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Statin therapy and plasma coenzyme Q10 concentrations—A systematic review and meta-analysis of placebo-controlled trials

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ABSTRACT

Statin therapy may lower plasma coenzyme Q10 (CoQ10) concentrations, but the evidence as to the significance of this effect is unclear. We assessed the impact of statin therapy on plasma CoQ10 concentrations through the meta-analysis of available RCTs. The literature search included selected databases up to April 30, 2015. The meta-analysis was performed using either a fixed-effects or random-effect model according to I^2 statistic. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). The data from 8 placebo-controlled treatment arms suggested a significant reduction in plasma CoQ10 concentrations following treatment with statins (WMD: −0.44 μmol/L, 95%CI: −0.52, −0.37, $p < 0.001$). The pooled effect size was robust and remained significant in the leave-one-out sensitivity analysis. Subgroup analysis suggested that the impact of statins on plasma CoQ10 concentrations is significant for all 4 types of statins studied i.e. atorvastatin (WMD: −0.41 μmol/L, 95%CI: −0.53, −0.29, $p < 0.001$), simvastatin (WMD: −0.47 μmol/L, 95% CI: −0.61, −0.33, $p < 0.001$), rosuvastatin (WMD: −0.49 μmol/L, 95%CI: −0.67, −0.31, $p < 0.001$) and pravastatin (WMD: −0.43 μmol/L, 95%CI: −0.69, −0.16, $p = 0.001$). Likewise, there was no differential effect of lipophilic (WMD: −0.43 μmol/L, 95%CI: −0.53, −0.34, $p < 0.001$) and hydrophilic statins (WMD: −0.47 μmol/L, 95%CI: −0.62, −0.32, $p < 0.001$). With respect to treatment duration, a significant effect was observed in both subsets of trials lasting <12 weeks (WMD: −0.51 μmol/L, 95%CI: −0.64, −0.39, $p < 0.001$) and ≥12 weeks (WMD: −0.40 μmol/L, 95%CI: −0.50, −0.30, $p < 0.001$). The meta-analysis showed a significant reduction in plasma CoQ10 concentrations following treatment with statins. Further well-designed trials are required to confirm our findings and elucidate their clinical relevance.

1. Introduction

Coenzyme Q10 (CoQ10) or ubiquinone or 2-methyl-5, 6-dimethoxy-1, 4-benzoquinone is a vitamin-like compound widely

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distributed in the body in two forms: reduced (ubiquinol), and oxidized (ubiquinone) form [1]. CoQ10 has several important roles in the human body such as: involvement in the biosynthesis of pyrimidine and beta-oxidation of fatty acids [2], modulation of the mitochondrial permeability transition pore [3], acting like a coenzyme for several important enzymatic steps in mitochondrial energy production, inhibition of the oxidation of proteins and DNA [4], stabilizing the membrane and preventing lipid peroxidation [5,6] and modulation the expression of genes [7], or recycling of radical forms of vitamin C and E [8].

Statins might play a role in statin-associated muscle symptoms (SAMS) [9] possibly through lowering muscle tissue and serum CoQ10 levels [10,11]. The mechanisms activated in statin-induced myopathy include the inhibition of mevalonic acid production, a precursor in the synthesis of ubiquinone (CoQ10) [12], the modification of the expression of proteins needed in cellular protection against oxidative stress [13], the changes in the mitochondrial respiratory chain with consecutive depolarization of the mitochondrial internal membrane, alteration of calcium homeostasis and appearance of "calcium waves" [14]. Since mitochondrial dysfunction might be induced by CoQ10 deficiency, a meta-analysis of randomized controlled trials analyzed the effects of CoQ10 supplementation in patients with statin-induced myopathy. The results did not suggest any significant benefit of CoQ10 supplementation in statin-induced myopathy [15], suggesting that different modifications of the mevalonate pathway might be responsible for SAMS [16,17]. However, the process of CoQ10 biosynthesis is dependent of the mevalonate pathway through a collection of reactions producing farnesyl pyrophosphate, the typical substrate for protein prenylation and CoQ10, cholesterol, dolichol and dolichyl posphate synthesis [18].

Statins decrease plasma low density lipoprotein cholesterol (LDL-C) levels and CoQ10 is predominantly transported by LDL, but the findings concerning changes in CoQ10 concentrations following statin therapy have been inconsistent. Therefore, in the present meta-analysis we evaluated the impact of statin therapy on plasma CoQ10 concentrations, and calculated the effect size quantitatively for all as well as individual statin formulations.

2. Methods

2.1. Search strategy

The guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement were used to design this study [19]. PubMed-Medline, SCOPUS, Web of Science and Google Scholar databases were searched using the following search terms in titles and abstracts: (atorvastatin OR simvastatin OR rosuvastatin OR fluvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR "statin therapy" OR statins) AND ("coenzyme Q10" OR "coenzymeQ10" OR "Coenzyme Q" OR coQ10 OR "co Q10" OR Q10 OR ubiquinone OR ubiquinol OR ubidecarenone) AND (placebo). The wild-card term "*" was used to increase the sensitivity of the search strategy. The search was limited to studies in humans published in English. The literature was searched from inception to April 30, 2015. Two reviewers (CS and AS) evaluated each article separately. Disagreements were resolved by discussion with a third party (MB).

2.2. Study selection

Original studies were included if they met the following criteria: (i) placebo-controlled trial with either parallel or cross-over design, (ii) investigated the impact of statin therapy, either as monotherapy or combination therapy, on serum/plasma concentrations of CoQ10, and, (iii) presented of sufficient information on CoQ10 concentrations at baseline and at the end of follow-up in each group or providing the net change values.

Exclusion criteria were: (i) non-interventional trials, (ii) lack of a placebo control group for statin therapy, (iii) observational studies with case-control, cross-sectional or cohort design, and, (iv) lack of sufficient information on baseline or follow-up CoQ10 concentrations.

2.3. Data extraction

Eligible studies were reviewed and the following data were abstracted: (1) first author's name, (2) year of publication, (3) country of origin, (4) study design, (5) number of participants in the statin and control groups, (6) type of statin administered in the study, (7) dose of statin therapy, (8) treatment duration, (9) age, gender and body mass index (BMI) of study participants, (10) baseline levels of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, high-sensitivity C-reactive protein (hsCRP) and glucose, (11) systolic and diastolic blood pressures, and (12) data regarding baseline and follow-up concentrations of CoQ10 concentrations.

2.4. Quantitative data synthesis

The meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [20]. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up—measure at baseline. For single-arm cross-over trials, net change in plasma concentrations of CoQ10 were calculated by subtracting the value after control intervention from that reported after treatment. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5. If the outcome measures were reported in median and range (or 95% confidence interval [CI]), mean and standard SD values were estimated using the method described by Hozo et al., [21]. Where standard error of the mean (SEM) was only reported, standard deviation (SD) was evaluated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects.

Net changes in measurements (change scores) were calculated for parallel and cross-over trials, as follows: (measure at the end of follow-up in the treatment group—measure at baseline in the treatment group)—(measure at the end of follow-up in the control group—measure at baseline in the control group). All values were collated in μmol/L. The results of selected trials were combined using the generic inverse variance method and a fixed- and random-effects model depending on the presence of high (≥50%) or low-to-moderate (<50%) heterogeneity, respectively. Inter-study heterogeneity was assessed using Cochran Q test and I^2 index. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e. iteratively removing one study each time and repeating the analysis [22,23].

2.5. Meta-regression

A weighted random-effects meta-regression using unrestricted maximum likelihood model was performed to assess the impact of duration of statin therapy, changes in plasma concentrations of LDL-C, molar doses of statins, and baseline plasma CoQ10 concentrations as potential moderator variables on the estimated effect size of statin therapy in altering plasma CoQ10 levels.