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Pilot study of safety and efficacy of polyprenols in combination with coenzyme Q10 in patients with statin-induced myopathy

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ABSTRACT

Background and objective: Statin-induced myopathy (SIM) has been partially attributed to deficiency of dolichol and coenzyme Q10 (CoQ10). We aimed to test the safety and efficacy of plant polyprenols in combination with CoQ10 for alleviation of SIM.

Materials and methods: In an open-label, one-center prospective pilot study patients with SIM received conifer-tree needle polyprenols (4 mg/day) and CoQ10 (100 mg/day) for 8 weeks. Symptoms and safety were evaluated according to symptom severity score (0–10), creatine kinase (CK) levels, exercise test, dynamometry, complete blood count, clinical biochemistry and electrocardiography.

Results: Of the 14 patients, 11 completed the study per protocol. Two patients withdrew consent due to travels abroad, and it was discontinued for one patient with stage 3 chronic kidney disease due to asymptomatic elevations of liver enzymes at week 4. No safety parameters changed significantly in per protocol group. Non-significant increase of CK levels was observed ($P = 0.231$). Muscle pain ($n = 10$) and weakness ($n = 7$) scores improved significantly ($P < 0.001$ and $P = 0.018$, respectively). Muscle pain completely disappeared in 2 patients, weakness resolved in 3 patients and cramps disappeared in two patients. Four patients assessed improvement strong enough to consider increase of statin dose. No changes were observed in exercise test or dynamometry.

Conclusions: Conifer-tree polyprenols in combination with CoQ10 may be generally safe in patients with SIM, but caution should be exercised in patients with glomerular filtration rate <60 mL/min and routine monitoring of the liver enzymes and CK is advocated in all patients. The observed efficacy provides the rationale for a larger, double-blind controlled study with polyprenols.

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1. Introduction

Treatment with statins is the cornerstone of primary and secondary cardiovascular disease prevention [1,2]. Statins are generally well tolerated, but myopathic symptoms known as statin induced myopathy (SIM) may preclude their administration. The manifestations may vary from subjective symptoms such as muscle pain, weakness and cramps to increased plasma creatine kinase (CK) levels. The most serious adverse muscle side effect, rhabdomyolysis, however is very rare: 1 in 10,000 patient years [3]. So-called statin-associated muscle symptoms such as muscle pain, aching, stiffness, weakness or cramps are encountered more frequently (7%–29%), in many cases without significant increase in plasma CK levels [3,4]. Although these symptoms are mostly not life threatening, they may lead to down-titration of the dose or discontinuation of statins in up to 75% of cases, which contributes to increased adverse cardiovascular outcomes [3,5–7].

Objective assessment of muscle side effects remains a challenge. Currently no unified recommendations to enhance accurate diagnosis and approve statin associated muscle symptoms or treatment approach are generally accepted. The common practice in case of suspicion of statin induced muscle side effects is to down-titrate the statin dose, switch to a different statin or discontinue the treatment [3]. Alternatively, etiopathogenic treatment of SIM can be considered. Statins are known to inhibit synthesis of several biologically active substances, including ubiquinone and dolichols, which have been related to SIM [8]. Supplementation with ubiquinone also known as coenzyme Q10 (CoQ10) has been used in clinical practice. However, there was no evidence of its efficacy in a meta-analysis of six trials including 302 patients and in a randomized trial with 120 patients [9,10].

Polyprenols are natural long-chain isoprenoid alcohols with chemical formula $H–[CH_2–C(CH_3)=CH–CH_2]_n–OH$ with n standing for the number of isoprene units. They are naturally present in conifer tree needles in small amounts and are known to be metabolized in human liver to dolichol which is an important bioregulator of N-glycoprotein synthesis [11].

We therefore hypothesized that supplementation with polyprenols in combination with CoQ10 could reduce statin induced muscle symptoms and improve objective myopathy parameters.

2. Materials and methods

2.1. Study design and patients

This was an open-label, one-center prospective pilot study. Between June 2014 and July 2015 patients at the Latvian Center of Cardiology were screened for suspected SIM symptoms. The study was approved by the local Committee of Ethics at the Paul Stradins Clinical Hospital (study protocol No. 160414 – 3L) and performed according to good clinical practice.

The inclusion criteria were as follows: (i) presence of at least one of symptoms associated with statin use (muscle pain or muscle weakness, or muscle cramps for at least 2 weeks, or elevated CK level >2× and <10× above the upper limit of reference (ULR); (ii) stable dose of a statin used for at least for 1 month; (iii) no indication to decrease statin dose (symptoms are tolerable and CK level <10× above ULR); (iv) expected to continue the same statin in the same dose during study period (as lipid targets are achieved or muscle symptoms are likely to increase with increasing statin dose); (v) patient has signed informed consent for participation in the study.

Patients were excluded from the study if they met any of the following exclusion criteria: CK level >10× ULR; muscle symptoms present before statin therapy; regular intramuscular injections; serious suspicion of other cause of muscle symptoms; myocardial infarction or extensive surgery, or major trauma during the last one month; any surgery during last 2 weeks (except of PCI); elective surgical procedure in next 2 months (except for PCI); concomitant use of fibrates, nicotinic acid, red yeast extract, grapefruit juice, macrolide antibiotics, oral antifungal drugs, HIV protease inhibitors, cyclosporine, oral glucocorticiods (if change in dosage expected in the following 2 months), fluoxetine (if change in dosage expected in the following 2 months); liver enzyme elevation (AlAT or AsAT >3× ULR and/or conjugated or unconjugated bilirubin >2× ULR, with exception for Gilbert's syndrome), glomerular filtration rate <30 mL/min as calculated by Cockroft-Gault formula; hyperkalemia ≥5 mmol/L; excessive consumption of alcohol (>5 units daily); established neuromuscular pathology, rheumatic polymyalgia, mitochondrial myopathies; established clinically significant hypothyroidism with planned change in thyroxin dosage; known or suspected poor compliance; any disease associated with poor life expectancy; regular excessive physical exertions; drug abuse; inability to perform exercise test; pregnancy or a possibility of conception during the following next 2 months; known intolerance of polyprenols or CoQ10; and allergies to conifer trees.

All patients received supplementation with conifer-tree needle polyprenols (4 mg daily) and CoQ10 (100 mg daily) for 8 weeks in the form of two food supplements registered in Latvia: 2 capsules of ''Poliprenols''® (containing 1 mg of needle-tree polyprenols) and one capsule of ''Kardiopren''® (containing 100 mg of CoQ10 and 2 mg of conifer-tree polyprenols) [12,13].

2.2. Data collection

After the baseline visit, two follow-up visits were planned: at 4 weeks (±7 days) and at 8 weeks (±7 days). At the baseline as well as at 4 and 8 weeks patients were asked to evaluate subjective muscle symptoms (muscle pain, weakness, cramps) by self-assessment score (0–10), and to define which muscle groups are involved, and to report level of everyday physical activity defined as follows: low (<3 metabolic equivalents, METs), moderate (3–6 METs) and intensive (>6 METs) activities measured in hours/per week.

The following investigations were performed at the baseline, at 4 weeks and at 8 weeks to evaluate safety and efficacy of the supplements: rest ECG; full blood count, plasma biochemical parameters (CK, total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, alanine amino transferase [AlAT], aspartate amino transferase [AsAT], conjugated bilirubin, uncojugated bilirubin, glucose, creatinine, glomerular filtration rate [GFR] calculated according to Cockcroft-Gault