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Inflammatory biomarkers in patients in Simvastatin treatment: No effect of co-enzyme Q10 supplementation

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ABSTRACT

Purpose: Atherosclerosis is a major risk factor for cardiovascular disease (CVD) and is known to be an inflammatory process. Statin therapy decreases both cholesterol and inflammation and is used in primary and secondary prevention of CVD. However, a statin induced decrease of plasma concentrations of the antioxidant coenzyme Q10 (CoQ10), may prevent the patients from reaching their optimal anti-inflammatory potential. Here, we studied the anti-inflammatory effect of Simvastatin therapy and CoQ10 supplementation.

Methods: 35 patients in primary prevention with Simvastatin (40 mg/day) were randomized to receive oral CoQ10 supplementation (400 mg/d) or placebo for 8 weeks. 20 patients with hypercholesterolemia who received no cholesterol-lowering treatment was a control group. Plasma concentrations of lipids and inflammatory biomarkers (interleukin-6 (IL6); -8 (IL8); -10 (IL10), tumor necrosis factor-α (TNFα); high-sensitivity C reactive protein (hsCRP)) as well as glycated hemoglobin (HbA1c) were quantified before and after the intervention.

Results: No significant change in inflammatory markers or lipids was observed after CoQ10 supplementation Patients in Simvastatin therapy had significantly ($P < 0.05$) lower baseline concentration of IL6 (0.31 ± 0.03 pg/ml), IL8 (1.6 ± 0.1 pg/ml) IL10 (0.16 ± 0.02 pg/ml) and borderline ($P = 0.053$) lower TNFα (0.88 ± 0.05 pg/ml), but not hsCRP (1.34 ± 0.19 mg/l) compared with the control group (0.62 ± 0.08, 2.6 ± 0.2, 0.25 ± 0.01, 1.07 ± 0.09, and 1.90 ± 0.35, respectively).

Conclusions: Simvastatin therapy has beneficial effects on inflammatory markers in plasma, but CoQ10 supplementation seems to have no additional potentiating effect in patients in primary prevention. In contrast, glucose homeostasis may improve with CoQ10 supplementation.

1. Introduction

Cardiovascular disease (CVD) is one of the major causes of deaths, representing about a third of all global deaths world wide. Atherosclerosis is a major risk factor for developing cardiovascular events and is known to be a chronic inflammatory process where cytokines and immune cells play a role in all phases from the initiation of plaque development to thrombosis formation [1,2].

Various types of medications and nutritional supplements have been investigated with the purpose of eliminating this inflammatory risk factor but the effect of targeted anti-inflammatory treatment on cardiovascular events is still debated [2]. Fish oil supplements [3] and vitamins C, D and E [4–6] have been examined and may lower plasma concentrations of inflammatory cytokines, but results are inconclusive.

One group of medication that has a documented effect on markers of inflammation in plasma is statin therapy [7–13] which is used in both primary and secondary prevention of CVD. Statins inhibit the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR), thus reducing the flux through the mevalonate pathway and thereby the synthesis of cholesterol [14].

The effects of statin treatment on inflammation may be extend beyond those expected from decreasing total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) concentrations in plasma, suggesting effects beyond cholesterol lowering. Such pleiotropic effects of statins may involve improved endothelial function, enhancing the stability of atherosclerotic plaques, and decreasing inflammation [8]. The

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JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial showed a decrease in cardiovascular events independent of the lipid-lowering effect, which was related to a reduced plasma concentration of C-reactive protein (CRP) after Rosuvastatin treatment [13]. Correspondingly, the PRINCE (Pravastatin inflammation/CRP evaluation) trial found a decrease in CRP, which was independent of LDL-C effects [15].

The inhibitory effect of statins on the HMGCR may also reduce the down-stream production of coenzyme Q10 (CoQ10) [16,17]. CoQ10 is present in all cells of the human body and plays a key role in the electron transport chain and production of adenosine triphosphate (ATP) [18]. More than 95% of CoQ10 exists in the reduced form (ubiquinol), which acts as an active antioxidant [19]. This lipid soluble substance is synthesized endogenously as well as found in small amounts in various types of food including meat and fish [20].

Previous studies have shown that statins may lower plasma concentrations of CoQ10 [17]. This effect has provided the arguments for supplementing statin treatment with CoQ10 in an attempt to alleviate statin induced myalgia, in the belief that a low plasma concentration of CoQ10 is reflected in the concentrations of CoQ10 within the skeletal muscle mitochondria [21–23]. The effect of CoQ10 on myalgia is, however, questionable [16,22,24]. An effect of CoQ10 supplementation on inflammatory biomakers in plasma seem to be present, with reductions in CRP [25,26], tumor necrosis factor (TNF)-α [26–28] and interleukin (IL)-6 [26]. However, in the face of a possible statin induced lowering of endogenous CoQ10 concentrations, the anti-inflammatory effect of CoQ10 may disappear.

Thus, statin treatment may inhibit CoQ10 synthesis and thereby prevent patients with hypercholesterolemia from reaching their optimal anti-inflammatory potential. The present study was undertaken in order to elucidate if statin treatment reduces plasma biomarkers of inflammation, and if supplementation with CoQ10 would have an additional anti-inflammatory effect.

2. Materials and methods

This study is part of the interdisciplinary project *LIFESTAT (Living with Statins)* [29] on the use of statins, and consists of two sub-studies; one cross-sectional and one interventional study (Fig. 1). From the cross-sectional study only the control group with hypercholesterolemia but no therapy is included. The interventional study consisted of eight weeks CoQ10 supplementation to patients with hypercholesterolemia in treatment with Simvastatin.

2.1. Patients

The inclusion criteria in the CoQ10 interventional study were overweight (body mass index (BMI) 25–35 kg/m^2), age 40–70 years and in primary prevention therapy for hypercholesterolemia with Simvastatin 40 mg or more. The control group from the cross-sectional study was weight and age matched and had untreated hypercholesterolemia (total cholesterol > 6 mmol/l or LDL-C > 3.5 mmol/l). The study protocol was conducted in accordance with the declaration of Helsinki, approved by the local ethical committee (H-2-2013-164) and registered in Clinical Trials (NCT02250677).

Patients were recruited by advertising via general practitioners, pharmacies and via newspaper announcements. Patients with previous thromboembolic episodes, metabolic disorders or other risk factors for CVD except elevated total cholesterol or LDL-C were excluded from the study although mild hypertension (< 145/100 mmHg) and antihypertensive treatment was accepted. Treatment with beta-blockers, an electrocardiogram (ECG) with signs of arrhythmia or other cardiac disorder or a physical condition that would affect the collection of data resulted in exclusion.

Table 1
Baseline characteristics.

	Statin + placebo (n = 17)	Statin + CoQ10 (n = 18)	Control (n = 20)
Male/female (n)	8/9	14/4	9/11
Age (years)	64 ± 2	62 ± 1	60 ± 2
BMI (kg m^{-2})	29 ± 1	28 ± 1	28 ± 1
SBP (mmHg)	137 ± 4	136 ± 3	131 ± 4
DBP (mmHg)	87 ± 2	85 ± 2	84 ± 2
Waist circumference (cm)	100 ± 2	99 ± 2	100 ± 2
Waist-hip-ratio	0.92 ± 0.01	0.96 ± 0.02	0.93 ± 0.02
Body fat (%)	37 ± 2	33 ± 2	37 ± 2
Visceral adipose tissue (kg)	1.7 ± 0.2	1.8 ± 0.2	1.6 ± 0.1
$\dot{V}O_2$max (ml O_2 min^{-1} kg^{-1})	27 ± 1	30 ± 1	29 ± 1

Values are mean ± SEM.
BMI, body mass index; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *$\dot{V}O_2$max*, maximal oxygen uptake per minute per kilogram of bodyweight.

2.2. Study design

The intervention was conducted as a double-blind, randomized, parallel, placebo-controlled trial. All patients were screened before beginning the experiments. A medical history was obtained, a resting ECG performed and written informed consent obtained. Following inclusion the patients reported to the laboratory in the morning after an overnight fast on three separate days with at least two days between each test day. Patients were instructed not to participate in any strenuous exercise 48 h before the tests.

On day 1 body composition by dual-energy X-ray absorptiometry (DXA) (Lunar iDXA, G&E Medical Systems Lunar, WI, USA; Encore Version 14.10.022)) and anthropometric measurements (weight,

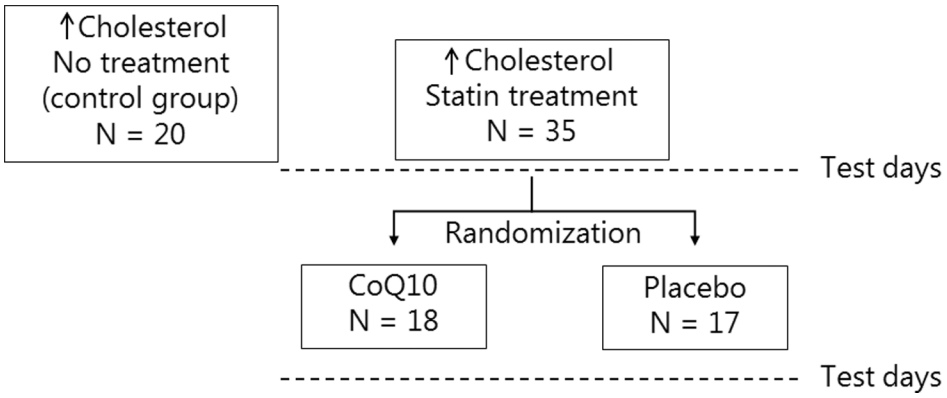

Fig. 1. An overview of the study design. Two patient groups with hypercholesterolemia were recruited. One group (n = 20) had never been treated ith statins, while the other (n = 35) were in regular treatment with Simvastatin 40 mg/day. Following tests (see text) a randomization procedure was carried out and the patients were allocated to receive coenzyme Q10 (CoQ10) 400 mg/day or placebo for eight weeks, where after the tests were repeated.

Table 2
Lipid concentrations in plasma at baseline and after intervention.

	Control n = 20	Statin + placebo n = 17			Statin + CoQ10 n = 18			Statin (n = 35) vs control (n = 20)[1]
		Baseline	After intervention		Baseline	After intervention		P
TC	5.9 ± 0.2	4.1 ± 0.2	4.3 ± 0.2	NS	4.2 ± 0.1	4.1 ± 0.2	NS	< 0.0001
HDL-C	1.5 ± 0.1	1.5 ± 0.1	1.5 ± 0.1	NS	1.4 ± 0.1	1.4 ± 0.1	NS	0.89
LDL-C	4.2 ± 0.2	2.5 ± 0.1	2.7 ± 0.2	NS	2.6 ± 0.1	2.5 ± 0.2	NS	< 0.0001
TG	1.5 ± 0.2	1.0 ± 0.1*	1.0 ± 0.1	NS	1.2 ± 0.1*	1.2 ± 0.1	NS	0.01

Values are mean ± SEM. * Significant difference between baselines in Statin + placebo and Statin + CoQ10.
[1]The baseline of the pooled group of statin users (CoQ10 + placebo) tested against the control group with hypercholesterolemia but no treatment.
TC, total cholesterol; *HDL-C*, high-density lipoprotein cholesterol; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglycerides.

height, waist-hip circumference) was measured. Blood pressure (UA-1020 Premier Blood Pressure Monitor, A&D, San Jose, CA, USA) was measured after approximately 10 min of rest in the supine position. On day 2 maximal oxygen uptake ($\dot{V}O_2$max) was measured on a cycle ergometer (Corival LODE cycle, Groningen, the Netherlands) during which respiratory data was collected (Quark PFT Ergo; Cosmed, Rome, Italy). After a warm-up period, the work-load increased gradually until exhaustion. On day 3, arterial blood was sampled in ice-cooled Vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) and the samples were centrifuged at 4000 rpm for 10 min at 4 °C, and plasma was stored at −80 °C until analysis.

The patients in the interventional study were then instructed to ingest two capsules twice a day, and due to the lipid solubility of CoQ10 all were advised to ingest the capsules in connection with a meal. The patients were randomly allocated into a CoQ10 (400 mg/d) or a placebo (soybean oil) group (Statin + CoQ10 and Statin + placebo, respectively). The randomization was conducted via an online randomization tool (www.randomizer.org), and managed by a third party not connected with the study. The intervention was administered for eight weeks and the three test days mentioned above were repeated thereafter. The patients continued to ingest the capsules until the last test day. CoQ10 supplementation was administered as Bio-Quinone Active Q10 Ubiquinone (100 mg/capsule).

Plasma concentrations of the cytokines TNF-α, IL-6, IL-8 and IL-10 were quantified by Meso Scale Discovery (Meso Scale Diagnostics, Gaithersburg, MD, USA) using the Custom V-PLEX Human Biomarkers kit.

Total coenzyme Q10 levels were measured by high performance liquid chromatography (HLPC). The analyses were monitored with a UV detector set at 275 nm, a Q10 column (# 68100, Chromsystems, Gräfelfing, Germany) and a flow rate at 2.5 ml/min of the mobile phase (# 68001, Chromsystems, Gräfelfing, Germany). Coenzyme Q10 was extracted from plasma and separated from lipophilic proteins. The subsequent solution was then cleaned up and concentrated by solid phase extraction by following the instructions of the reagent kit (# 68000, Chromsystems, Gräfelfing, Germany), and then the mixture (50 µl) were injected into the HPLC system. An internal standard was used to minimize analytical variations and to provide reliable quantification. A plasma standard calibrator (# 68003, Chromsystems, Gräfelfing, Germany) was analyzed to calculate the final concentration of the sample.

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and high-sensitivity C reactive protein (hsCRP) concentrations in plasma were quantified by the Roche/Hitachi Cobas 6000 Analyzer (Roche Diagnostics, Indianapolis, IN, USA).

2.3. Statistics

All statistical analyses were performed using SAS Enterprise Guide 7.1. Data are presented as mean ± SEM. Student's *t*-test for independent samples or Mann-Whitney *U* test was used for comparing the baselines of the groups. Paired sample *t*-test or Wilcoxon signed-rank test was used when analysing within group differences before and after the intervention. The power of the analysis of change of concentrations of the cytokines in response to the CoQ10 intervention was calculated by the use of the number of subjects (N = 16) and the obtained data of the change in plasma concentration of the given cytokine and the standard deviation of this change. Correlations between variables were calculated with Pearson's or Spearman's correlation coefficient for normal and not-normally distributed data, respectively. $P < 0.05$ was considered significant.

3. Results

3.1. Patient characteristics

35 patients in primary prevention with Simvastatin completed the CoQ10 interventional study and 20 controls with hypercholesterolemia but without cholesterol-lowering treatment completed the cross-sectional study. The patients' characteristics are shown in Table 1. There were no significant differences between the groups in any of the parameters including age, percent body fat, blood pressure, or $\dot{V}O_2$ max.

After eight weeks of intervention with oral CoQ10 supplementation or placebo there were no changes in the above mentioned parameters in the two statin groups. No significant changes were noted in the placebo group.

3.2. CoQ10 concentrations in plasma

Baseline plasma CoQ10 concentrations were similar in control, statin + Q10 and statin + placebo (868 ± 62, 968 ± 29, and 962 ± 39 µg/l). Following eight weeks of supplementation plasma CoQ10 concentrations increased significantly ($P < 0.05$) in the statin + CoQ10 group (to 1029 ± 20 µg/l) while no change was seen in the statin + placebo group (952 ± 24 µg/l).

3.3. Lipid concentrations in plasma

Baseline plasma concentrations of total cholesterol, HDL-C or LDL-C were similar in the two statin-treated intervention groups, while concentrations of triglycerides differed ($P = 0.04$) slightly, despite the randomization (Table 2). With 8 weeks of intervention no changes were observed in lipid concentrations in the statin + CoQ10 or the statin + placebo group.

If the control group is compared with the combined group of all statin users (i.e. pooling statin + placebo and statin + CoQ10) the total cholesterol mean was 29% lower in the statin group compared with control subjects (Table 2). Correspondingly, the concentrations of LDL-C and triglycerides were 39% and 29% lower. No difference was found between the groups regarding HDL-C.

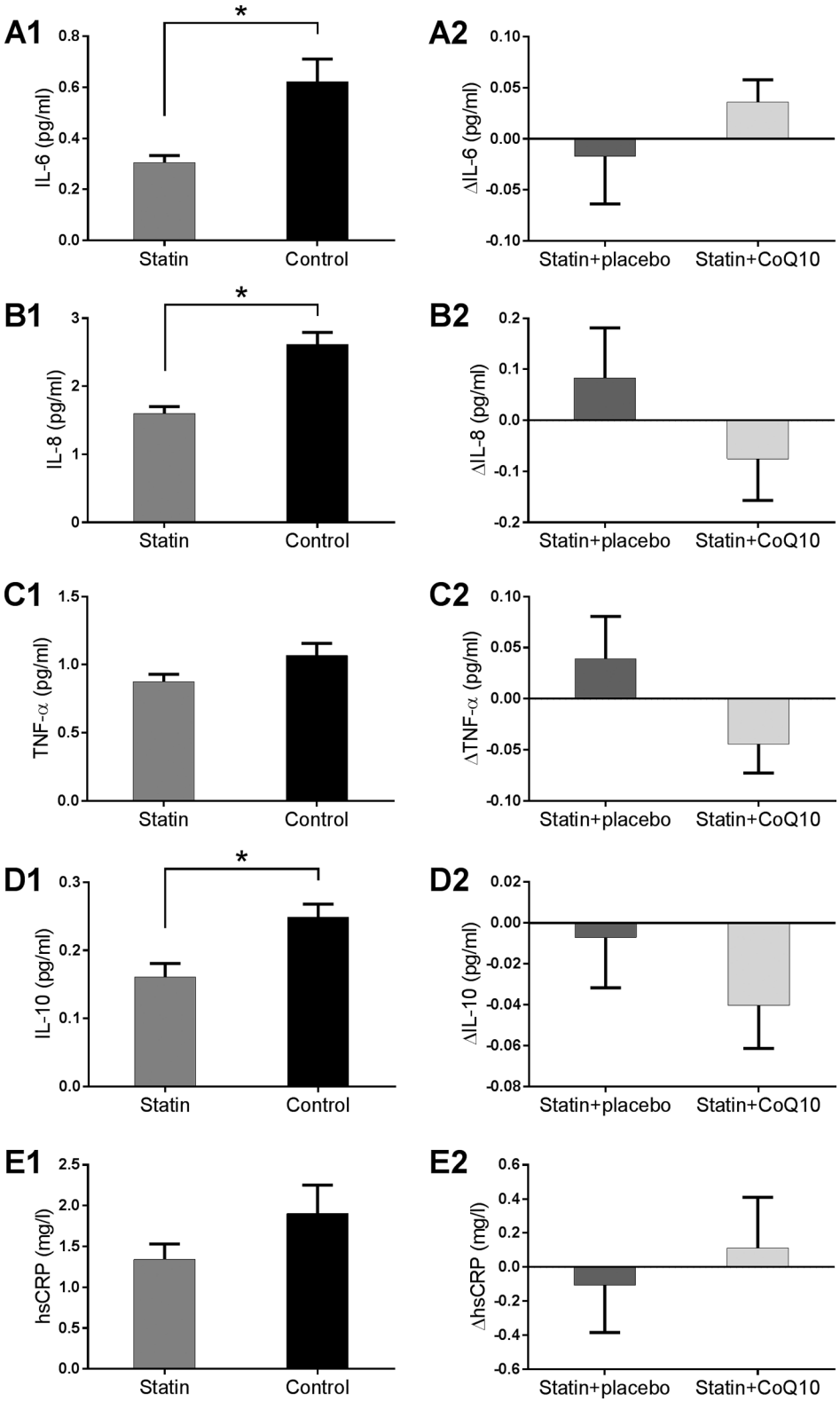

Fig. 2. A1–E1: Baseline plasma concentrations of inflammatory markers. A2–E2: The changes in the concentrations of inflammatory markers in the two statin-treated groups after intervention with CoQ10 or placebo. * $P < 0.05$ between control and pooled statin group (CoQ10 + placebo). IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α; IL-10, interleukin-10; hsCRP, high-sensitivity C-reactive protein.

3.4. Inflammation biomarker concentrations in plasma

Baseline plasma concentration of IL-6 in the statin-treated groups was ~50% ($P < 0.05$) of that in the control group (Fig. 2). Similarly, IL-8 and IL-10 were lower ($P < 0.05$) in the statin-treated group compared with controls (Fig. 2). However, the difference in baseline concentrations of TNF-α between the statin-treated patients and the control group only tended ($P = 0.053$) to be different (Fig. 2). Baseline plasma concentration of hsCRP were similar in the statin-treated group and in the control group (Fig. 2). Intervention with CoQ10

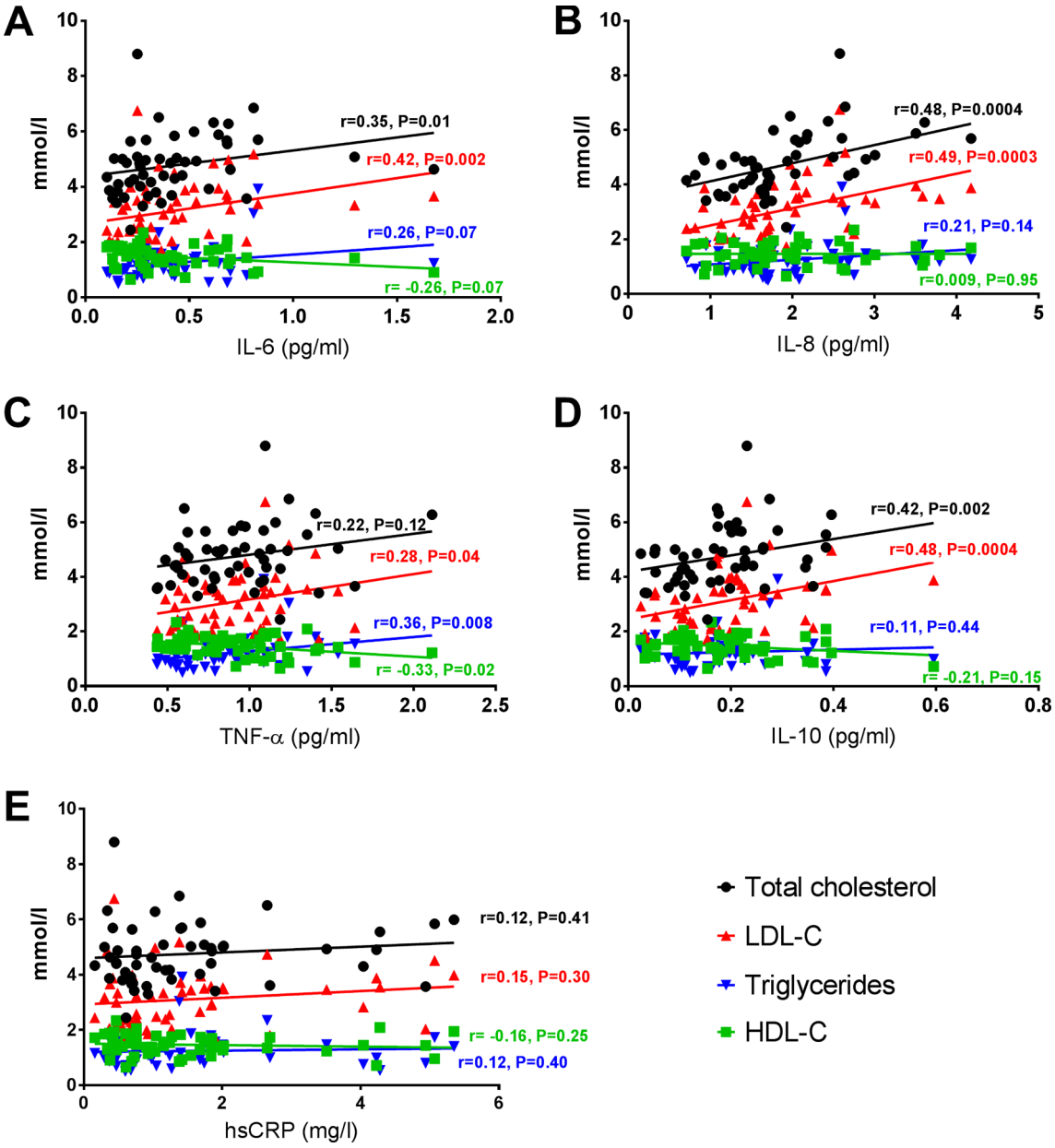

Fig. 3. Relationships between baseline inflammatory markers and lipid concentrations indicated by the correlation coefficient and corresponding P value. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; IL-6, interleukin-6; IL-8, interleukin-8, TNF-α, tumor necrosis factor-α; IL-10, interleukin-10; hsCRP, high-sensitivity C-reactive protein.

supplementation or placebo resulted in no within group changes in the concentrations of IL-6, IL-8, TNF-α, IL-10 or hsCRP (Fig. 2). The statistical power of the analyses were 0.82, 0.93, 0.99, 0.99 and 0.29, respectively.

3.5. Correlations between cytokine and lipid concentrations

The total cholesterol and LDL-C concentrations were significantly correlated with IL-6, IL-8 and IL-10, though the correlation coefficient was small (Fig. 3). Plasma concentrations of IL-6 tended to correlate negatively and positively with HDL-C and triglyceride concentrations, respectively (both P = 0.07). Plasma concentrations of TNF-α correlated significantly with concentrations of triglycerides, LDL-C (positively) and HDL-C (negatively).

4. Discussion

The results of this study indicate that 8 weeks of oral CoQ10 supplementation in statin-treated patients in primary prevention has no impact on cytokine/inflammatory biomarker concentrations in plasma. However, Simvastatin treatment per se seems to have an anti-inflammatory effect.

Several studies have found a lowering effect of coenzyme Q10 on various pro-inflammatory cytokines in plasma, including IL-6 and TNF-α [25,30–33]. A possible mechanism for this effect was found by Schmelzer et al., who investigated the TNF-α response in a murine macrophage cell line [34]. They demonstrated an anti-inflammatory involvement of CoQ10 through inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway in monocytes.

Despite the strict randomization of the intervention groups

(statin + CoQ10 or statin + placebo) the baseline concentrations of IL-6, IL-8 and TNF-α were significantly different ($P < 0.05$). However, we have chosen to report the baseline data as pooled data as this difference in baseline data, i.e. before the CoQ10 supplementation had started, do not have an impact on the response to the intervention.

The lack of effect by CoQ10 supplementation found in this study is in accordance with other studies on the effect of CoQ10 on plasma IL-6 or TNF-α in healthy sedentary men or CRP in obese patients [35–39]. The fact that the study populations in these studies were relatively healthy may have attenuated the effect of the CoQ10 supplementation. The same may apply in this study, where the prophylactic treatment with Simvastatin seems to have reduced the plasma cytokine concentrations to levels where CoQ10 supplementation has no further effect. In line with this notion, plasma interleukin-1β was also measured in the present study but the concentrations were below the limit of detection.

Comparison of the other trials is difficult to do because of the major differences between the groups studied. To our knowledge, the inflammatory response after CoQ10 supplementation has only been investigated in one other group with hypercholesterolemia in statin therapy and with no previous cardiovascular events [39]. In this study Mabuchi et al. found no effect on plasma CRP concentration but unlike the present study no other inflammatory markers were measured. Other studies have included patients with acute myocardial infarction [30] and multiple sclerosis [31], but their inflammatory baseline is completely different from the patients studied here. Certain inflammatory diseases (i.e. rheumatoid arthritis) progress over time, and trials have attributed the anti-inflammatory effect of CoQ10 to the ability to attenuate this progression [27,40,41].

A common side-effect to statin treatment is myalgia, and in the present study 13 patients (8 in the Statin + CoQ10 and 5 in the Statin + placebo group) reported myalgia. The CoQ10 supplementation did not change these numbers. Furthermore, there where no differences between patients with or without myalgia in the cytokine concentrations.

This study has confirmed the anti-inflammatory effect of statin therapy [9–13]. Certainly the plasma concentration of pro-inflammatory cytokines IL-6, IL-8 and TNF-α were decreased in the statin group, but the same was true for the anti-inflammatory cytokine IL-10. This is in contrast to other studies, where statins seem to increase plasma IL-10 concentrations [42–44]. Those studies only include short-term treatments (4 weeks) in contrast to the present study where the patients were in long-term therapy with Simvastatin. One possible explanation for the decrease in plasma IL-10 concentrations may be the gradual decrease of pro-inflammatory cytokines, which may reduce the need for additional anti-inflammatory activity. Thus, plasma IL-10 may decrease over time as a sign of inflammatory stabilization with long-term statin therapy.

Correlations between lipid and plasma cytokine concentrations showed a small positive but significant association between total cholesterol, triglycerides and LDL-C and most of the cytokines but not hsCRP (Fig. 3). Interestingly the correlation between HDL-C and the plasma cytokines were generally negative, i.e. with increasing HDL-C the lower the inflammatory markers. HDL-C is considered to be anti-inflammatory and higher levels are strongly correlated with the survival to 85 years of age [45].

Some limitations pertain to this study. The short duration of the intervention makes it difficult to interpret long-term effects of CoQ10 supplementation. Secondly, it would have been interesting to investigate the effect of supplementation in the control group with hypercholesterolemia as they seem to have a higher baseline concentration of the various cytokines, but this was not possible in the present design.

In conclusion, this study confirms the anti-inflammatory effect of statin therapy, whereas oral CoQ10 supplementation seems to have no additional effect.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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