Simvastatin-induced decrease of mitochondrial function in healthy subjects and its reversibility by ubiquinol

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INTRODUCTION

Mitochondrial dysfunction may play a role in the pathophysiology of many age related conditions. Mitochondrial function cannot be enhanced beyond physiological levels, so pharmacology of compounds that enhance mitochondrial function (MiF) cannot be proven in healthy subjects. Simvastatin is known to decrease MiF at least partly by depletion of co-enzyme Q10. The goal of this study was to evaluate a model of simvastatin-induced decrease of MiF and to determine whether this could be pharmacologically reversed by treatment with ubiquinol, the reduced form of co-enzyme Q10.

METHODS

- N = 27 healthy volunteers, aged 40 – 70 years
- Week 1 – 8: simvastatin 40 mg daily
- Week 4 – 8: simvastatin + ubiquinol 300 mg daily (n = 14) or simvastatin + placebo daily (n = 13)
- Q10 plasma concentration were taken at baseline, week 4 and week 8.
- MiF measurements: baseline, week 2, 4 and 8
- Measurement techniques:

I. Phosphocreatine (PCr) recovery time by phosphorus Magnetic Resonance Spectroscopy (31P-MRS)
II. Mitochondrial oxygen consumption in the skin by oxygen dependent fluorescence of protoporphyrin-9
III. Mitochondrial membrane potential (MMP) in circulating peripheral blood mononuclear cells (PBMCs)
   - Only measured at baseline and 4 weeks and in 8 subjects

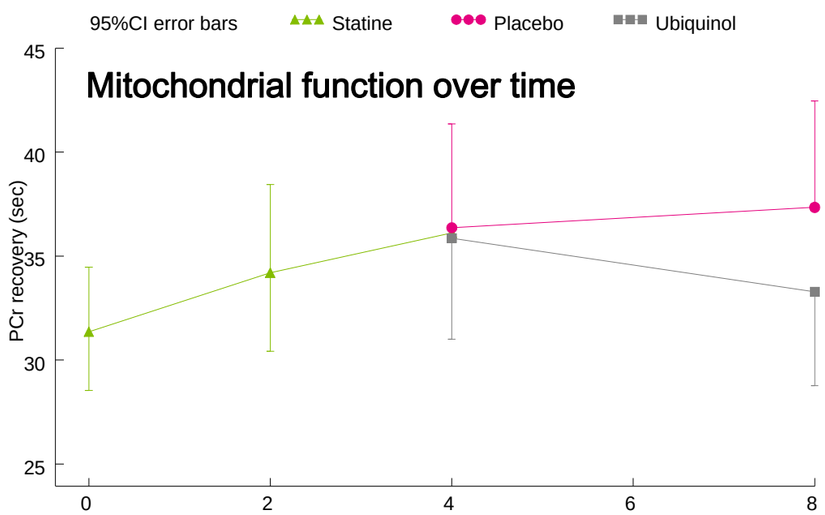

Fig. 1: PCr recovery time increases significantly after 4 weeks of simvastatin administration and is partially reversed in the ubiquinol group

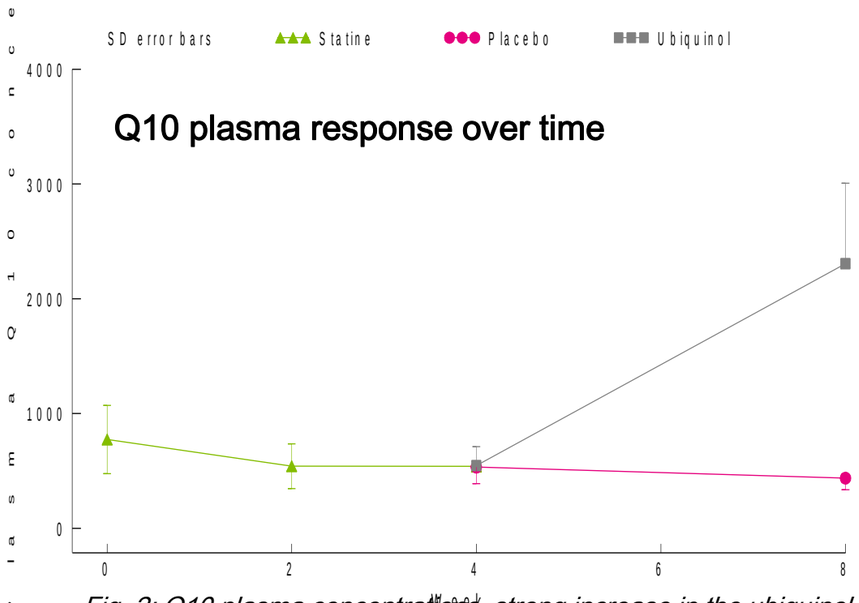

Fig. 2: Q10 plasma concentrations, strong increase in the ubiquinol group

RESULTS

After 4 weeks of simvastatin administration, **PCr recovery** time was significantly prolonged with 15.2% (95%CI: 2.5%; 29.4%). Mitochondrial function at week 8 was no longer significantly different from baseline in the ubiquinol group (9.1% (95%CI: -7.9%;29.2%) while it was still significantly prolonged in the placebo group (18.5% (95%CI: 1.1%; 38.9%). See figure 1.
The mean **Q10 plasma concentration** decreased after the first 4 weeks, increased in the ubiquinol group and further decreased in the placebo group. See figure 2.

During the first 4 weeks of simvastatin treatment:
Mitochondrial oxygen consumption increased from 7.53 mmHg/sec to 8.88 mmHg/sec (95%CI: -0.014; 2.716).
The **percentage of dysfunctional PBMCs** increased significantly in the first 4 weeks from 5.2% to 14.43% (95%CI: 2.416;16.056).

CONCLUSIONS

- Simvastatin causes decrease of mitochondrial function, disruption of mitochondrial membrane potential and increase of oxygen consumption after 4 weeks of administration in healthy volunteers.
- Addition of ubiquinol at 4 weeks reverses this decrease after 8 weeks so that the mitochondrial function is not longer significantly different from baseline.
- Simvastatin directly inhibits mitochondrial complex III* and therefore suppleting Q10 will only achieve partial reversibility of mitochondrial function.

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*Schirris TJ *et al.* Statin-Induced Myopathy Is Associated with Mitochondrial Complex III Inhibition Cell Metab. 2015 Sep 1;22(3):399-407.