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Effect of statin therapy on serum trace element status in dyslipidaemic subjects

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Abstract

Patients previously not treated with a lipid-lowering agent ($n = 20$; mean age 49.15 ± 3.28 years) were treated with either 10 mg/day of Simvastatin ($n = 11$), or Atorvastatin ($n = 9$) for 4 months. Fourteen additional patients were recruited from the same clinic at the same hospital 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 groups. Serum concentrations of zinc, copper, caeruloplasmin, selenium, glutathione peroxidase (GPx) and C-reactive protein (CRP) were measured together with their lipid profiles pre- and post-treatment. In addition to reducing serum total and low-density lipoprotein (LDL) cholesterol ($p < 0.0001$), statin treatment was associated with a significant reduction in mean serum zinc (9%, $p = 0.03$), copper (9%, $p < 0.01$), caeruloplasmin (24%, $p < 0.05$), and median CRP (45%, $p < 0.03$). Similar changes were not observed in the control patients. No significant effects were observed for serum selenium, copper/caeruloplasmin ratio, or GPx ($p > 0.05$) in either statin or control groups. These changes may be related to the known anti-inflammatory properties of the statin class of drugs.

Keywords: Statins; Copper; Zinc; Selenium; C-reactive protein

Introduction

Hydroxy-methyl-glutaryl-coenzyme A reductase inhibitors (statins) are widely used in the management of coronary risk [1]. Several primary and secondary prevention trials have demonstrated their efficacy in reducing low-density lipoprotein (LDL) cholesterol [2–4], and their utility in reducing coronary events [2–4]. However, a debate has ensued as to whether the benefits of statin therapy are entirely due to their cholesterol-lowering properties, or whether other 'pleiotropic' effects also have a role [5,6]. Several studies have demonstrated that statins have anti-inflammatory properties, reducing the inflammatory cell content and cytokine expression by plaque cells [7,8]. A number of studies have also demonstrated that statin treatment reduces levels of serum C-reactive protein (CRP) (reviewed by Ferns [9]), and it appears that this is a dose-dependent effect [9]. Other investigators have reported that statins have antioxidant properties, protecting LDL from being oxidized and hence preventing the deleterious effects of oxidatively modified LDL [10,11].

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Copper, zinc and selenium are essential components of the functional groups of several enzymes that may play a key role in atherosclerosis prevention. These include the antioxidant enzymes superoxide dismutase and glutathione peroxidase (Gpx) [12,13], and endothelial nitric oxide synthase [14], the enzyme responsible for the basal elaboration of nitric oxide by the endothelium [15]. For several years it has also been proposed that the ratio between serum copper and zinc may be an important determinant of coronary risk, operating in part through their effects on lipid metabolism [12,16]. However, this is not a consistent finding in all populations [17]. Data from the Helsinki Heart Study suggest that plasma concentrations of caeruloplasmin, the major copper-containing serum protein, are positively related to coronary risk [18].

Hence we wished to investigate the effects of statins on trace element status, and have also measured caeruloplasmin, Gpx, an important plasma selenium-containing enzyme, and CRP as a marker of inflammation.

Materials and methods

Subjects

Twenty patients, who were not originally on a lipid-lowering agent were recruited from the Lipid Clinics at the Royal Surrey County Hospital, Guildford. An additional 14 patients were recruited from the same clinic at the same hospital 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 groups. The demographic data for the statin groups are shown in Table 1. Each patient gave informed written consent to participate in the study, which had previously been given approval by the South-West Surrey Ethics Committee. Patients with evidence of established coronary heart disease and inflammatory disease were excluded from the study.

Statin treatment

Patients were assigned to treatment for 4 months with 10 mg/day of either Atorvastatin ($n = 9$) or Simvastatin ($n = 11$) as clinically indicated. All other medication 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, taking care to avoid possible sources of trace element contamination.

Materials

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 [19], except for patients with triglycerides >4.0 mmol/l.

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

Group	Atorvastatin	Simvastatin	Combined
n	9	11	20
Mean age (years)	45.3 ± 5.5	52.3 ± 3.9	49.2 ± 3.3
M/F sex ratio	7/2	7/4	14/6
Smoking habit			
Current no. (%)	0 (0)	2 (18)	2 (10)
Former no. (%)	4 (44)	3 (27)	7 (35)
Diabetic no. (%)	2 (22)	2 (18)	4 (20)
Hypertensive no. (%)	4 (44)	3 (27)	7 (35)
Established CHD no. (%)	0 (0)	0 (0)	0 (0)
Drug therapy no. (%)			
Calcium channel blockers	0 (0)	0 (0)	0 (0)
Aspirin	2 (22)	2(18)	4 (20)
β blockers	0 (0)	2 (18)	2 (10)
ACE inhibitors	0 (0)	0 (0)	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.