

## TOCOTRIENOLS

Results from a preliminary study* using tocotrienols with no tocopherols					
Product used and Daily dose	Total Chol.	LDL	HDL	Triglycerides	
<i>Delta-Tocotrienol: 100mg/day</i>	-27%	-24%	+8%	-20%	
<i>Gamma-Tocotrienol: 100mg/day</i>	-21%	-21%	+12%	-15%	
<i>UltraTrienol: 75mg/day consisting of: 67.5mg Delta-Tocotrienol+7.5 mg Gamma-Tocotrienol</i>	-15%	-10%	+10%	-20%	

\* This was an internal study performed on 10 subjects by Bristol Meyer's Squib for 2 months

Clin Biochem 1999 Jul;32(5):309-19

### **Tocotrienol: a review of its therapeutic potential.**

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**OBJECTIVES:** To summarize new knowledge surrounding the physiological activity of tocotrienol, a natural analogue of tocopherol. **RESULTS:** The biological activity of vitamin E has generally been associated with its well-defined antioxidant property, specifically against lipid peroxidation in biological membranes. In the vitamin E group, alpha-tocopherol is considered to be the most active form. However, recent research has suggested tocotrienol to be a better antioxidant. Moreover, tocotrienol has been shown to possess novel hypocholesterolemic effects together with an ability to reduce the atherogenic apolipoprotein B and lipoprotein(a) plasma levels. In addition, tocotrienol has been suggested to have an anti-thrombotic and anti-tumor effect indicating that tocotrienol may serve as an effective agent in the prevention and/or treatment of cardiovascular disease and cancer. **CONCLUSION:** The physiological activities of tocotrienol suggest it to be superior than alpha-tocopherol in many situations. Hence, the role of tocotrienol in the prevention of cardiovascular disease and cancer may have significant clinical implications. Additional studies on its mechanism of action, as well as, long-term intervention studies, are needed to clarify its function. From the pharmacological point-of-view, the current formulation of vitamin E supplements, which is comprised mainly of alpha-tocopherol, may be questionable.

Atherosclerosis 2002 Mar;161(1):199-207

### **Dose-dependent suppression of serum cholesterol by tocotrienol-rich fraction (TRF25) of rice bran in hypercholesterolemic humans.**

**Qureshi AA, Sami SA, Salser WA, Khan FA.**

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Tocotrienols are effective in lowering serum total and LDL-cholesterol levels by inhibiting the hepatic enzymic activity of beta-hydroxy-beta-methylglutaryl coenzymeA (HMG-CoA) reductase through the post-

transcriptional mechanism. alpha-Tocopherol, however, has an opposite effect (induces) on this enzyme activity. Since tocotrienols are also converted to tocopherols in vivo, it is necessary not to exceed a certain dose, as this would be counter-productive. The present study demonstrates the effects of various doses of a tocotrienol-rich fraction (TRF25) of stabilized and heated rice bran in hypercholesterolemic human subjects on serum lipid parameters. Ninety (18/group) hypercholesterolemic human subjects participated in this study, which comprised three phases of 35 days each. The subjects were initially placed on the American Heart Association (AHA) Step-1 diet and the effects noted. They were then administered 25, 50, 100, and 200 mg/day of TRF25 while on the restricted (AHA) diet. The results show that a dose of 100 mg/day of TRF25 produce maximum decreases of 20, 25, 14 ( $P < 0.05$ ) and 12%, respectively, in serum total cholesterol, LDL-cholesterol, apolipoprotein B and triglycerides compared with the baseline values, suggesting that a dose of 100 mg/day TRF25 plus AHA Step-1 diet may be the optimal dose for controlling the risk of coronary heart disease in hypercholesterolemic human subjects.

J Nutr Biochem 2001 Jun;12(6):318-329

### **Synergistic effect of tocotrienol-rich fraction (TRF(25)) of rice bran and lovastatin on lipid parameters in hypercholesterolemic humans.**

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Tocotrienols exert hypocholesterolemic action in humans and animals. Lovastatin is widely used for that purpose. Both agents work by suppressing the activity of beta-hydroxy-beta-methylglutaryl coenzyme A reductase through different mechanisms, post-transcriptional vs competitive inhibition. A human study with 28 hypercholesterolemic subjects was carried out in 5 phases of 35 days each, to check the efficacy of tocotrienol-rich fraction (TRF(25)) of rice bran alone and in combination with lovastatin. After placing subjects on the American Heart Association (AHA) Step-1 diet (phase II), the subjects were divided into two groups, A and B. The AHA Step-1 diet was continued in combination with other treatments during phases III to V. Group A subjects were given 10 mg lovastatin, 10 mg lovastatin plus 50 mg TRF(25), 10 mg lovastatin plus 50 mg alpha-tocopherol per day, in the third, fourth, and fifth phases, respectively. Group B subjects were treated exactly to the same protocol except that in the third phase, they were given 50 mg TRF(25) instead of lovastatin. The TRF(25) or lovastatin plus AHA Step-1 diet effectively lower serum total cholesterol (14%, 13%) and LDL-cholesterol (18%, 15%  $P < 0.001$ ), respectively, in hypercholesterolemic subjects. The combination of TRF(25) and lovastatin plus AHA Step-1 diet significantly reduces of these lipid parameters of 20% and 25% ( $P < 0.001$ ) in these subjects. Substitution of TRF(25) with alpha-tocopherol produces insignificant changes when given with lovastatin. Especially significant is the increase in the HDL/LDL ratio to 46% in group (A) and 53% ( $P < 0.002$ ) in group (B). These results are consistent with the synergistic effect of these two agents. None of the subjects reported any side-effects throughout the study of 25-weeks. In the present study, the increased effectiveness of low doses of tocotrienols (TRF(25)) as hypocholesterolemic agents might be due to a minimum conversion to alpha-tocopherol. The report also describes in vivo the conversion of gamma-[4-3H], and [14C]-desmethyl (d-P(21)-T3) tocotrienols to alpha-tocopherol.

Atherosclerosis 2002 Jan;160(1):21-30

### **Tocotrienol is the most effective vitamin E for reducing endothelial expression of adhesion molecules and adhesion to monocytes.**

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Alpha-tocopherol and its esterified derivatives have been shown to be effective in reducing monocytic-endothelial cell adhesion. However, the effect of alpha-tocotrienol (alpha-T3) has not been characterized. In the present study, using human umbilical vein endothelial cells (HUVEC) as the model system, we examined the relative inhibitory effects of alpha-T3 and other vitamin E derivatives on cell surface adhesion molecule expression under TNF-alpha stimulation. Using enzyme-linked immunosorbent assay, we demonstrated that alpha-T3 markedly inhibited the surface expression of vascular cell adhesion molecule-1 in TNF-alpha activated HUVEC in a dose- and time-dependent manner. The optimal inhibition was observed at 25 micromol/l alpha-T3 within 24 h (77+/-5%) without cytotoxicity. In addition, the surface expression of intercellular adhesion molecule-1 and E-selectin were also reduced by 40+/-7 and 42+/-5%, respectively. In order to further evaluate the effects of alpha-T3 on the vascular endothelium, we investigated the ability of monocytes to adhere to endothelial cells. Interestingly, a 63+/-3% decrease in monocytic cell adherence was observed. Compared to alpha-tocopherol and alpha-tocopheryl succinate, alpha-T3 displayed a more profound inhibitory effect on adhesion molecule expression and monocytic cell adherence. This inhibitory action by alpha-T3 on TNF-alpha-induced monocyte adhesion was shown to be NF-kappaB dependent and was interestingly reversed with co-incubation with farnesol and geranylgeraniol, suggesting a role for prenylated proteins in the regulation of adhesion molecule expression. In summary, the above results suggest that alpha-T3 is a potent and effective agent in the reduction of cellular adhesion molecule expression and monocytic cell adherence.

## CARNITINE

### **1. Davini P, Bigalli A, Lamanna F, Boem A. Controlled study on L-carnitine therapeutic efficacy in post-infarction.** *Drugs Exp Clin Res.* 1992;18(8):355-65.

Department of Cardiovascular Medicine, Santa Chiara Hospital, U.S.L., Pisa, Italy.

A controlled study was carried out on 160 patients of both sexes (age between 39 and 86 years) discharged from the Cardiology Department of the Santa Chiara Hospital, Pisa, with a diagnosis of recent myocardial infarction. L-carnitine was randomly administered to 81 patients at an oral dose of **4g/day for 12 months**, in addition to the pharmacological treatment generally used. For the whole period of 12 months, these patients showed, in comparison with the controls, an improvement in heart rate ( $p < 0.005$ ), systolic arterial pressure ( $p < 0.005$ ) and diastolic arterial pressure (NS); a decrease of anginal attacks ( $p < 0.005$ ), of rhythm disorders (NS) and of clinical signs of impaired myocardial contractility (NS), and a **clear improvement in the lipid pattern** ( $p < 0.005$ ). The above changes were accompanied by a lower mortality in the treated group (1.2%,  $p < 0.005$ ), while in the control group there was a mortality of 12.5%. Furthermore, in the control group there was a definite prevalence of deaths caused by reinfarction and sudden death. On the basis of these results, it is concluded that L-carnitine represents an effective treatment in post-infarction ischaemic cardiopathy, since it can improve the clinical evolution of this pathological condition as well as the patient's quality of life and life expectancy.

### **2. Cacciatore L, Cerio R, Ciarimboli M, Cocozza M. The therapeutic effect of L-carnitine in patients with exercise-induced stable angina: a controlled study.** *Drugs Exp Clin Res.* 1991;17(4):225-35.

IV Internal Medicine Department, II Medical School, University of Naples, Italy.

An investigation on the therapeutic effect of L-carnitine was performed at three different centres and included two hundred patients, 40 to 65 years of age, with exercise-induced stable angina. In one hundred randomly selected patients the drug was administered orally in **daily doses of 2 g** in addition to the already instituted therapy, and the effect studied over a **6-month period**. Compared with the control group, these patients showed

a significant reduction in the number of premature ventricular contractions (PVC) at rest, as well as an increased tolerance during ergometric cycle exercise as demonstrated by an increased maximal cardiac frequency, increased maximal systolic arterial blood pressure and therefore also increased double cardiac product and reduced ST-segment depression during maximal effort. This was accompanied by improvement in cardiac function and resultant performance, as shown by an increase in the number of patients belonging to class I of the NYHA classification and a reduction in the consumption of cardioactive drugs. Laboratory analysis showed **an improvement in plasma lipid levels**. The authors conclude, after having discussed the particular metabolic mechanisms, that L-carnitine undoubtedly represents an interesting therapeutic drug for patients with exercise-induced stable angina

**3. Rossi CS, Siliprandi N. Effect of carnitine on serum HDL-cholesterol: report of two cases.** Johns Hopkins Med J. 1982 Feb;150(2):51-4.

In two otherwise normal male subjects selected for normal serum cholesterol and triglycerides but low serum high-density lipoprotein (HDL) levels, oral administration of **1 g per day of L-carnitine over a period of 10-15 weeks** caused a **substantial increase in high-density lipoprotein levels, as well as a decrease in serum triglycerides**. The **ratio of HDL-cholesterol to total cholesterol increased**, but this change was not due to an obligatory lowering of total cholesterol. Possible mechanisms of the carnitine effect are discussed. Since elevated high-density lipoprotein levels significantly reduce the risk of arteriosclerotic cardiovascular disease, this action of carnitine deserves further study.

**4. Maebashi M, Kawamura N, Sato M . Lipid-lowering effect of carnitine in patients with type-IV hyperlipoproteinaemia.** Lancet. 1978 Oct 14;2(8094):805-.

Serum-lipid concentrations were determined in patients with type-IV hyperlipoproteinaemia treated with **900 mg/day** oral DL-carnitine chloride. Serum-**triglyceride was significantly reduced** and concentrations continued to decline as carnitine administration continued. Total and esterified cholesterol concentrations did not change. **Intravenous infusion of carnitine produced the same effects**. The results suggest that carnitine is of value in the therapy of type-IV hyperlipoproteinaemia. Increased oxidation of free fatty acids in the tissues seems to account for the effects of carnitine on serum-lipid concentrations.

**5. Fernandez C, Proto C. [L-carnitine in the treatment of chronic myocardial ischemia. An analysis of 3 multicenter studies and a bibliographic review]** Clin Ter. 1992 Apr;140(4):353-77.

[Article in Italian]

Servizio di Cardiologia Ambulatoriale, USL 61, Palermo.

The authors selected, from a general sample of 3525 cardiopathic patients treated with **2 g daily of L-carnitine during 1 year**, 220 stable effort angina TNT-responder patients, presenting more than 15 anginal episodes per month; moreover, other 59 anginal patients in congestive heart failure have been taken into account. The evaluation of the results obtained in these samples has been done in parallel with the ones of cardiopathic patients studied in 2 multicentric trials carried out, according to a very similar protocol, in Switzerland (148 patients treated at the same posology for 6 months) and Germany (143 patients, 3 months of treatment). The analysis of the three trials showed net reduction of both rate of anginal episodes and therapeutic use of nitrates, substantiated by improvement of physical performance (demonstrated by ergometric test in the German trial) as well as of the quality of life (the Swiss trial). Furthermore, from the general sample of 3525 patients the authors selected 737 subjects with clearly pathological levels of plasma cholesterol, in order to **evaluate the effect of L-carnitine treatment on lipidemic parameters**; after 12 months of administration only 282 patients showed abnormal levels of cholesterolemia. **Analysis of the results of the three trials and a review of the literature**

**on carnitine identify the compound as a fundamental drug for the treatment of patients with myocardial ischemia.**

**6. Muller DM, Seim H, Kiess W, Loster H, Richter T. Effects of oral L-carnitine supplementation on in vivo long-chain fatty acid oxidation in healthy adults.** *Metabolism.* 2002 Nov;51(11):1389-91.

University of Leipzig, Children's Hospital, Germany.

Despite an abundance of literature describing the basic mechanisms of action of L-carnitine metabolism, there remains some uncertainty regarding the effects of oral L-carnitine supplementation on in vivo fatty acid oxidation in normal subjects under normal conditions. **It is well known that L-carnitine normalizes the metabolism of long-chain fatty acids** in cases of carnitine deficiency. However, it has not yet been shown that L-carnitine influences the metabolism of long-chain fatty acids in subjects without disturbances in fatty acid metabolism. Therefore, we investigated the effects of oral L-carnitine supplementation on in vivo long-chain fatty acid oxidation by measuring 1-[(13)C] palmitic acid oxidation in healthy subjects before and after L-carnitine supplementation (3 x 1 g/d for 10 days). We observed a significant increase in (13)CO(2) exhalation. **This is the first investigation to conclusively demonstrate that oral L-carnitine supplementation results in an increase in long-chain fatty acid oxidation in vivo in subjects without L-carnitine deficiency** or without prolonged fatty acid metabolism. Copyright 2002, Elsevier Science (USA). All rights reserved.

**9. Sirtori CR, Calabresi L, Ferrara S . L-carnitine reduces plasma lipoprotein(a) levels in patients with hyper Lp(a).** *Nutr Metab Cardiovasc Dis.* 2000 Oct;10(5):247-51.

Center E. Grossi Paoletti, Institute of Pharmacological Sciences, University of Milano, Italy.

BACKGROUND AND AIMS: Elevated Lp(a) levels are a significant cardiovascular risk factor, particularly for young individuals and for subjects with concomitant high LDL cholesterol. Increased Lp(a) is believed to be linked to an enhanced production of the lipoprotein, controlled by genetic factors; it can be reduced by agents such as nicotinic acid, lowering free fatty acid inflow to the liver. METHODS AND RESULTS: L-carnitine, a natural compound stimulating fatty acid oxidation at the mitochondrial level, was tested in a double blind study in 36 subjects with Lp(a) levels ranging between 40-80 mg/dL, in most with concomitant LDL cholesterol and triglyceride elevations. L-carnitine (**2 g/day**) **significantly reduced Lp(a) levels (-7.7% vs baseline and -11.7% vs placebo** treatment), the reduction being more dramatic in the subjects with the more marked elevations. In particular, in the L-carnitine group, 14 out of 18 subjects (77.8%) had a significant reduction of Lp(a) vs only 7 out of 18 (38.9%) in the placebo group ( $\chi^2 = 4.11$ ,  $p = 0.0452$ ). In a significant number of subjects the reduction of Lp(a) resulted in a return of this major cardiovascular risk parameter to the normal range. CONCLUSIONS: L-carnitine offers a potentially useful therapeutic agent for atherogenic conditions characterized by high Lp(a) levels, also in view of the excellent tolerability and essential lack of major side effects.

**10. Scholte HR, Luyt-Houwen IE, Vaandrager-Verduin MH. The role of the carnitine system in myocardial fatty acid oxidation: carnitine deficiency, failing mitochondria and cardiomyopathy.** *Basic Res Cardiol.* 1987;82 Suppl 1:63-73.

Department of Biochemistry, Medical Faculty, Erasmus University, Rotterdam, The Netherlands.

The carnitine system functions in the transport of activated acyl groups over the mitochondrial inner membrane, and is needed for oxidation of long-chain fatty acids by all mitochondria. The rate of cardiac fatty acid oxidation is determined by availability of fatty acids, oxygen and the activity of carnitine palmitoyltransferase I, which is regulated by a variety of factors. It is inhibited by malonyl-CoA, which in rat heart was found to be synthesized by acetyl-CoA carboxylase. It is also inhibited by long-chain acylcarnitine. Linoleoylcarnitine was

found to be a better inhibitor than palmitoylcarnitine. The concentration of carnitine in human heart, muscle and other tissues is much higher than is needed for the optimal beta-oxidation rate. In contrast to controls, we found in several myopathic patients that extra carnitine (from 1/2 to 5 mM) caused a considerable increase in beta-oxidation rate of isolated muscle mitochondria. In some of these patients we detected medium-chain acyl-CoA dehydrogenase deficiency. Patients with primary carnitine deficiency caused by a renal carnitine leak often show cardiomyopathy, which completely disappears under carnitine therapy. Cardiomyopathy may also be the cause of secondary carnitine deficiency resulting from a mitochondrial defect in acyl-CoA metabolism, or by the mitochondrial defect itself, which may be induced by drugs or viral attack, or be the result of a genetic error. In cardiomyopathic patients with a (subclinical) myopathy, study of isolated mitochondria and homogenate from skeletal muscle may reveal a mitochondrial dysfunction, which, in some patients, is treatable by dietary measures and supplementation with vitamins, CoQ and/or carnitine. When the cause of cardiomyopathy is not known, determination of plasma carnitine and carnitine supplementation of hypocarnitinemic patients is of great therapeutic value.

**11. Digiesi V, Cantini F, Bisi G, Guarino G, Brodbeck B. L-carnitine adjuvant therapy in essential hypertension.** Clin Ter. 1994 May;144(5):391-5.

Florence University Medical School, Third Institute of Clinical Medicine and Medical Therapy.

This study was undertaken to demonstrate L-carnitine therapeutical effect in patients with essential hypertension. Two groups were tested, A and B. First group (A) was split in two subgroups, A1 and A2. Subgroup A1 included 14 patients with essential hypertension, they were treated with antihypertensive drugs and L-carnitine. Subgroup A2 included 14 patients with essential hypertension, that were treated with antihypertensive drugs only. Group B included 9 patients with essential hypertension and they were treated with L-carnitine only. Subgroup A1 patients were treated with **oral L-carnitine 2 gm per day** for 22 weeks; group B patients were treated with the same dose for 10 weeks. The asthenia symptom was evaluated, a resting and dynamic E.C.G. was carried out, serum triglycerides, **serum total and high-density lipoprotein (HDL) cholesterol, serum sodium and potassium, serum creatinine, serum glucose and blood pressure were determined** before and at the end of test in group A patients. Test procedure of group B patients included also serum evaluation of apolipoproteins A1 and B and radionuclide angiocardiology. In subgroup A1 patients extrasystoles as well as some electrocardiographic signs of minor changes of ventricular repolarization reversed or diminished, the asthenia symptom was improved significantly and triglyceride values decreased from 148 +/- 15.8 mg/dl to 121 +/- 14.3 mg/dl ( $p < 0.025$ ). (ABSTRACT TRUNCATED AT 250 WORDS)

Biol Trace Elem Res. 1996 Dec;55(3):297-305.

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**Effect of chromium nicotinic acid supplementation on selected cardiovascular disease risk factors.**

**Thomas VL, Gropper SS.**

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The effects of daily supplemental chromium (200 micrograms) complexed with 1.8 mg nicotinic acid on plasma glucose and lipids, including total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, were assessed in 14 healthy adults and 5 adults with noninsulin-dependent diabetes mellitus (NIDDM) using a double-blind crossover study with 8-wk experimental periods. Eight of the 14 healthy subjects and all 5 subjects with NIDDM also underwent an oral glucose tolerance test with assessment of 90 min postprandial plasma glucose and insulin concentrations. No statistically significant effects of chromium nicotinic acid supplementation were found on plasma insulin, glucose, or lipid concentrations, although chromium **nicotinic**

**acid supplementation slightly lowered fasting plasma total and LDL cholesterol, triglycerides, and glucose concentrations, and 90-min postprandial glucose concentrations in individuals with NIDDM.**

Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. J Lipid Res. 1989 Jun;30(6):785-807.

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Epidemiological studies in Greenland Eskimos led to the hypothesis that marine oils rich in n-3 fatty acids (also referred to as omega (omega)-3 fatty acids) are hypolipidemic and ultimately antiatherogenic. Metabolically controlled trials in which large amounts of fish oil were fed to normal volunteers and hyperlipidemic patients showed that these fatty acids (FAs) are effective at lowering plasma cholesterol and triglyceride levels. Although more recent trials using smaller, more practical doses of fish oil supplements have confirmed the hypotriglyceridemic effect, they have shown little effect on total cholesterol levels; hypertriglyceridemic patients have even experienced increases in low density lipoprotein cholesterol (LDL-C) levels of 10-20% while taking n-3 FA supplements. Discrepancies among fish oil studies regarding the effects of n-3 FAs on LDL-C levels may be understood by noting that, in the majority of studies reporting reductions in LDL-C levels, saturated fat intake was lowered when switching from the control diet to the fish oil diet. When fish oil is fed and saturated fat intake is constant, LDL-C levels either do not change or may increase. Levels of high density lipoprotein cholesterol have been found to increase slightly (about 5-10%) with fish oil intake. Plasma apolipoprotein levels change in concert with their associated lipoprotein cholesterol levels. Although the decrease in triglyceride levels appears to result from an inhibition in hepatic triglyceride synthesis, the mechanisms leading to the increases in LDL and HDL have not been determined. Finally, fatty fish or linolenic acid may serve as alternative sources of long-chain n-3 FAs, but further studies will be needed to document their hypolipidemic and/or antiatherogenic effects.

**Serum concentration of lipoprotein(a) decreases on treatment with hydrosoluble coenzyme Q10 in patients with coronary artery disease: discovery of a new role.** Int J Cardiol. 1999

Jan;68(1):23-9.

**Singh RB, Niaz MA.**

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**OBJECTIVE:** To examine the effect of coenzyme Q10 supplementation on serum lipoprotein(a) in patients with acute coronary disease. **STUDY DESIGN:** Randomized double blind placebo controlled trial. **SUBJECTS AND METHODS:** Subjects with clinical diagnosis of acute myocardial infarction, unstable angina, angina pectoris (based on WHO criteria) with moderately raised lipoprotein(a) were randomized to either coenzyme Q10 as Q-Gel (60 mg twice daily) (coenzyme Q10 group, n=25) or placebo (placebo group, n=22) for a period of 28 days. **RESULTS:** Serum lipoprotein(a) showed significant reduction in the coenzyme Q10 group compared with the placebo group (31.0% vs 8.2% P<0.001) with a net reduction of 22.6% attributed to coenzyme Q10. HDL cholesterol showed a significant increase in the intervention group without affecting total cholesterol, LDL cholesterol, and blood glucose showed a significant reduction in the coenzyme Q10 group. Coenzyme Q10 supplementation was also associated with significant reductions in thiobarbituric acid reactive substances, malon/dialdehyde and diene conjugates, indicating an overall decrease in oxidative stress. **CONCLUSION:** Supplementation with hydrosoluble coenzyme Q10 (Q-Gel) decreases lipoprotein(a) concentration in patients with acute coronary disease.

## **Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction.**

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In a randomized, double-blind, controlled trial, the effects of oral treatment with coenzyme Q10 (CoQ10, 120 mg/day), a bioenergetic and antioxidant cytoprotective agent, were compared for 1 year, on the risk factors of atherosclerosis, in 73 (CoQ, group A) and 71 (B vitamin group B) patients after acute myocardial infarction (AMI). After 1 year, total cardiac events (24.6 vs. 45.0%,  $p < 0.02$ ) including non-fatal infarction (13.7 vs. 25.3%,  $p < 0.05$ ) and **cardiac deaths were significantly lower in the intervention group** compared to control group. The extent of cardiac disease, elevation in cardiac enzymes, left ventricular enlargement, previous coronary artery disease and elapsed time from symptom onset to infarction at entry to study showed no significant differences between the two groups. Plasma level of vitamin E (32.4 +/- 4.3 vs. 22.1 +/- 3.6 umol/L) and high density lipoprotein cholesterol (1.26 +/- 0.43 vs. 1.12 +/- 0.32 mmol/L) showed significant ( $p < 0.05$ ) increase whereas thiobarbituric acid reactive substances, malondialdehyde (1.9 + 0.31 vs. 3.1 + 0.32 pmol/L) and diene conjugates showed significant reduction respectively in the CoQ group compared to control group. Approximately half of the patients in each group ( $n = 36$  vs. 31) were receiving lovastatin (10 mg/day) and both groups had a significant reduction in total and low density lipoprotein cholesterol compared to baseline levels. It is possible that treatment with CoQ10 in patients with recent MI may be beneficial in patients with high risk of atherothrombosis, despite optimal lipid lowering therapy during a follow-up of 1 year. Adverse effect of treatments showed that fatigue (40.8 vs. 6.8%,  $p < 0.01$ ) was more common in the control group than CoQ group.

Mol Aspects Med. 1994;15 Suppl:S265-72.

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## **Treatment of essential hypertension with coenzyme Q10.**

**Langsjoen P, Langsjoen P, Willis R, Folkers K.**

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A total of 109 patients with symptomatic essential hypertension presenting to a private cardiology practice were observed after the addition of CoQ10 (average dose, 225 mg/day by mouth) to their existing antihypertensive drug regimen. In 80 per cent of patients, the diagnosis of essential hypertension was established for a year or more prior to starting CoQ10 (average 9.2 years). Only one patient was dropped from analysis due to noncompliance. The dosage of CoQ10 was not fixed and was adjusted according to clinical response and blood CoQ10 levels. Our aim was to attain blood levels greater than 2.0 micrograms/ml (average 3.02 micrograms/ml on CoQ10). Patients were followed closely with frequent clinic visits to record blood pressure and clinical status and make necessary adjustments in drug therapy. Echocardiograms were obtained at baseline in 88% of patients and both at baseline and during treatment in 39% of patients. A definite and gradual improvement in functional status was observed with the concomitant need to gradually decrease antihypertensive drug therapy within the first one to six months. Thereafter, clinical status and cardiovascular drug requirements stabilized with a significantly improved systolic and diastolic blood pressure. Overall New York Heart Association (NYHA) functional class improved from a mean of 2.40 to 1.36 ( $P < 0.001$ ) **and 51% of patients came completely off of between one and three antihypertensive drugs at an average of 4.4 months after starting CoQ10. Only 3% of patients required the addition of one antihypertensive drug. In the 9.4% of patients with echocardiograms both before and during treatment, we observed a highly significant improvement in left ventricular wall thickness and diastolic function.**(ABSTRACT TRUNCATED AT 250 WORDS)

## **Dose-related decrease of serum coenzyme Q10 during treatment with HMG-CoA reductase inhibitors.**

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Coenzyme Q10 (ubiquinone) the essential mitochondrial redox-component and endogenous antioxidant, packaged into the LDL + VLDL fractions of cholesterol, has been suggested as an important anti-risk factor for the development of atherosclerosis as explained by the oxidative theory. Forty-five hypercholesterolemic patients were randomized in a double-blind trial in order to be treated with increasing dosages of either lovastatin (20-80 mg/day) or pravastatin (10-40 mg/day) over a period of 18 weeks. Serum levels of coenzyme Q10 were measured parallel to the levels of cholesterol at baseline on placebo and diet and during active treatment. A dose-related significant decline of the total serum level of coenzyme Q10 was found in the pravastatin group from 1.27 +/- 0.34 at baseline to 1.02 +/- 0.31 mmol/l at the end of the study period (mean +/- S.D.),  $P < 0.01$ . After lovastatin therapy the decrease was significant as well and more pronounced, from 1.18 +/- 0.36 to 0.84 +/- 0.17 mmol/l,  $P < 0.001$ . Although HMG-CoA reductase inhibitors are safe and effective within a limited time horizon, continued **vigilance of a possible adverse consequence from coenzyme Q10 lowering seems important during long-term therapy.**

Clin Investig. 1993;71(8 Suppl):S112-5.

[Related Articles, Links](#)

## **Coenzyme Q10 and coronary artery disease.**

**Hanaki Y, Sugiyama S, Ozawa T, Ohno M.**

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It has been postulated that oxidatively modified low-density lipoprotein (LDL) contributes to the genesis of atherosclerosis. Ubiquinone has been suggested to be an important physiological lipid-soluble antioxidant and is found in LDL fractions in the blood. We measured plasma level of ubiquinone using high-performance liquid chromatography and plasma levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in 245 normal subjects (186 males, 59 females) and in 104 patients (55 males, 49 females) who had coronary artery disease not receiving pravastatin and 29 patients (12 males, 17 females) receiving pravastatin. In the normal subjects, the plasma ubiquinone levels did not vary with age. In the patient groups, the plasma total cholesterol and LDL levels were higher and the plasma ubiquinone level lower than in the normal subject group. The LDL/ubiquinone ratio was higher in the patient groups. We found that ubiquinone level, either alone or when expressed in relation to LDL levels, was significantly lower in the patient groups compared with the normal subject group. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor is thought to prevent atherosclerosis, however, it also inhibits ubiquinone production. The present study revealed that HMG CoA reductase inhibitor decreased plasma cholesterol level, and that it did not improve either the ubiquinone level or the LDL/ubiquinone ratio. **From these results, the LDL/ubiquinone ratio is likely to be a risk factor for atherogenesis, and administration of ubiquinone to patients at risk might be needed.**

Mol Aspects Med. 1994;15 Suppl:s67-72.

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## **Metabolic implications of coenzyme Q10 in red blood cells and plasma lipoproteins.**

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Plasma coenzyme Q10 (CoQ10) is currently assayed in our laboratory for its well-known diagnostic meaning; in fact plasma CoQ10 levels are inversely related to metabolic demand. Definite levels of CoQ10 are also found in white and red blood cell components, as well as in platelets. Plasma and erythrocyte CoQ10 has a well assessed antioxidant role, which was demonstrated through a series of experiments. Erythrocytes previously enriched with exogenous CoQ10 were found more resistant to a hemolysis induced by a free radical initiator. Several enzymatic activities of erythrocyte ghosts were also protected by different side chain CoQ homologues, both when reduced and, although at a lesser extent, in the oxidized state. CoQ was not effective in preventing metal-catalyzed oxidation of erythrocyte membrane enzymes, and this effect is likely to be due to lack of interaction of CoQ with the metal target. Moreover CoQ was able to protect isolated enzymes and erythrocyte membrane bound enzymes from the inactivating effect of free radicals generated by water sonolysis or radiolysis. As far as plasma lipoproteins are concerned **it is well known that LDL isolated from healthy volunteers supplemented with CoQ10 are more resistant to peroxidation** induced by an azoinitiator. We started to systematically investigate CoQ10 and vitamin E levels in isolated human LDL and HDL. Both CoQ10 and vitamin E concentrations, referred to protein, were found higher in LDL than in HDL. Susceptibility to exogenously applied peroxidation did not correlate with the endogeneous content of the two antioxidants, possibly on the basis of different lipid content of these lipoproteins.