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Investigation of the Effects of Statin Therapy on Serum Vitamin E Status in Patients with Dyslipidemia

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Abstract: There are limited data on the effects of statins on serum vitamin E status in dyslipidaemic patients, and no comparisons between statins have been published previously. We have investigated the effect of Atorvastatin and Simvastatin on serum vitamin E status in dyslipidaemic patients. A total of 20 dyslipidaemic patients (14 males, 6 females, mean age 49.15±3.28 years), previously not treated with a lipid lowering agent, were recruited into the study. These patients were randomized to treatment group and received either: Simvastatin 10mg/day (n = 11) or Atorvastatin 10mg/day (n = 9) for 4 months. The control group comprised 14 patients from the same clinic, who were given lifestyle advice, but whose drug treatment remained unchanged for the duration of the study. Serum concentrations of vitamin E, high sensitivity C-reactive protein (hs-CRP) and fasted lipid profiles pre- and post-treatment were measured in all subjects. There were the expected significant reductions in serum lipids in the patients treated with either statin (P<0.001). Overall statin treatment was also associated with a significant reduction in serum vitamin E (21%, P<0.001) and hs-CRP (45%, P<0.05). There was no significant change in these parameters in the control patients. The serum vitamin E / total cholesterol ratio was not significantly altered in patients receiving Atorvastatin, or Simvastatin despite the significant reduction in serum vitamin E. No change in vitamin E status was observed in the controls.

Key words: Atorvastatin, simvastatin, vitamin E, cholesterol, high sensitivity C-reactive protein (hs-CRP)

Introduction

Inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme. A reductase or statins constitute the most powerful class of cholesterol lowering drugs. The use of these agents in the treatment of dyslipidaemia has been shown to improve survival and significantly reduce the onset of cardiac events, in both primary and secondary prevention (Anonymous, 1994; Heart Protection Collaborative Study Group, 2002b; Downs et al., 1998; Sacks et al., 1996; Shepherd et al., 1995).

Over the recent past the so-called pleiotropic actions of statins (effects unrelated to their cholesterol lowering properties) have emerged as being potentially important (Blake and Ridker, 2000; Munford, 2001; Takemoto and Liao, 2001). These properties include anti inflammatory, immunoregulatory and antioxidant effects (Blake and Ridker, 2000; Takemoto and Liao, 2001). Statin-induced reductions in C-Reactive Protein (CRP) provide support for the anti inflammatory effect of these agents (Ridker et al., 2001; Ridker et al., 1999). Furthermore, it has been proposed that statins improve endothelial function, limit oxidative processes, stabilize atherosclerotic plaques and inhibit the thrombogenic response (McFarlane et al., 2002; Node et al., 2003).

Vitamin E is a major lipid-soluble antioxidant in cellular membranes. Epidemiological studies indicate that a high intake of dietary vitamin E is associated with decreased CHD risk (Klipstein-Grobusch et al., 1999; Knekt et al., 1994; Kushi et al., 1996; Rimm et al., 1993; Smith et al., 1996) and this has been proposed to be due to the ability of vitamin E to inhibit cell-mediated LDL oxidation by reducing cellular production and release of reactive oxygen species.

It has been demonstrated that dietary supplementation with vitamin E can inhibit the oxidation of LDL (Princen et

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Table 1: Baseline demographic data for groups of patients treated with statin

	n	Mean age (years)	Male/female Sex ratio	Current smoking habit no (%)	Former smoking habit no (%)	Diabetic no (%)	Hypertensive no (%)	CHD No(%)
Atorvastatin	9	45.3 ± 5.5	7/2	0 (0)	4 (44)	2 (22)	4 (44)	0 (0)
Simvastatin	11	52.3 ± 3.9	7/4	2 (18)	3 (27)	2 (18)	3 (27)	0 (0)
Combined	20	49.2 ± 3.3	14/6	2 (10)	7 (35)	4 (20)	7 (35)	0 (0)

Categorical data were compared by Fisher's exact tests. No significant differences were found. The mean ages of the groups were compared by student's t-test, and did not differ significantly.

al., 1992; Reaven, 2002). Not all antioxidants share vitamin E's ability to inhibit the oxidation of LDL. It has also been reported that vitamin E supplementation in the patients with existing CHD may have a beneficial effect in preventing new myocardial infarction (MI) and delaying the progression of arterial damage. It is unclear whether vitamin E is of any benefit in delaying or preventing restenosis in patients who have undergone coronary angioplasty (Hodis *et al.*, 1995; Stephens *et al.*, 1996). It has been suggested that antioxidants including vitamin E may be of value in limiting the oxidative damage to the heart muscle that occurs during ischaemia reperfusion (Stephens *et al.*, 1996).

At least part of the beneficial effect of vitamin E against CHD maybe due to decreased platelet ability to aggregate in humans (Reaven, 2002). Vitamin E may also have a beneficial acute effect on vascular endothelial function (Vogel *et al.*, 1997).

Most of the more recent work in animal models has supported the hypothesis that vitamin E supplementation can prevent or slow the development of atherosclerosis, although the results of early animal experiments were equivocal (Verlangieri and Bush, 1992).

The other potentially protective effects of vitamin E include inhibition of smooth muscle cell proliferation, preservation of endothelial function, inhibition of monocyte-endothelial adhesion and inhibition of platelet aggregation (Diaz *et al.*, 1997; Kaul *et al.*, 2001; Nojiri *et al.*, 2001; Pryor, 2000). Although recent intervention trials do not support a protective role for antioxidant supplementation in high risk patients (Heart Protection Collaborative Study Group, 2002a; Lonn *et al.*, 2005; Marchioli *et al.*, 2002) it is still possible that the antioxidants are of benefit in the early phases of disease. Hence, we wished to investigate the effects of statins, on serum vitamin E status in dyslipidaemic patients.

Materials and Methods

Subjects: Twenty patients with dyslipidaemia who were not originally on a lipid lowering agent were recruited from the lipid clinic at the Royal Surrey County Hospital, Guilford, UK. Fourteen patients from the same clinic but in whom life style advice was the first line of intervention was used as a control group. The medication of these latter patients was unaltered for 4 months and the same parameters were measured as for the statin-treated group.

The characteristics of the statin group are shown in Table 1. All patients and controls were informed of the aims of the study and signed the informed consent form before entering the study which had previously been given approval by the South-West Surrey Ethics Committee. Patients with evidence of established CHD and inflammatory disease were excluded from the study.

Statin treatment: The patients treated with a statin were randomized to two groups: Simvastatin 10mg/day (11 patients) and Atorvastatin 10mg/day (9 patients), each for 4 months. All other medications remained constant for the duration of the study.

Blood sampling: Blood samples were collected between 8.30 and 10.30 a.m. after a 12-h fast by venepuncture of the antecubital vein. Blood was collected into plain Vacutainer tubes (Becton-Dickenson, Cowley, Oxford, UK), allowed to clot and then serum removed.
All chemicals were obtained from Sigma (Sigma Chemical Co, Dorset, UK) unless stated otherwise.

Lipid profiles and blood glucose: A full, fasted lipid profile, comprising total cholesterol, triglycerides, and high density lippoprotein (HDL) cholesterol, was determined for each patient. LDL cholesterol was calculated using the Friedwald equation (Friedewald *et al.*, 1972), except for patients with triglycerides >4.0 mmol/l. Lipid and blood glucose measurements were made by routine enzymatic methods using a Bayer Advia 1650 analyzer (Bayer, Newbury, UK).

High-sensitivity CRP: Serum CRP was determined by PEG enhanced immuno-turbidometry on a Bayer Advia 1650 autoanalyser.

Serum vitamin E assay: Serum vitamin E was determined by HPLC (Ferns *et al.*, 2000). Briefly, internal standard (10mg/mld-tocopherol in isopropyl alcohol) was added to 200mL serum and vortex mixed. Aqueous ammonium sulphate (3.9 M) was added (200mL) and the solution was again vortex mixed. After centrifugation (1000 g for 5 minutes), 50mL of supernatant was used for analysis using a prodigy 50mm ODS2 (50x4.6nm) column (Phenomenex Ltd, Macclesfield, Cheshire, UK) with methanol as mobile phase, and UV-detection at 294 nm.
At a flow rate of 1.0 ml/minute, the retention time for internal standard and vitamin E were 6.6 and 8.7

Table 2: Biochemical parameters in patients treated with statins and control group.

	No	Serum total cholesterol (mmol/l)	Serum triglyceride (mmol/l)	Serum HDL - C (mmol/l)
Pretreatment patients (Simvastatin)	11	7.34±0.31	1.68 (1.45-2.10)	1.39±0.08
Posttreatment patients (Simvastatin)	11	5.20±0.23**	1.62 (1.30-1.81)*	1.36±0.08
Pretreatment patients (Atorvastatin)	9	8.40±0.81	2.12 (1.28-3.23)	1.50±0.10
Posttreatment patients (Atorvastatin)	9	6.97±0.94**	1.74 (1.28-3.10)*	1.44±0.12
Pretreatment patients (combined statins)	20	7.82±0.43	1.93 (1.48-3.00)	1.44±0.06
Posttreatment patients (combined statins)	20	6.00±0.47**	1.65 (1.30-2.02)*	1.40±0.07
Pretreatment controls	14	6.09±0.31	1.69 (0.89-2.99)	1.43±0.06
Posttreatment controls	14	6.15±0.29	1.86 (1.00-2.99)	1.46±0.11

Table 2: continued

	Serum LDL - C (mmol/l)	Serum Hs - CRP (mg/dl)	Serum Vitamin E (µg/ml)	Serum Vitamin E/ total cholesterol
Pretreatment patients (Simvastatin)	5.16±0.30	0.98 (0.19-3.43)	18.06±1.74	2.53±0.21
Posttreatment patients (Simvastatin)	3.15±0.24**	0.67 (0.0-3.12)*	13.75±1.88***	2.68±0.32
Pretreatment patients (Atorvastatin)	6.16±2.26	1.69 (0.70-2.52)	19.12±2.24	2.32±0.22
Posttreatment patients (Atorvastatin)	4.48±2.64**	0.85 (0.43-2.08)*	15.37±1.71***	2.31±0.20
Pretreatment patients (combined statins)	5.61±0.40	1.38 (0.54-3.18)	18.81±1.37	2.46±0.16
Posttreatment patients (combined statins)	3.74±0.45**	0.76 (0.40-2.13)	14.92±1.26***	2.56±0.20
Pretreatment controls	3.83±0.24	0.86 (0.34-2.92)	16.62±1.04	2.63±0.14
Posttreatment controls	3.74±0.28	1.15 (0.63-6.61)	16.85±1.30	2.70±0.26

Values are expressed as mean ± SEM, or median and interquartile range. Comparisons between pre-and post- treatment were assessed by paired t-tests for normally distributed data, or by Mann-whitney test for non-parametric data (*P<0.05, **P<0.01,***P<0.001).

minutes respectively. Vitamin E standard, internal standard and quality control material were obtained from BioRad Laboratories Ltd, Hemel Hempstead, UK. The inter-assay precision was 7.6% and 6.9% for low and high control vitamin E material concentrations respectively.

Statistical analysis: Comparisons between pre- and post-treatment biochemical parameters were assessed by paired *t*-tests for normally distributed data, or by a Mann-Whitney test for non-parametric data. Categorical data were compared using Fisher's exact tests. Values are expressed as mean ± SEM, or median and interquartile range for triglycerides and hs-CRP. A p value of <0.05 was considered significant.

Results
Demographic data: As it is shown in Table 1, their was a high prevalence of type II diabetes, hypertension and smoking habit in the patient groups, which is quite typical for a lipid clinic population. The medication for diabetic and hypertensive patients was unaltered during the study, nor did smoking habit change over this period. There was no significant difference in any of the characteristics between Atorvastatin and Simvastatin groups.

Effect of Statins on the Lipid Profile: Treatment with 10mg/day of Atorvastatin, or Simvastatin caused a 27% and 29% reduction in total cholesterol, respectively (P<0.001, Table 2). Statin therapy was also associated with a modest effect on triglycerides (P<0.05, Table 2). No significant effect was seen on HDL cholesterol. There was no significant change in the lipid profile of patients in the control group (Table 2).

Effect of statins on serum hs-CRP: A reduction in median serum hs-CRP concentration was seen in patients treated with Atorvastatin and Simvastatin. The reductions were 50% and 24%,respectively for each group individually and 45% in the groups combined (P<0.05, Table 2). These changes on basal serum hs-CRP concentrations were similar to previous reports of the effects of statin on hs-CRP levels. Again there was no significant change in the control group (P>0.05, Table 2).

Effect of statins on serum vitamin E status: Both statins reduced serum vitamin E significantly, Atorvastatin by 19.7% (P<0.05) and Simvastatin by 22% (P<0.01), and in a group combined by 21% (P<0.001, Table 2). However, the serum vitamin E /total cholesterol ratio was not altered significantly (P>0.05) by treatment with either statin (Table 2). Serum concentrations of vitamin E, nor the vitamin E / total cholesterol ratio changed significantly in the control patients (Table 2).

Discussion
The effects of statins on the lipid profiles of the patients were similar to those previously reported using the doses of Atorvastatin and Simvastatin as we have (Ferns, 2003; Jialal *et al.*, 2001), indicating that the patients were compliant with their medication over the period of the study.

The effect of the statins on serum hs-CRP concentration was also similar to those reported previously for the doses of drug and duration of treatment used in this study (Ferns, 2003).

To date few studies have investigated the effects of statins on serum vitamin E status, and only one has

compared the effects of Simvastatin to Atorvastatin. Furthermore, previous studies have been inconsistent. Passi and colleagues showed that treatment with Atorvastatin, Simvastatin or Pravastatin was not associated with a significant change in serum vitamin E concentrations even using doses up to 20 mg/d (Passi *et al.*, 2003). This is difficult to explain as LDL is the major carrier of vitamin E in blood. Leonhardt *et al.* (1997) have reported that the vitamin E content of LDL was unchanged in patients treated with Fluvastatin (Leonhardt *et al.*, 1997) which is in accordance with our finding. Three other studies have also concluded that treatment with simvastatin (Colquhoun *et al.*, 2005; Vasankari *et al.*, 2004), atorvastatin (Vasankari *et al.*, 2004) and pravastatin (Blaha *et al.*, 1998) is associated with a significant decrease in plasma vitamin E, which is consistent with our results. But they have also reported a significant increase in the vitamin E / total cholesterol ratio, whereas we have found no significant effect on serum vitamin E / total cholesterol following statin treatment. This may be explained by the differences in dosing regime used, and the duration of the studies.

We have shown that serum vitamin E concentrations are reduced in patients treated with either Simvastatin or Atorvastatin, but that lipid standardized values of vitamin E are unaffected at the doses used. It is possible that the vitamin E/ total cholesterol ratio may be affected by the use of higher doses of statins, and we are currently investigating this. However our data suggest that vitamin E status is not adversely affected in patients on low dose statin therapy.

Acknowledgement

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