron sulphur cluster; **FMN** = flavin adenine mononucleotide; **NADH** = nicotinamide adenine dinucleotide.

The first step in the synthesis of the benzoquinone nucleus, the conversion of tyrosine/phenylalanine to 4-hydroxyphenylpyruvic acid, requires pyridoxine (vitamin B_6) in the form of pyridoxal 5′ phosphate.[35] The synthesis of subsequent aromatic intermediates in the CoQ_{10} biosynthetic pathway requires the availability of riboflavin (vitamin B_2), folic acid (vitamin B_9), cyanocobalamin (vitamin B_{12}) and ascorbic acid (vitamin C) and the cofactors nicotinamide, calcium pantothenate (panthothenic acid) and tetrahydrobiopterin.[36] In contrast to yeast and bacteria, the final stages of the CoQ_{10} biosynthesis following the condensation of the benzoquinone ring with the isoprenoid side chain are not well defined in mammalian systems.[33]

2. CoQ_{10} Deficiency and its Relationship to Disease

A decrease in CoQ_{10} status has been reported in a number of diseases. These include certain cancers, multisystemic inherited metabolic diseases, the mitochondrial encephalomyopathies and certain movement disorders, including Parkinson's disease and some of the cerebellar ataxias. The relative contribution of a CoQ_{10} deficiency to disease pathophysiology either from a failure of energy metabolism or decreased cellular antioxidant capacity or other undescribed mechanisms is as yet unresolved and the reader is referred to the reviews by Shults[37] and Hargreaves,[38] where putative relationships are discussed in more detail.

2.1 Kinetic Considerations for CoQ_{10}

Kinetic studies using beef heart mitochondria have estimated the Michaelis-Menten constant (K_m) of NADH cytochrome c reductase (complex I-III) for CoQ_{10} to be 2.4 ± 1.7 nmol/mg protein, which is within the range of the natural level of mitochondrial CoQ_{10} (1–4 nmol/mg protein).[39] In contrast, succinate cytochrome c reductase (complex II-III) was found to have higher affinity for CoQ_{10}, with an estimated K_m value of 0.24 ± 0.23 nmol/mg protein.[39] Therefore, the K_m of NADH oxidation is sufficiently high to theoretically make the physiological concentration range of CoQ_{10} non-saturating for the maximum rate of electron transference. Thus, a small decrease in the CoQ_{10} level may be sufficient to depress ATP production and cause possible organ dysfunction.[39,40] The relationship between ETC function and CoQ_{10} availability is illustrated in the first documented case of neonatal CoQ_{10} deficiency, with a patient who presented with severe global developmental delay, dystonia, microcephaly, renal tubulopathy, cardiomyopathy and a raised plasma lactate level of 7.6 mmol/L (reference interval: 0.9–1.9 mmol/L).[41] Skeletal muscle from this patient was found to have a detectable but markedly decreased CoQ_{10} level of 37 pmol/mg (reference interval: 140–580 pmol/mg). Complex II-III activity was undetectable in the biopsy. Addition of the exogenous CoQ_{10} analogue (CoQ_1) was found to restore *in vitro* complex II-III activity to control levels, indicating the presence of normal functioning apoenzymes of the complexes. Treatment of the patient with oral CoQ_{10} supplementation (200 mg/day) was accompanied by a decrease in plasma lactate level to 2.5–2.9 mmol/L, which is consistent with improved ETC function. The patient survived for 2 years, having been treated for 12.5 months with CoQ_{10} supplementation, despite the severity of his multisystem presentation.

2.2 Cardiovascular Disease

Some patients with cardiac failure have been noted to have a deficiency of myocardial CoQ_{10}, with tissue levels of 67%[42] and 58%[43] of the control mean. A possible relationship has also been reported between the degree of CoQ_{10} deficiency in blood and myocardial tissue and the severity of the condition.[44]

The variable and continuous energetic requirements of the heart make it particularly vulnerable to impairments of mitochondrial energy metabolism.[45,46] The cause of CoQ_{10} deficiency in patients with cardiovascular disease has yet to be established. Treatment of underlying hyperlipidaemias may be a factor, particularly in the elderly. Moreover, this factor may be compounded by the documented age-related decrease in tissue levels of CoQ_{10}. These have been reported to steadily decline after 20 years of age in most tissues and particularly in the heart and brain.[47]

A pathophysiological role for oxidative stress has also been implicated in cardiovascular disease.[48,49] The low levels of myocardial CoQ_{10}[42-44] may be of

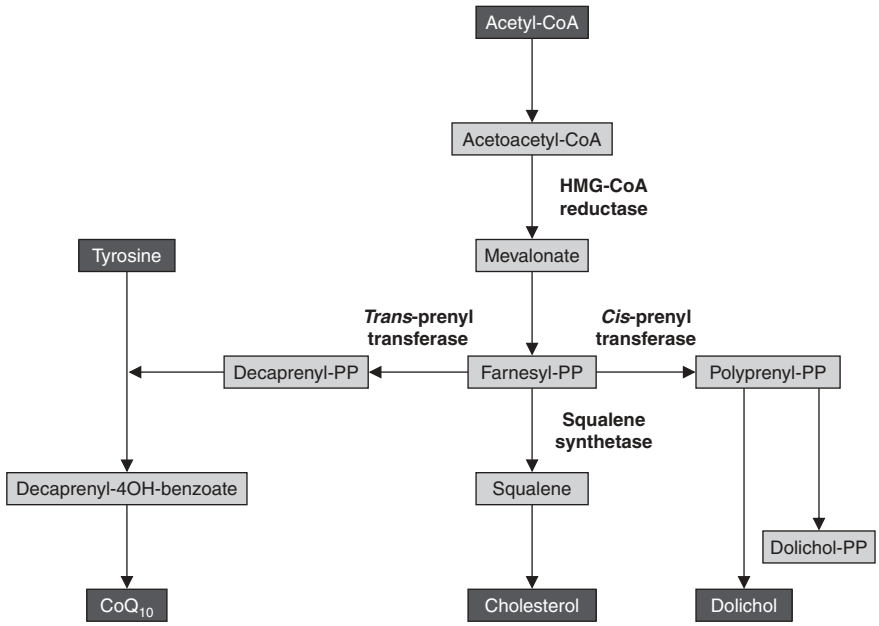

Fig. 3. The mevalonate pathway in humans illustrating the biosynthesis of coenzyme Q_{10} (CoQ_{10}). This schematic diagram illustrates the enzymatic conversion of acetyl-CoA to farnesyl-pyrophosphate (PP) and the subsequent biosynthesis of CoQ_{10}, cholesterol and dolichol. Key enzymes in the mevalonate pathway are indicated in bold.

great importance in this context since any reduction of tissue CoQ_{10} levels will significantly impair the cellular antioxidant defence systems that are necessary to protect against free radical tissue damage. Thus, in atherosclerosis in which oxidative modification of LDL is implicated in disease progression,[50] studies have suggested decreased levels of CoQ_{10} in both plasma and LDL of patients.[51,52] Moreover, in hypercholesterolaemic patients, a decreased plasma ratio of reduced to total CoQ_{10} has been reported.[53] It should be noted that this observation could simply reflect a degree of mild hepatic dysfunction in these patients.[54] Thus, a recent review of the use of CoQ_{10} in cardiovascular disease patients concluded that there was only evidence for its use in selected patients with chronic heart failure and not in those with angina or hypertension.[55]

2.3 Mevalonate Metabolism and the Pharmacological Principles of Statin Treatment

HMG-CoA reductase is the regulating step for the early stages of cholesterol and ubiquinone synthesis. The later pathway, known as the mevalonate pathway (figure 3), has several branch-point enzymes. These are: squalene synthetase for the synthesis of cholesterol; *cis*-prenyl transferase for the synthesis of dolichol; and *trans*-prenyl transferase for the synthesis of CoQ_{10}. These represent the main regulatory enzymes of the respective metabolic pathways.[56] To estimate the relative importance of these regulatory steps the flux diversion hypothesis can be applied. In essence, it is recognised that each branch-point enzyme has a different affinity for the common starting substrate for each pathway, namely farnesyl pyrophosphate. Thus, an alteration in the level of that substrate would be expected to have differential effects upon the rate of synthesis of each the various pathway end products: cholesterol, dolichols and CoQ_{10}.[57] Compared with the other branch-point enzymes, squalene synthetase has the lowest affinity for farnesyl pyrophosphate. Therefore, a decrease in the level of this substrate would be expected to have a more pronounced effect on cholesterol biosynthesis than the synthesis of dolichol or CoQ_{10}.[57] This rationale is fundamental to the use of statins in the treatment of patients with hypercholesterolaemia.[58] Thus, in theory, statin

treatment at the correct dose and causing decreased flux through HMG-CoA reductase could be expected to decrease cholesterol biosynthesis while still allowing the biosynthesis of an adequate level of farnesyl pyrophosphate to maintain dolichol and CoQ_{10} biosynthesis. However, since their introduction over a decade ago, case reports and adverse reaction reporting have suggested that the use of statins may be associated with decreased tissue CoQ_{10} levels.[59-64] This appears to be especially true, as would be predicted, if the statins are used at high dose or in combination with other antihyperlipidaemic agents.

3. Statins: Types and Mode of Action

Currently available statins can be divided into two groups: (i) natural or fungal-derived first-generation statins (lovastatin, pravastatin and simvastatin);[65] and (ii) synthetic or hepatenoic acid-derived second-generation statins (atorvastatin, fluvastatin and rosuvastatin).[66,67] The structures of a synthetic statin (fluvastatin) and a natural statin (lovastatin) are illustrated in figure 4. Simvastatin and lovastatin are administered as inactive lactone prodrugs that are enzymatically hydrolysed to generate their active forms,[65] whereas pravastatin, atorvastatin, fluvastatin and rosuvastatin are administered as active compounds.[68,69] Statins undergo first-pass hepatic extraction and are selectively distributed to the liver where they competitively inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis.[70] The resultant decrease in hepatocyte cholesterol levels results in increased expression of hepatic LDL receptors that bind to apolipoproteins B and E on the surface of LDL and very low-density lipoprotein (VLDL) particles, resulting in the hepatic uptake and degradation of these particles and a subsequent lowering of their circulatory levels and, thus, serum cholesterol levels.[71]

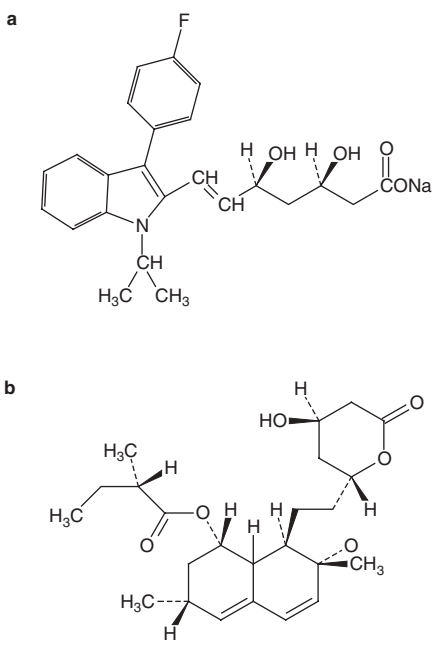

Fig. 4. Structures of a synthetic statin (**a**) [fluvastatin] and a natural statin (**b**) [lovastatin].

The major differences among statins in terms of pharmacokinetic and pharmacological properties are associated with their relative lipophilicity.[72] Table I illustrates this point and shows that of those statins currently licensed the least lipophilic is pravastatin. Clinically, the differences have a major effect on tissue affinity/selectivity and penetration and may govern the frequency of adverse effects.[73] Lipophilic statins (cerivastatin, simvastatin and fluvastatin) may penetrate biological membranes more easily than the hydrophilic statins (pravastatin and rosuvastatin).[71] Hepatocytes actively take up statins, while their lipophilicity influences the amount distributed in the cell.[71] In extra-hepatic tissues, cell concentrations are limited by the rate of passive diffusion across membranes and are, therefore, dependent upon statin lipophilicity,[74] with those exhibiting lower lipohilicity tending not to enter muscle. The relative protection of extra-hepatic tissues may be ameliorated if a statin has a low concentration that produces 50% inhibition (IC_{50}), for example rosuvastatin. Cerivastatin has both a low IC_{50} and is relatively lipophilic, thus explaining its potential to be myotoxic (see table I).

Statins may be excreted unchanged by the kidney or are metabolised and detoxified by different subgroups of isoenzymes of the hepatic cytochrome P450 (CYP) system.[75,76] Simvastatin, lovastatin and atorvastatin are metabolised by the CYP3A4 isoenzyme,[71] whereas fluvastatin is metabolised by the CYP2C9 isoenzyme.[71] The concomitant administration of drugs that are either substrates and thus compete for or are inhibitors of the various CYP

Table I. Concentration that produces 50% inhibition (IC_{50}) and relative lipophilicity/hydrophilicity of currently marketed statins

Statins	IC_{50} for HMG-CoA reductase inhibition (nmol/L)[a]	Relative lipophilicity[b]
Pravastatin	44.1	−0.84
Rosuvastatin	5.4	−0.33
Atorvastatin	8.2	1.14
Fluvastatin	27.6	1.25
Simvastatin	11.2	1.64
Cerivastatin	10.0	1.75

a Concentration of statin (nmol/L) required to inhibit 50% of purified human HMG-CoA reductase activity.[71]

b The relative lipophilicity of statins given as octanol-water coefficients (log D at pH 7.4). The higher the value of this coefficient the more lipophilic the statin.[71]

systems (such as amiodarone, quinidine, cyclosporin, erythromycin, diltiazem, verapamil, the azole antifungal agents and the antiretroviral agents) can result in greater circulating concentrations of the statins, thus increasing their bioavailability and consequently their potential for adverse effects.[66,75,76] Moreover, even small amounts of grapefruit juice increase the plasma concentration of simvastatin and enhance both the pharmacological effect and risk of adverse effects of the drug.[77]

Pravastatin and rosuvastatin are not significantly metabolised by the CYP system, with the majority of these drugs being excreted unchanged via the kidneys and a small amount in the bile.[78] Elevated plasma concentrations of statins have also been reported when they are used in combination with other hypolipidaemic agents, especially the fibrate gemfibrozil.[79] The precise mechanism by which this elevation is caused is unknown. One possibility is that up-regulation of the peroxisome proliferator-activated family of nuclear receptors occurs, leading to down-regulation of hepatic CYP function and thus decreased metabolism of the statins.[80] Finally, statin toxicity may be mediated by effects upon P-glycoprotein transport. Lovastatin, simvastatin and to a lesser extent atorvastatin are inhibitors of P-glycoprotein transport. Interestingly and uniquely, pravastatin appears not to have this property.[81]

Adverse effects of statin treatment can include lens abnormalities, constipation, flatulence, dyspepsia and gastrointestinal disturbances such as cholestatic hepatitis.[68,78] Elevations of the serum transaminase alanine aminotransferase to levels >3 times the upper reference limit have been reported in approximately 1% of patients receiving statins and is usually dose dependent.[82,83] Although the diagnostic value of relatively small rises of enzyme measurements in predicting liver dysfunction is questionable,[84,85] statin treatment has been associated with rare cases of hepatotoxicity and jaundice.[86,87] Mild adverse reactions involving skeletal muscle (mainly myalgia) have been reported to have an incidence of 1–5% of all patients.[8,79] However, more severe muscle toxicity including myositis and potentially life-threatening rhabdomyolysis is rare, with an overall incidence of probably <0.25%.[8] The statins usually associated with these adverse effects are those that are relatively lipophilic, especially if they have a low IC_{50} (see table I).

The incidence of myositis (defined as elevations in serum creatine kinase activity to >10 times the upper reference limit with associated muscle weakness or myalgia[83]) during statin monotherapy has been reported to be in the range 0.1–0.5% of patients. The myositis appears to be dose dependent[88] and is exacerbated by other drugs such as nicotinic acid, fibrates or ciclosporin.[89] The progression of myositis to rhabdomyolysis without intervention has been reported to occur in ~0.1% of patients treated with statin monotherapy.[90] The synthetic lipophilic statin cerivastatin was withdrawn from the market in 2001 after 52 cases of cerivastatin-related fatal rhabdomyolysis had been reported worldwide.[91] These deaths were associated with high dosages of cerivastatin (0.8 mg/day) and particularly when used in combination with gemfibrozil.[92] The high risk of muscle toxicity associated with cerivastatin treatment may have been related to the lipophilicity of the drug[93] (see table I) and its high systemic bioavailability. Hence, after an oral dose 60% of the drug is systemically bioavailable compared with 24% for fluvastatin, ~20% for rosuvastatin, 17% for pravastatin, ~14% for atorvastatin and <5% simvastatin.[71]

The pathogenesis of statin-induced muscle toxicity remains to be elucidated. A number of mechanisms have been proposed, including mitochondrial dysfunction secondary to statin-induced CoQ_{10} deficiency.[94] Support for this hypothesis comes from the observation that a patient with familial mitochondrial encephalomyopathy resulting from CoQ_{10}

deficiency had elevated levels of serum creatine kinase activity, which were up to 20 times the upper reference limit, and clinically associated muscle pain and weakness and recurrent episodes of myoglobinuria. No impairment of renal function was observed.[95]

4. The Relationship between Statin Treatment and CoQ10 Deficiency

From 1990 to 2004, 15 human studies were published that investigated the effect of statin treatment on endogenous CoQ_{10} status;[96-110] these studies are shown in table II. A diminution in CoQ_{10} status as the result of statin treatment has been reported in 13 of these 15 studies.[96-107,110] Inspection of these studies shows large but highly variable decreases in serum CoQ_{10} levels, ranging from approximately 19%[96] to 54%[98] of basal levels. In two studies, clear dose-related effects were noted.[97,106] Effects may also be dependent upon the length of time a drug has been taken. Thus, although pravastatin and atorvastatin appeared to be without effect after a month of treatment,[109] more extended use was accompanied by substantial decreases in plasma CoQ_{10} status.[98,104]

However, the interpretation of such studies is not without its problems. All of the studies that have reported a decrease in CoQ_{10} levels following statin treatment have used plasma or serum measurements and few have examined other tissues or cell types such as platelets or, more obviously, skeletal muscle.

Plasma/serum CoQ_{10} levels are dependent on both dietary supply and hepatic biosynthesis.[38] This is in contrast to other tissues, which depend upon *de novo* biosynthesis.[17] The effect of diet is particularly important. CoQ_{10} has a relatively long circulatory half-life (approximately 24 hours) and dietary intake contributes up to 25% of the plasma/serum CoQ_{10} level;[111] this does not appear to have been accounted for in several studies.[96,102,106] Moreover, a range of other factors including serum levels of γ-glutamyltranspeptidase activity, gender, the intensity of conditioning exercise and age all appear to influence CoQ_{10} levels[38,112] and do not appear to have been controlled for.

Most importantly, the relationship between CoQ_{10} levels and blood lipids has largely been ignored. Several studies have revealed that plasma CoQ_{10} levels are highly dependent upon serum lipid levels.[113,114] This is hardly surprising as lipoproteins, the very pharmacological target for statin therapy (specifically LDL), are the major carriers of CoQ_{10} in the circulation.[28] Thus, it has been suggested that the plasma/serum CoQ_{10} level should be standardised to either total serum lipids or total cholesterol levels.[115] Indeed, if this is done there is controversy as to whether statins lower serum/plasma CoQ_{10} levels independently of a reduction in circulating LDL levels.[97] This is illustrated in eight studies where an apparent statin-induced lowering of plasma/serum CoQ_{10} level is nullified when normalised to total cholesterol or LDL-cholesterol levels.[99-101,103,104,106,107,110] In three studies, the decrease in plasma CoQ_{10} was found to be more pronounced than either the fall in total cholesterol or LDL-cholesterol level, which suggests that the statin treatment in these studies may be eliciting an inhibitory effect on hepatic CoQ_{10} biosynthesis.[97,98,105] This is in agreement with studies in rats that show statistically significant decreases in levels of both liver and blood CoQ_9, the intrinsic ubiquinone in rats, following lovastatin treatment.[116] However, it is important to note that the group of patients who were treated with statins in two of these studies[97,98] consisted of a number of patients with proven coronary artery disease and hypertension, conditions which themselves have been linked to CoQ_{10} deficiency.[55] Thus, as CoQ_{10} may be taken up into tissues that are deficient,[44,117] the possibility arises that the decrease in plasma CoQ_{10} level may not be fully attributable to statin treatment alone, but may be a consequence of cellular uptake.

Evidence of pre-existing CoQ_{10} deficiency has been noted in a study that assessed the effect of statin treatment on patients with diabetes mellitus.[108] In this study, statin-treated diabetes patients were found to have serum CoQ_{10} levels that were comparable to non-statin-treated normocholesterolaemic diabetes patients. However, diabetes patients with or without statin treatment were found to have significantly lower serum CoQ_{10} levels compared with healthy volunteers. It was postulated that the decreased serum CoQ_{10} status of diabetes pa-

Table II. Studies assessing the effect of statin treatment on endogenous coenzyme Q_{10} (CoQ_{10}) status

Study	Statin	Dosage (mg/day)	No. of patients	Age (y)[a]	Length of study	Tissue[b]
Folkers et al.[96]	Lovastatin	20–40	5	43–72	Variable	Blood
	Lovastatin	40	1[c]	43	29d	Blood
Watts et al.[97]	Simvastatin	10–80	20	55 ± 8.9	15 ± 8mo	Plasma
Ghirlanda et al.[98]	Pravastatin	20	20	39–59	3mo	Plasma
	Simvastatin	20				
Bargossi et al.[99]	Simvastatin	20	34	NR	3mo	Plasma, platelet
Laaksonen et al.[100]	Simvastatin	20–40	17	38–65	4.7y	Serum
	Lovastatin	20–40			12wk	
Laaksonen et al.[101]	Simvastatin	20	22	25–55	4wk	Serum, muscle
De Pinieux et al.[102]	Lovastatin	NR	60	21–76	NR	Serum
	Simvastatin	NR				
	Pravastatin	NR				
	Fluvastatin	NR				
Laaksonen et al.[103]	Simvastatin	20	19	25–55	6mo	Serum, muscle
Davidson et al.[104]	Atorvastatin	10–20	1049	18–80	1y	Plasma
	Lovastatin	20–40				
Human et al.[105]	Simvastatin	10–20	25	35.9 ± 11.8	14wk	Plasma
Mortensen et al.[106]	Lovastatin	20–80	45	30–75	18wk	Serum
	Pravastatin	10–40				
De Lorgeril et al.[107]	Simvastatin	20	32	54.1	12wk	Serum
Miyake et al.[108]	Pravastatin	10–20	97	58.1 ± 10	NR	Serum
	Simvastatin	5				
Bleske et al.[109]	Pravastatin	20	12	NR	4wk	Serum
	Atorvastatin	10				
Rundek et al.[110]	Atorvastatin	80	34	70 ± 7	14 + 30d	Plasma

a Patient ages are expressed as either a range or mean ± SD.

b Tissue in which CoQ_{10} was monitored.

c Hypercholesterolaemic volunteer.

NR = not reported.

tients may have been associated with subclinical diabetic cardiomyopathy.[108] In the study by Human et al.[105] it is interesting to note that although there was a significant decrease in the ratio of plasma CoQ_{10} to total cholesterol level (9.8% decrease from the basal level) in patients with familial hypercholesterolaemia, no effect was observed on this parameter in patients with non-familial hypercholesterolaemia treated with the same statin regimen. In addition, the ratio of plasma α-tocopherol to total cholesterol was found to be consistently decreased in patients with familial hypercholesterolaemia compared with patients with non-familial hypercholesterolaemia. This observation prompted the authors to suggest that LDL from patients with familial hypercholesterolaemia may be more susceptible to lipid peroxidation than patients with non-familial hypercholesterolaemia and thus the lower LDL CoQ_{10} content may be a reflection of oxidative loss of this compound.

Oral supplementation of CoQ_{10} to patients receiving statin treatment has been reported to restore plasma/serum and platelet[99,108] levels of CoQ_{10} without affecting the cholesterol-lowering effect of these drugs. The reported restoration of plasma/serum CoQ_{10} levels upon supplementation in these studies occurred in the absence of a concomitant rise in total cholesterol level (a marker of circulating lipoprotein level), which suggests that either there is an increased enrichment of the lipoprotein fraction with CoQ_{10} (as proposed in a study by Palomaki et al.[118]) or that plasma CoQ_{10} transport is mediated by as yet unidentified vehicles in the absence of available lipoproteins.

4.1 Deleterious Effects of Statin Treatment in Human CoQ_{10} Evaluation Studies

In the 15 studies in humans that have evaluated the effect of statin treatment on CoQ_{10} status, three have reported deleterious effects following statin administration;[4,18,96,104] these are shown in table III. In the most recent study, brief exposure to atorvastatin 80 mg/day was reported to cause a marked decrease in blood CoQ_{10} levels.[110] However, the results are difficult to assess as baseline levels were twice those shown in other studies,[109] they were not normalised to blood cholesterol levels and muscle levels were not assessed.

In the study by Davidson et al.[104] 7% and 8% of the patients receiving lovastatin (20–40 mg/day) and atorvastatin (10–20 mg/day), respectively, were reported to have had a serious adverse advent. One patient developed pancreatitis in the atorvastatin-treated patient cohort, but no details of the other adverse events were documented in this paper although no patient was reported to have had a persistent elevation in plasma creatine kinase activity >10 times the upper limit of normal.[104] In the study by Folkers et al.,[96] the effect of lovastatin (20–40 mg/day) treatment on five patients with pre-existing cardiomyopathy (four of whom were receiving CoQ_{10} supplementation [100–133 mg/day] prior to statin treatment; all patients received supplementation during treatment) was investigated. A fall in the blood CoQ_{10} level (51–74.6% decrease in the post-CoQ_{10} supplemented blood level) was reported following lovastatin treatment and this was accompanied by deterioration in cardiac function.[96] On examination of the reported pre-supplemented blood CoQ_{10} levels, it is apparent that the blood CoQ_{10} level following lovastatin treatment (post-CoQ_{10} supplementation) had decreased by 4.5% in one patient and increased by 27% and 44% in two patients, respectively, from its pre-supplemented level. Therefore, in this study it may not be appropriate to specifically link the decline in clinical status from the period prior to supplementation to the period following supplementation/lovastatin treatment to a diminution in CoQ_{10} status.[96] The patients evaluated in this study had cardiomyopathy, which may be caused by CoQ_{10} deficiency;[42] therefore, the clinical improvement reported in this study following supplementation is perhaps not unexpected.[96]

In contrast, a study by De Lorgeril et al.[107] reported an improvement in cardiac function in patients with primary hypercholesterolaemia following 12 weeks of treatment with simvastatin (20 mg/day) in conjunction with a 19.4% decrease in plasma CoQ_{10} level. Improvement in cardiac function has also been reported in patients with idiopathic dilated cardiomyopathy following short-term statin therapy.[61]

Table III. The endogenous coenzyme Q_{10} (CoQ_{10}) status and reported clinical adverse events of patients following statin treatment

Study	CoQ_{10} status	Adverse events
Folkers et al.[96]	Patients received CoQ_{10} supplementation during statin treatment and, therefore, the effect of statin on endogenous CoQ_{10} was not able to be determined. 18.8% ↓ in blood CoQ_{10} in study volunteers during 29d of lovastatin treatment (16.9% ↓ in TC)	↓ in cardiac function reported in both patients and volunteers
Watts et al.[97]	23.8% ↓ in plasma CoQ_{10} in simvastatin-treated patient group compared with untreated patients. In addition, 24.3% ↓ in CoQ_{10} : TC and 30.0% ↓ in CoQ_{10} : LDL-C ratios	None
Ghirlanda et al.[98]	In the 10 patients receiving pravastatin there was a 50.0% ↓ in plasma CoQ_{10} (22.3% ↓ in TC and 20.4% ↓ in LDL-C). In the 10 patients receiving simvastatin there was a 54% ↓ in plasma CoQ_{10} (23.1% ↓ in TC and 28.6% ↓ in LDC)	None
Bargossi et al.[99]	In the 2 groups of 10 patients there was a 26.4% ↓ (19.5% ↓ TC, 30.1% ↓ LDL-C) and 47.7% ↓ (28.9% ↓ TC, 36.6% ↓ LDL-C) in plasma CoQ_{10} following simvastatin monotherapy. Platelet CoQ_{10} ↓ by 12.5% after 90d of monotherapy	None
Laaksonen et al.[100]	25.2% ↓ and 21.2% ↓ in serum CoQ_{10} following simvastatin and lovastatin treatment, respectively. No ↓ in CoQ_{10} when normalised to TC or LDL-C	None
Laaksonen et al.[101]	31.2% ↓ in serum CoQ_{10} (25.7% ↓ in TC and 34.7% ↓ and LDL-C). 46.6% ↑ in muscle CoQ_{10}	None
De Pinieux et al.[102]	21% ↓ in serum CoQ_{10} compared with non-statin-treated patients, although serum CoQ_{10} in statin-treated patients was comparable to the cholesterol patients. 23.0% ↓ and 16.3% ↓ in CoQ_{10} : LDL-C compared with treated and control groups, respectively	None
Laaksonen et al.[103]	27.3% ↓ in serum CoQ_{10} (28.3% ↓ in LDL-C). 9.0% ↑ in muscle CoQ_{10}	None
Davidson et al.[104]	38.0% ↓ (37.0% ↓ in LDL-C) and 27.0% ↓ (29.0% ↓ in LDL-C) in plasma CoQ_{10} with atorvastatin and lovastatin, respectively	Serious adverse events reported in 7–8% of patients
Human et al.[105]	25.5%↓ in plasma CoQ_{10} and 9.1% ↓ in CoQ_{10} : TC	None
Mortensen et al.[106]	19.7% ↓ in serum CoQ_{10} (18.3% ↓ in TC and 25.5% ↓ in LDL-C) after pravastatin treatment. 28.8% ↓ in serum CoQ_{10} (27.2% ↓ in TC and 36.6% ↓ in LDL + VLDL-C) after lovastatin treatment	None
De Lorgeril et al.[107]	19.4% ↓ in serum CoQ_{10} (37.2% ↓ in LDL-C and 26.4% ↓ in TC)	None
Miyake et al.[108]	No difference in serum CoQ_{10} between statin-treated diabetes mellitus patients and non-statin-treated normocholesterolaemic diabetes mellitus patients	None
Bleske et al.[109]	No effect on serum CoQ_{10} (32.0% ↓ and 49.0% ↓ in LDL-C with pravastatin and atorvastatin, respectively)	None
Rundek et al.[110]	49% ↓ and 52% ↓ in plasma CoQ_{10} after 14d and 30d, respectively. 41% ↓ in plasma TC and 51% ↓ in LDL-C after 30d	None

LDL-C = low-density lipoprotein-cholesterol; **TC** = total cholesterol; **VLDL-C** = very low-density lipoprotein-cholesterol; ↓ indicates decrease; ↑ indicates increase.

4.2 Effect of Statin Treatment on Tissue Levels of CoQ_{10}

Several studies have evaluated CoQ_{10} levels in samples other than blood, serum or plasma. A non-significant decrease of 12.5% from basal levels has been reported in isolated platelets from primary hypercholesterolaemia patients treated with simvastatin (20 mg/day) for 90 days.[99] Two studies that evaluated the effect of simvastatin (20 mg/day) treatment for 4 weeks[101] and 6 months,[103] respectively, on skeletal muscle CoQ_{10} levels in hypercholesterolaemic patients, observed no evidence of a statin-induced lowering of CoQ_{10} level. In contrast, increases of 46.6% for the 4-week study[101] and 9% for the 6-month study[103] were reported in skeletal muscle CoQ_{10} levels following statin treatment. An explanation for this apparent paradox may lie in the complex control of the biosynthetic pathway.[31] All cell types appear to have the ability to synthesise sufficient CoQ_{10} for their own metabolic demands.[17] Usually, hepatic biosynthesis contributes the majority of extra-hepatic CoQ_{10}.[68,119] Thus, extra-hepatic cellular CoQ_{10} biosynthetic flux is invariably suboptimal.[68] However, if statin treatment impairs hepatic CoQ_{10} synthesis, an up-regulation of extra-hepatic CoQ_{10} synthesis may occur, which results in higher non-hepatic levels. Such a mechanism is known to occur for cholesterol itself.[120] The failure to demonstrate a simvastatin-induced decrease in skeletal muscle

CoQ_{10} level[101,103] is in agreement with other studies, which indicate that >90% of the simvastatin dose is taken up by the liver and only minute amounts of active simvastatin metabolites have the possibility of entering extra-hepatic tissue.[65,121] A study examining the effect of simvastatin and pravastatin treatment (50 mg/kg for 14 days) on tissue levels of CoQ_{10} in New Zealand White rabbits found that simvastatin treatment significantly decreased cardiac and liver CoQ_{10} content.[122] Although 'severe lesions' (sic) were detected in skeletal muscle following simvastatin treatment, no decrease in the CoQ_{10} content of this tissue was detected; this prompted the authors to conclude that there may not be a direct correlation between myositis and CoQ_{10} deficiency. Pravastatin treatment had no effect on tissue levels of CoQ_{10}.[122] In a recent publication, a correlation has been reported between the degree of myotoxicity and the level of skeletal muscle CoQ_{10} following statin treatment.[123] However, in this study, no such correlation was observed in the other patients who underwent a muscle biopsy.

Evidence of skeletal muscle necrosis and elevated creatine kinase levels paralleling a decrease in skeletal muscle CoQ_{10} level (22–72% decrease from basal level) have been reported in rabbits treated with high dosages of simvastatin (50 mg/kg/day) for 4 weeks and pravastatin (200 mg/kg/day) for 3 weeks.[124] This study supports the view that supra-pharmacological plasma concentrations of statins may be required to induce a pathological decrease in extra-hepatic CoQ_{10} levels.[125,126]

4.3 Evidence of Statin-Induced Mitochondrial Dysfunction

The mitochondrial ETC may not be saturated with CoQ_{10}. Thus, a small decrease in CoQ_{10} levels may be sufficient to compromise mitochondrial energy production.[39,40] Few studies have evaluated the effect of statin treatment on the essential relationship between CoQ_{10} availability and mitochondrial function. Evidence of disordered cellular redox status, possibly indicating mitochondrial dysfunction as suggested by an elevated lactate to pyruvate ratio of ≥20 has been reported in only one human study in which hypercholesterolaemic patients were treated with pravastatin, simvastatin and fluvastatin.[102] In this study, 40% of the statin-treated hypercholesterolaemic patients were found to have a lactate to pyruvate ratio of ≥20, which was accompanied by a highly significantly decreased serum CoQ_{10} : LDL-cholesterol compared with the non-statin-treated hypercholesterolaemic patients.[102] However, 10% of the non-statin-treated hypercholesterolaemic group were also found to have a lactate to pyruvate ratio of ≥20, which was associated with a significantly decreased serum CoQ_{10} : LDL-cholesterol compared with the non-hypercholesterolaemic control group. Thus, although the results of this study suggest that a statin-induced decrease in CoQ_{10} may compromise mitochondrial function, it is by no means certain. This view supports the findings of Mikaelian et al.,[127] who reported decreased lymphocyte mitochondrial enzyme activities in an animal model of hypercholesterolaemia. Lactic acidosis has been reported in a case study by Goli et al.[60] in a patient who presented with rhabdomyolysis and hepatitis. This followed 3 months of combined treatment with simvastatin (40 mg/day) and the calcium blocker diltiazem (30mg three times a day), although the patient had been treated uneventfully for 3 years with the statin. Thus, toxicity of the combined drug therapy probably relates to the effect diltiazem has on the pharmacokinetics of simvastatin, which is to increase both its serum peak concentration and its elimination half-life.[128] No assessment of CoQ_{10} status was made.

A study by Laaksonen et al.[103] evaluated the skeletal muscle levels of CoQ_{10}, ATP and creatine phosphate, as indicators of mitochondrial function, in 20 hypercholesterolaemic patients and found no alteration in the levels of these compounds following 6 months' treatment with simvastatin (20 mg/day). The results of this study differ from the animal studies, which have found a decrease in tissue ATP level and a reduced potential to phosphorylate adenosine diphosphate (ADP) to ATP after statin treatment.[129-131] However, on a statin dose/bodyweight basis the amount of statin administered to these animals vastly exceeded that given to humans.[103] This suggests that it is only when excessive doses are used or when the bioavailability of the statin is increased, perhaps by co-therapy, that the risk of adverse effects becomes significant. Furthermore, in

two of the studies[10,11,15] no assessment of CoQ_{10} status was undertaken. Thus, it is uncertain to what extent the decreases in tissue ATP level may be directly attributable to a diminution in CoQ_{10} level secondary to statin administration.

One animal study has documented both a decrease in CoQ_{10} level and the phosphorylation potential in cardiac muscle from 2-year-old guinea pigs treated with lovastatin. However, in younger animals (2–4 months old) treated with the same dose of statin no significant decreases were noted in either parameter.[129] The sensitivity of the older animals raises the possibility that age may increase the susceptibility of patients to statin toxicity and needs to be considered when assessing the results of clinical studies.

A clinical presentation of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome with associated skeletal muscle CoQ_{10} deficiency (13.1 mg/g; reference interval: 15.5–21.7 mg/g) has been reported in a 63-year-old patient who lacked the common 3243 A to G mtDNA mutation, following treatment with simvastatin (20 mg/day) for 8 months.[132] Thus, it is possible that the patient had another confounding defect that the statin treatment may have unmasked, giving rise to mitochondrial dysfunction. In those patients who develop evidence of muscle dysfunction while receiving statin treatment, it may be prudent to exclude the involvement of other underlying diseases before the symptoms are ascribed solely to the treatment.[1,22]

4.4 The Effect of Statin Treatment on Ubiquinol Status and Low-Density Lipoprotein Oxidation

Substantial evidence implicates oxidative modification of LDL as an important risk factor for atherosclerosis.[133] Ubiquinol ($CoQ_{10}H_2$) is believed to represent the first line of antioxidant defence against oxidative damage to LDL.[134] Studies assessing the effect of statin treatment specifically upon the $CoQ_{10}H_2$ content of LDL have reported decreases of 13%[135] and 17%[118] following statin treatment. Commensurate with this decrease, diminished *ex vivo* antioxidant resistance of LDL to oxidative stress was observed.[1,16,118] A recent study has highlighted the intensification of free radical oxidation of LDL in the plasma of ischaemic heart disease patients prescribed statins. Thus, it is possible that the coadministration of antioxidants with statin therapy may reduce the incidence of LDL peroxidation.[136] However, the relevance of CoQ_{10} supplementation to improve LDL antioxidant capacity is questionable and its clinical value is uncertain.[118]

5. Benefits and Risks of Statin Treatment

A large number of well conducted clinical trials have provided evidence that the long-term use of statins results in a marked reduction in the risk of experiencing cardiovascular events in patients with or without a history of heart disease.[136-142] Statins are reported to be the safest and most effective of the lipid-modifying drugs that reduce the incidence of coronary heart disease.[6] However, despite the overall safety and efficacy of these drugs, there are concerns about the muscle and hepatic toxicity associated with statin treatment.[6] For this reason, assays evaluating these parameters were incorporated into the protocols of the clinical trials and the incidence of liver dysfunction and myositis associated with statin treatment was found to be infrequent and comparable to the placebo group.[137-143]

The definition of myositis in these clinical trials was muscle aching/weakness in conjunction with serum creatine kinase activity >10 times the upper limit of normal.[144] Therefore, the possibility arises that if patients presented with the recently described statin-associated myositis with normal creatine kinase activity,[123] they may not have been classified as having myositis. This could have resulted in an underestimate of the true incidence of the adverse effect in these trials. Several studies have suggested that statin treatment may exacerbate exercise-related muscle injury.[145-147] Whether this effect is related to CoQ_{10} deficiency has yet to be established. Unfortunately, this has not been investigated in clinical trials.[1,3,4,6,9-11,16,43] Thus, a reappraisal of the effect of statin treatment on skeletal muscle CoQ_{10} status may be appropriate.[101,103] Clearly, when used at recommended doses, statins have been proven to be efficacious and reduce the incidence of coronary heart disease with little clinical evidence of adverse effects or associated CoQ_{10} deficiency.[1,3,4,6,9-11,16,43,148] The incidence of myositis and

rhabdomyolysis becomes more prevalent when statins are administered at high doses or when they are used in combination with agents that elevate their plasma concentrations.[75,82] The risk of statin-induced myositis and rhabdomyolysis is increased with renal and hepatic dysfunction, hypothyroidism, diabetes, serious infections and age.[79,149] In 13 of the 15 studies that assessed the effect of statin treatment on CoQ_{10} status, no adverse clinical effects of the treatment regimen were reported.[6,18,97-103,105-110] Thus, it appears likely that when taken at the recommended doses, the adverse effects of statin treatment resulting from CoQ_{10} deficiency are, at best, extremely rare. However, it may be prudent, given the documented association between primary muscle CoQ_{10} deficiency and myositis and rhabdomyolysis in patients with familial mitochondrial encephalomyopathy,[95,150] to monitor CoQ_{10} status in patients presenting with evidence of myositis following statin treatment.[151] It may also be judicious to assess the CoQ_{10} status of patients who may be deficient as a result of age[47] or established cardiovascular disease[42-44] prior to the instigation of statin treatment. If CoQ_{10} deficiency is noted, supplementation should be considered as this has been shown to resolve the myositis and rhabdomyolysis reported in patients with familial mitochondrial encephalomyopathy.[1,52,95] However, evidence suggests that high doses may be required as gastrointestinal absorption of CoQ_{10} is poor.[9,18]

5.1 Monitoring of CoQ_{10} Status

Monitoring the CoQ_{10} status of patients presents technical problems. The tissue of choice is muscle, but this is clearly not practical. In plasma or serum, the level of CoQ_{10} represents an equilibrium between gut absorption and *in vivo* biosynthesis.[38] Moreover, the absolute level is dependent upon the levels of the cholesterol fractions LDL and VLDL. Of course, it is hoped that these are being reduced by the statin therapy. Thus, CoQ_{10} levels need to be normalised to the LDL/VLDL levels. Consequently, plasma/serum levels may have limited value as a means of assessing CoQ_{10} status.[152,153] An alternative is to measure CoQ_{10} in another sample type such as mononuclear cells as they represent a stable, easily isolated sample type that reflect changes in cellular CoQ_{10} status following supplementation.[154] We have established a chromatographic method for assessing mononuclear cell CoQ_{10} levels[11,18] and this has allowed reference intervals to be derived, deficient patients to be diagnosed and the effect of supplementation therapy to be assessed. The application of this method to samples from patients presenting with myositis that is apparently secondary to statin therapy may help answer the question 'is myositis and rhadomyolysis secondary to statin-induced CoQ_{10} deficiency?'

6. Conclusion

The development of statins has contributed markedly to the effective treatment of hypercholesterolaemia and to a reduction in the incidence of both primary and secondary cardiovascular events. However, although statins generally have a favourable safety profile, a small percentage of patients have presented with serious adverse effects. Whether these adverse effects are related to a CoQ_{10} deficiency has yet to be confirmed in human studies, which have failed to establish a firm relationship between statin treatment and tissue CoQ_{10} deficiency. This may be a reflection of the therapeutic doses of statins used in human studies, as the low systemic bioavailability of these drugs limits their uptake by extra-hepatic tissues. The incidence of serious adverse effects such as myositis and rhabdomyolysis increases when statins are used at high doses and in conjunction with agents that increase their plasma concentrations. Moreover, those statins with high systemic bioavailability and those that are relatively more lipophilic exhibit greater diffusion into extrahepatic tissues such as muscle. Studies in animals have shown evidence of blood and muscle CoQ_{10} deficiency, particularly if supra-pharmacological doses of statin treatment have been administered.

Statins are so effective in treating hyperlipidaemias that to withdraw them would not always appear to be in the patient's best interest. Therefore, in those patients with clinical myositis and/or rhabdomyolysis and severe hyperlipidaemia, it would appear prudent to assess their tissue CoQ_{10} status with a view to administering supplementation if it is found to be deficient. In view of the limitations of plasma/serum measurements, it is suggested that blood mononuclear cells may represent an appropriate alternative sample type as initial studies

have indicated that mononuclear cell CoQ_{10} status may reflect that of skeletal muscle (Hargreaves IP et al., unpublished data). Finally, it is suggested that further clinical studies that take particular note of the tissue specificity and pharmacokinetic characteristics of the statins are warranted. Only then will it be possible to define any pathophysiological relationship between specific statin treatments, CoQ_{10} deficiency and the muscle adverse effects of this class of drugs.

Acknowledgements

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest that are directly relevant to the content of this study.

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