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

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**A B S T R A C T**

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.

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1. Introduction

Coenzyme Q10 (CoQ10) or ubiquinone or 2-methyl-5, 6-dimethoxy-1, 4-benzoquinone is a vitamin-like compound widely...
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 phosphate 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 [(SDpre-treatment)2 + (SDpost-treatment)2 − (2R × SDpre-treatment × SDpost-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 I2 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.
Table 1

Demographic characteristics and baseline parameters of the included studies.

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Australia</td>
<td>Finland</td>
<td>The Netherlands</td>
<td>Finland</td>
<td>New Zealand</td>
<td>Italy</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized double-blind placebo-controlled parallel trial</td>
<td>Randomized double-blind placebo-controlled crossover trial</td>
<td>Randomized double-blind placebo-controlled parallel trial</td>
<td>placebo-controlled crossover trial</td>
<td>Double-blind placebo-controlled parallel trial</td>
<td>Double-blind placebo-controlled parallel trial</td>
</tr>
<tr>
<td>Duration of trial</td>
<td>26 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>8 weeks</td>
<td>6 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Patients with chronic heart failure who were clinically stable</td>
<td>Hypercholesterolemic men aged 35–64 years (serum cholesterol ≥232 mg/dL)</td>
<td>Type 2 diabetes patients, treated with oral glucose-lowering agents and/or insulin. At inclusion, HbA1c had to be &lt;10%, BMI &lt;35 kg/m², and at two occasions within 2 months before start of the study, fasting total cholesterol &lt;6.5 mmol/L.</td>
<td>Patients with hypercholesterolemia aged between 31 and 69 years</td>
<td>Patients with symptomatic heart failure (New York Heart Association Functional Class II or III), reduced left ventricular ejection fraction (&lt;40%) on echocardiography</td>
<td>Hypercholesterolemic patients</td>
</tr>
<tr>
<td>Statin form</td>
<td>Rosuvastatin</td>
<td>Simvastatin</td>
<td>Atorvastatin</td>
<td>Atorvastatin</td>
<td>Simvastatin</td>
<td>Pravastatin</td>
</tr>
<tr>
<td>Statin intervention</td>
<td>40 mg/day</td>
<td>20 mg/day</td>
<td>10 mg/day</td>
<td>40 mg/day</td>
<td>40 mg/day</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Participants</td>
<td>Case 37</td>
<td>120</td>
<td>9</td>
<td>24</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Control 32</td>
<td></td>
<td>10</td>
<td>14</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Case 60.6 ± 13.4</td>
<td>NR</td>
<td>64 ± 8</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Control 80.0</td>
<td>100.0</td>
<td>63 ± 8</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Male (%)</td>
<td>Case NR</td>
<td>NR</td>
<td>70.0</td>
<td>NR</td>
<td>NR</td>
<td>70.0</td>
</tr>
<tr>
<td></td>
<td>Control NR</td>
<td>NR</td>
<td>30.0 ± 3.7</td>
<td>NR</td>
<td>NR</td>
<td>24 ± 1.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Case NR</td>
<td>NR</td>
<td>28.4 ± 3.1</td>
<td>NR</td>
<td>NR</td>
<td>23 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Control NR</td>
<td>NR</td>
<td>216.93 ± 25.09</td>
<td>223.88 ± 32.81</td>
<td>202.65 ± 7.72</td>
<td>207.11 ± 19.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>Case NR</td>
<td>NR</td>
<td>205.74 ± 28.18</td>
<td>221.95 ± 38.6</td>
<td>227.74 ± 35.13</td>
<td>245.11 ± 42.46</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>Case NR</td>
<td>NR</td>
<td>124.29 ± 35.90</td>
<td>140.89 ± 24.70</td>
<td>142.05 ± 32.42</td>
<td>247.04 ± 15.44</td>
</tr>
<tr>
<td></td>
<td>Control NR</td>
<td>NR</td>
<td>106.54 ± 21.62</td>
<td>140.89 ± 32.81</td>
<td>142.05 ± 32.42</td>
<td>162.12 ± 15.44</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>Case NR</td>
<td>3 (0.4) [2–5]</td>
<td>33.58 ± 6.56</td>
<td>49.02 ± 14.28</td>
<td>47.09 ± 3.09</td>
<td>151.31 ± 19.3</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>Case NR</td>
<td>NR</td>
<td>53.65 ± 17.76</td>
<td>48.64 ± 13.90</td>
<td>54.43 ± 16.60</td>
<td>51.72 ± 15.44</td>
</tr>
<tr>
<td></td>
<td>Control NR</td>
<td>NR</td>
<td>189.39 (94.69–531.0)</td>
<td>171.69 ± 83.19</td>
<td>141.6 ± 11.50</td>
<td>49.79 ± 11.58</td>
</tr>
<tr>
<td>Plasma coenzyme Q10 (µmol/L)</td>
<td>Case 1.15 ± 0.43</td>
<td>1.15 ± 0.43</td>
<td>0.71 ± 0.19</td>
<td>1.19 ± 0.09 [0.59–2.08]</td>
<td>3.89 ± 0.32</td>
<td>49.79 ± 11.58</td>
</tr>
<tr>
<td></td>
<td>Control 0.39 ± 0.35</td>
<td></td>
<td>0.74 ± 0.19</td>
<td>NR</td>
<td>NR</td>
<td>3.99 ± 0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>3.57 ± 0.05</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
Abbreviations: BMI: body mass index; NR: not reported; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BMI: body mass index.

* Only differences between simvastatin and placebo shown as mean (SD) [95% CI].
* Values are expressed as median (range).
* Data presented as box-and-whiskers plots.
* Values are expressed as mean ± SE, with ranges in brackets.
2.6. Publication bias

Potential publication bias was explored using visual inspection of Begg’s funnel plot asymmetry, and Begg’s rank correlation and Egger’s weighted regression tests. Duval & Tweedie “trim and fill” and “fail-safe N” methods were used to adjust the analysis for the effects of publication bias method was used to adjust the analysis for the effects of publication bias [24].
Fig. 4. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of hydrophobic (upper plot) and hydrophilic (lower plot) statins on plasma CoQ10 concentrations.

Table 2
Assessment of risk of bias in the included studies using Cochrane criteria.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref.</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other potential threats to validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashton et al.</td>
<td>[25]</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Jula et al.</td>
<td>[26]</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Oranje et al.</td>
<td>[27]</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Päivä et al.</td>
<td>[28]</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Strey et al.</td>
<td>[29]</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Ghirlanda et al.</td>
<td>[30]</td>
<td>U</td>
<td>U</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
</tbody>
</table>

Abbreviations: L: low risk of bias; H: high risk of bias; U: unclear risk of bias.

Fig. 5. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of statin therapy on plasma CoQ10 concentrations in trials with treatment durations of <12 weeks (upper plot) and ≥ 12 weeks (lower plot).
3. Results

3.1. Flow and characteristics of included studies

The initial screening for potential relevance removed the articles in whose titles and/or abstracts were irrelevant. Among the 16 full text articles assessed for eligibility, 10 were excluded for the following reasons: uncontrolled study (n = 1), not placebo-controlled (n = 1), reporting LDL CoQ10 level (n = 1), not measuring plasma/serum CoQ10 (n = 6) and duplicate report (n = 1).

After assessment, 6 RCTs met the inclusion criteria (8 placebo controlled treatment arms) and were used for the final meta-analysis [25–30]. In total, 240 participants were allocated to the statin group and 210 to the control group. The number of participants in these trials ranged from 19 to 120. Included studies were published between 1993 and 2011, and were conducted in Finland (n = 2), Australia, New Zealand, the Netherlands and Italy. The following statin doses were administered in the included trials: 10–40 mg/day atorvastatin, 20–80 mg/day simvastatin, 40 mg/day rosuvastatin and 20 mg/day pravastatin. Duration of statin intervention ranged between 6 weeks and 26 weeks. There were 4 trials were designed as parallel-group studies and 2 had a crossover design. Demographic and baseline parameters of the included studies are shown in Table 1.

3.2. Risk of bias assessment

According to the Cochrane Collaboration, a specific tool for assessing risk of bias in each included study comprises judgment of specific features of the study (Table 2) [31]. This involves evaluating the risk of bias as ‘low risk’, ‘high risk’ or ‘unclear risk’. The final category implies either lack of information or doubt over the potential for bias. There are seven analyzed domains comprising: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias (Fig. 1).

3.3. Effect of statin therapy on plasma CoQ10 concentrations

Meta-analysis of 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 statistically significant in the leave-one-out sensitivity analysis (Fig. 2). Subgroup analysis suggested that the impact of statins on plasma CoQ10 concentrations was significant for all preparations of statins (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), rosvastatin (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) (Fig. 3).

Likewise, there was no differential effect between lipophilic (atorvastatin and simvastatin) (WMD: −0.43 μmol/L, 95%CI: −0.53, −0.34, p < 0.001) and hydrophilic (rosuvastatin and pravastatin) (WMD: −0.47 μmol/L, 95%CI: −0.62, −0.32, p < 0.001) in terms of changing plasma CoQ10 concentrations (Fig. 4). 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) (Fig. 5).

3.4. Meta-regression

Random-effects meta-regression was performed to evaluate the impact of putative moderators i.e. treatment duration and changes in plasma LDL-C concentrations on the estimated effect size. Neither treatment duration (slope: −0.0002; 95%CI: −0.01, 0.01; p = 0.964) nor changes in plasma LDL-C concentrations (slope: 0.005; 95%CI: −0.001, 0.011; p = 0.083) and molar dose of statin (slope: −1.09; 95%CI: −2.62, 0.44; p = 0.163) were found to be associated with changes in plasma CoQ10 concentrations (Fig. 6). The negative association between the changes in plasma CoQ10 levels following statin therapy and baseline plasma CoQ10 concentrations (slope: −0.58; 95%CI: −1.22, 0.05; p = 0.071) did not reach statistical significance (Fig. 6).
3.5. Publication bias

The funnel plot of precision (inverse standard error) versus effect size (mean difference) was asymmetric and suggested a potential publication bias in the meta-analysis of the statin effect on plasma CoQ10 concentrations. Using "trim and fill" correction, 3 potentially missing studies were imputed leading to a corrected effect size of −49 μmol/L (95%CI: −0.56, −0.41) (Fig. 7). The presence of publication bias was excluded by Egger’s linear regression (intercept = 0.66, standard error = 1.06; 95%CI = −1.93, 3.26, t= 0.63, df = 6, two-tailed p = 0.554) and Begg’s rank correlation (Kendall’s Tau with continuity correction = 0.11, z = 0.37, two-tailed p-value = 0.711) tests. The "fail-safe N" test showed that 219 studies would be needed to bring the WMD down to a non-significant (p > 0.05) value.

4. Discussion

To our knowledge, this meta-analysis is the first to assess the effect of statins on plasma CoQ10 concentrations. Data from 6 trials (8 placebo-controlled treatment arms) suggests a significant reduction in plasma CoQ10 concentrations following treatment with statins, independent of statin formulations, duration or dose. Although a higher effect size was observed for trials with <12 weeks treatment duration, a significant effect of statin therapy on plasma CoQ10 concentrations was observed in both trials lasting <12 weeks and ≥12 weeks. The results reveal that the importance of estimated pooled effect size is not biased by any type of study. These findings are important since CoQ10 might be a potential therapeutic target for statin intolerance; however, our previous meta-analysis on this subject did not confirm the effect of CoQ10 supplementation (with doses up to 600 mg/day) in reducing statin-induced myalgia [32,33].

The mechanisms associated with statin-induced CoQ10 depletion and clinical consequences are not completely known. Several factors were found to be responsible for the depletion of serum levels after statin therapy such as insufficient dietary CoQ10 [1], inhibition of CoQ10 biosynthesis [34] or excessive consumption of CoQ10 [35]. The biological consequences of statin-induced CoQ10 depletion may include: increased production of free radicals with consecutive damage of mitochondrial DNA [10], decrease of the mitochondrial oxidative phosphorylation capacity leading to mitochondrial dysfunction [36] and the dysfunction or injury of skeletal muscle [37], defective activity of cell division and apoptosis with increased tendency to malignancy [38]. A phenomenon of CoQ10 depletion associated with increased oxidative stress or inflammatory states [39] was reported in elderly individuals [40], intense physical training [41], in arterial hypertension, diabetes mellitus, periodontal disease, depression, chronic fatigue syndrome, Parkinson disease [38] and breast cancer [42]. Moreover, it has been shown that CoQ10 depletion might modify the serotoninergic system in patients with fibromyalgia through changing the serotonin content in neurons of the central nervous system and platelets [43]. Since serotonin is considered an essential modulator of mood, cognition, fatigue and sleep in healthy individuals, SAMS might also be the result of various modifications of the serotonin metabolism, content or transmission [44]. Moreover, the role of CoQ10 in the production of adenosine triphosphate via oxidative phosphorylation is recognized [1]. Therefore, the depletion of CoQ10 levels might generate decreased levels of adenosine triphosphate levels in the platelets of patients with fibromyalgia, further accentuated by the modification of the hypothalamic-pituitary-adrenal axis [45].

Statin-induced CoQ10 depletion is also considered to be one of the mechanisms responsible for statin-therapy related new onset diabetes [46–48]. Mitochondria play an initial role in insulin secretion by producing ATP as a result of electron transport through the oxidative chain of the inner membrane, where CoQ10 is synthesized from geranyl-pyrophosphate [49]. ATP production precedes the electron transport through the inner membrane by, among others, electron carrier complexes I-IV. CoQ10 transfers electrons from complexes I and II to complex III. Statins, by inhibiting HMG-CoA reductase, decrease the amount of geranyl-pyrophosphate and thus the level of CoQ10 and in the consequence might impair mitochondrial ATP synthesis in pancreatic beta cells [50].

The present meta-analysis has several limitations. Most importantly, there were only few eligible RCTs and most of them included relatively small populations. Furthermore, these studies were heterogeneous regarding factors like population characteristics and study design. A conservative random-effects model was used to evaluate the heterogeneity between the studies. Sensitivity analysis was performed using the one-study remove strategy to examine the impact of each individual study on the overall effect size.

In conclusion, this 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.

Declaration of interest

This meta-analysis was written independently; no company or institution supported it financially. No professional writer was involved in the preparation of this meta-analysis.