Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/medici

Original Research Article

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

Gustavs Latkovskis [a,b,c,*], Vita Saripo [a], Emma Sokolova [a], Dana Upite [a], Ilona Vanaga [d], Ugis Kletnieks [d], Andrejs Erglis [a,b,c]

[a] Latvian Center Cardiology, Pauls Stradins Clinical University Hospital, Riga, Latvia
[b] Faculty of Medicine, University of Latvia, Riga, Latvia
[c] Latvian Institute of Cardiology and Regenerative Medicine, University of Latvia, Riga, Latvia
[d] Pharma and Chemistry Competence Center of Latvia Ltd., Riga, Latvia

ARTICLE INFO

Article history:
Received 6 November 2015
Received in revised form
22 April 2016
Accepted 10 May 2016
Available online 30 May 2016

Keywords:
Statins
Myopathy
Polyprenols
Coenzyme Q10
Ubiquinone

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.

* *Corresponding author at*: Latvian Center Cardiology, Pauls Stradins Clinical University Hospital, Pilsonu 13, 1002 Riga, Latvia.
E-mail address: gustavs.latkovskis@lu.lv (G. Latkovskis).
Peer review under the responsibility of the Lithuanian University of Health Sciences.
http://dx.doi.org/10.1016/j.medici.2016.05.002

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

formula, potassium, gamma-glutamyl transpeptidase [GGT], alkaline phosphatase [AP], high-sensitivity C-reactive protein [hs-CRP]); electroneuromyography (will be reported separately). The following investigations were performed at baseline and at 8 weeks: dynamometry with Baseline® hydraulic hand dynamometer (3 measurements of grip strength in each arm, results registered in kg, the information about which arm is dominant was also recorded); exercise electrocardiography test (veloergometry) assessing load in watts (W), baseline and maximal heart rate in beats per minute (bpm), total ST depression sum in millimeters (mm), time until 1 mm ST depression in seconds (s), heart rate/ST index; thyroid stimulating hormone (TSH), free thyroxin (FT4), free triiodothyronine (FT3) and 25-OH-vitamine D.

2.3. *Statistical analysis*

Statistical analysis was performed with IBM© SPSS© (version 22.0). Quantitative variables were described as mean value and standard deviation with exception of variables with non-normal distribution in which case median and interquartile range is reported. Categorical variables were described by amount and percentage. When two independent groups were compared, *t* test for independent samples, Mann–Whitney *U* test, chi-square test and Fisher exact tests were used as appropriate.

Repeated measures ANOVA was used to test significance of changes in quantitative variables during study period. In cases when assumption of sphericity was violated as estimated by Mauchly's test of sphericity, Greenhouse–Geisser correction was used. Sidak adjustment was used for pairwise comparisons. Quantitative variables with non-normal distributions were tested with non-parametric Friedman's test for repeated measures. Changes of binary variables in repeated measures were tested with Cochran's Q test. *P* values less than 0.05 were considered as statistically significant.

3. Results

3.1. *Baseline characteristics*

Of the 14 patients (7 men and 7 women) enrolled in the study, 11 completed it *per protocol* (Fig. 1). Two patients withdrew informed consent during the study. One patient was not willing to undergo repeated electromyography scheduled at 8 weeks. Another patient was unable to attend 8 weeks follow-up due to work assignments abroad. The study agents were discontinued by an investigator in the third patient due to liver safety concerns, which is described separately (see below *Safety*). The baseline characteristics of *per protocol* group and three excluded patients are summarized and compared in Table 1. Alkaline phosphatase levels were significantly lower in excluded group, and no other parameters were significantly different. Statin doses and muscle symptoms are given in Table 2. The localization of the muscle symptoms in per protocol group was the following: hips/thighs ($n = 7$, 63.4%), calves ($n = 7$, 63.4%), upper arms ($n = 4$, 36.4%), lower arms ($n = 2$, 18.2%), lower back ($n = 3$, 27.3%), upper back and other locations were less prevalent ($n < 3$). None of patients received

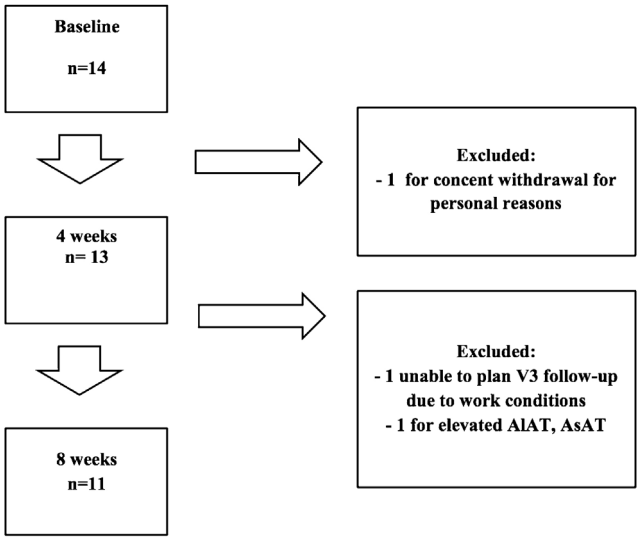

Fig. 1 – Study flow diagram.

other lipid-lowering drugs. The mean duration of statin treatment at the current dose before inclusion in the study was 9.9 ± 11.6 months (range: 1–36 months) in the total sample. The corresponding treatment duration was 10.8 ± 12.9 months (range: 1–36 months) and 6.6 ± 5.2 (range: 2–12 months) in *per protocol* and excluded groups, respectively ($P = 0.602$). History of previous statin dose reduction due to muscle symptoms or CK elevations was reported by 7 patients (63.6%) and 3 patients (100%) in per protocol and excluded groups, respectively ($P = 0.505$). Five (45.5%) and one (33.3%) patients reported previous intolerance of other than currently used statin in respective groups. Five patients (45.5%) had a history of intolerance of at least one other statin. Majority of patients had established atherosclerotic cardiovascular disease (Table 1). At the entry only 4 of the 14 patients (28.6%) had reached their therapeutic target of LDL-C below 1.8 mmol/L. The safety and efficacy findings are reported for *per protocol* group. The results of electromyography will be reported separately.

3.2. *Safety*

None of the patients in *per protocol* group ($n = 11$) experienced major adverse events during the 8 weeks. One patient underwent uncomplicated elective PCI during the study between week 4 and 8. No statistically significant increase was observed in levels of studied biochemical, hematologic and ECG variables (Table 3). There was a statistically significant mild reduction of triglyceride levels ($P = 0.023$). Higher CK levels at 8 weeks were observed, but were not statistically significantly different from those at baseline and at 4 weeks ($P = 0.765$ and $P = 0.718$, respectively; Sidak adjustment for multiple comparisons). Three patients had CK levels >ULR at the baseline. At 4 and 8 weeks 5 and 4 patients had such elevations of CK, respectively ($P = 0.223$).

One patient (65-year-old female) was excluded from the study due to asymptomatic increase of liver enzymes at the

Table 1 – Baseline characteristics of the study patients.

Characteristics	Per protocol group ($n = 11$)	Excluded ($n = 3$)
Female gender, *n* (%)	5 (45.5%)	2 (66.7%)
Age, years (mean ± SD)	67.73 ± 8.59	55.00 ± 18.19
History of coronary heart disease	11 (100)	3 (100)
Myocardial infarction	6 (54.5)	1 (33.3)
PCI	8 (72.7)	2 (66.7)
CABG	1 (9.1)	1 (33.3)
Peripheral artery disease	2 (18.2)	0
Blood biochemistry (mean ± SD)		
Total cholesterol, mmol/L	4.45 ± 1.24	4.30 ± 0.78
Triglycerides, mmol/L	2.25 ± 1.39	1.56 ± 0.75
HDL-cholesterol, mmol/L	1.33 ± 0.27	1.09 ± 0.24
LDL-cholesterol, mmol/L	2.25 ± 0.95	2.76 ± 0.83
Glucose, mmol/L	5.43 ± 0.77	5.53 ± 1.06
Creatine kinase (CK), U/L	240.09 ± 303.08	236.00 ± 204.21
CK >ULR, *n* (%)	2 (18.2)	1 (33.3)
AlAT, U/L	29.82 ± 11.69	32.22 ± 6.11
AsAT, U/L	34.27 ± 14.00	25.33 ±5.69
GGT, U/L	65.82 ± 74.83	22.33 ± 8.96
AP, U/L	89.91 ± 15.16	64.33 ± 3.21*
Conjugated bilirubin, μmol/L	3.85 ± 1.55	2.97 ± 0.91
Unconjugated bilirubin, μmol/L	7.28 ± 2.37	5.20 ±1.06
Creatinine, μmol/L	73.18 ± 17.93	95.33 ±30.29
GFR, mL/min	96.30 ± 25.61	97.67 ± 73.24
Potassium, mmol/L	4.60 ± 0.74	4.50 ± 0.26
TSH, mU/L	1.57 ± 1.25	2.37 ± 1.59
25-OH-Vitamin D, ng/L	24.17 ± 6.71	23.69 ± 5.06
hs-CRP, mg/L (medium, IQR)	1.17 (0.97–2.47)	1.07 (–)
Other cardiovascular risk factors		
Smoking, *n* (%)	1 (9.09)	0 (0)
Hypertension, *n* (%)	8 (72.73)	2 (66.66)
Diabetes, *n* (%)	2 (18.18)	0 (0)
Body mass index, kg/m^2 (mean ± SD)	27.96 ± 2.13	29.38 ± 5.53
Alcohol units per week (mean ± SD)	2.18 ± 1.54	1.67 ± 1.16
Physical activities, h per week (mean, SD)		
Mild	33.27 ± 12.56	28.00 ± 12.12
Moderate	7.27 ± 8.46	8.33 ± 5.13
Intensive	1.18 ± 3.06	0

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; ULR, upper limit of reference range; IQR, interquartile range; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AlAT, alanine amino transferase; AsAT, aspartate amino transferase; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; AP, alkaline phosphatase; hs-CRP, high sensitivity C-reactive protein; TSH, thyroid-stimulating hormone.

* $P = 0.015$, all other $P > 0.05$.

4-week follow-up visit. The summary of the relevant biochemical data is given in Table 4. Considering liver enzyme elevations more than 3 times above ULR, the statin (20 mg atorvastatin used for 7 weeks before inclusion and continued at the same dose during the study) was also discontinued. After 1 week of follow-up rapid normalization of the biochemical parameters was observed (Table 4). Other possible hepatotoxic factors were excluded (negative foe viral hepatitis B and C, no structural changes in liver and biliary system on ultrasound, patient denied use of any other drugs or substances). These changes were not accompanied by any symptoms or increase in CK or bilirubins. Of note, the patient had chronic kidney disease with GFR 50 mL/min, mild subclinical hypothyroidism (TSH 4.2 mU/L with URL 4.0 mU/L), and mildly decreased 25-OH-vitamin D levels (21.81). The renal function, however, did not worsen.

3.3. *Efficacy*

3.3.1. *Muscle symptoms*

Gradual and significant self-reported improvement of muscle pain ($n = 10$) and weakness ($n = 7$) was observed during the follow-up over 8 weeks according to self-assessment symptom scores ($P < 0.001$ and $P = 0.018$, respectively; Fig. 2). Regarding muscle pain there was a statistically significant improvement at weeks 4 and 8 compared to baseline ($P = 0.010$ and $P = 0.001$, respectively), but not at week 8 compared to week 4 ($P = 0.070$). Reduction of muscle cramp severity ($n = 5$) was not statistically significant across the study ($P = 0.069$), but differed at week 8 compared to baseline (adjusted $P = 0.012$, Fig. 2).

Muscle pain completely disappeared in 2 patients (20%), and 4 patients (40%) observed the reduction of the muscle pain

Table 2 – Statin therapy and muscle symptoms at the inclusion.

	Total (n = 14)	Per protocol (n = 11)	Excluded (n = 3)
Statin therapy			
Atorvastatin 20 mg, n (%)	2 (14.29)	1 (9.09)	1 (33.33)
Atorvastatin 30 mg, n (%)	1 (7.14)	1 (9.09)	1 (33.33)
Atorvastatin 40 mg, n (%)	1 (7.14)	1 (9.09)	1 (33.33)
Rosuvastatin 5 mg, n (%)	2 (14.29)	1 (9.09)	–
Rosuvastatin 10 mg, n (%)	3 (21.43)	3 (27.27)	
Rosuvastatin 20 mg, n (%)	4 (28.57)	3 (27.27)	
Rosuvastatin 40 mg, n (%)	1 (7.14)	1 (9.09)	
Muscle symptoms and signs			
Pain, n (%)	13 (92.86)	10 (90.90)	3 (100)
Pain at rest, n (%)	11 (78.57)	9 (81.82)	2 (66.67)
Pain severity score (mean, SD)*	5.69 ± 1.84	6.00 ± 1.70	4.67 ± 2.31
Weakness, n (%)	8 (57.14)	7 (63.64)	1 (33.33)
Weakness severity score (mean, SD)	6.00 ± 1.51	6.14 ± 1.57	5.00
Cramps, n (%)	6 (42.86)	5 (45.46)	1 (33.33)
Cramps severity score	5.33 ± 2.58	6.00 ± 2.34	2.00
Elevated CK levels >ULR	577.00 ± 342.46	614.00 ± 409.51	466.00 ± 0

[a] Symptom severity score based on subjective symptom assessment by a patient (range 0–10). The score is calculated only for the patients with presence of the symptom.
CK, creatine kinase; ULR, upper limit of reference range.

score by at least 50%. The score did not change in 1 patient and decreased by less than 50% in 3 patients. Muscle weakness completely resolved in 3 patients (42%), did not change in 2 patients (29%) and decreased by less than 50% in 2 patients (29%). Cramps disappeared in two patients (40%) and decreased by at least 50% in other two patients (40%), while did not change in one patient (20%).

Overall, among 11 patients completing the study only 2 patients did not have any improvements of any of their symptoms. At the end of the study, 4 (40%) of the 10 patients in whom there was an indication to use higher than previously maximal tolerated statin dose, assessed subjective symptoms as having improved enough to consider up-titration of statin dose. One (10%) of patients had such improvement at week 4.

3.3.2. *Dynamometry, exercise test and physical activities*

All patients reported right arm as the dominant. The maximal and average results of the three measurements for each arm did not change during the study (Table 5). No changes in any parameters of exercise veloergometry test were observed. The self-reported mild physical activities increased during the study (33.27 ± 12.56, 35.82 ± 16.20 and 39.55 ± 18.93 hours per week at baseline, 4 and 8 weeks, respectively, P = 0.008, Fig. 3).

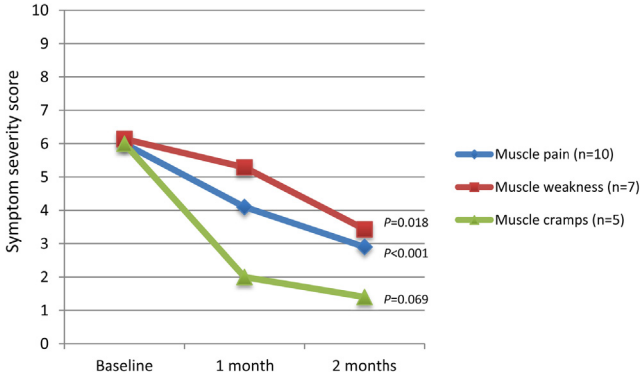

Fig. 2 – Self-reported muscle symptom scores during the study period. P values represent statistical significance across all repeated measurements.

4. Discussion

To our knowledge this is the first pilot study evaluating safety and efficacy of polyprenols in combination with CoQ10 in patients with SIM symptoms. Although this combination appeared to be generally well tolerated and safe in the majority of patients, we observed significant, but asymptomatic and reversible elevations of liver enzymes in one case. The patient was female with GFR <60 mL/min and mild subclinical hypothyroidism, mild vitamin D deficiency and no compelling evidence of liver disease. It is impossible to conclude if any of these factors alone or in combination were predisposing the patient to this event. The role of the baseline statin treatment on liver enzyme elevations cannot be ruled out either. Nevertheless, for future studies we recommend to either avoid the combination of polyprenols and CoQ10 in patients with GFR <60 mL/min or monitor such patients closely if any of these factors are present. If polyprenols are used, for safety reasons we currently recommend to test liver enzymes and CK levels at 4 weeks routinely, and to consider these tests at 2 weeks in patients with GFR <60 mL/min and/or with elevated TSH. The role of vitamin D deficiency as a risk factor for hepatotoxicity, however, seems less likely, as the mean 25-OH-vitamine D level was low in most patients of per protocol group (24.17 ± 6.17 ng/mL), although higher than in the patient with elevated liver enzymes (21.81 ng/mL). Of note, only two out of 11 patients in *per protocol* group had normal vitamin D levels ≥30 ng/mL, an intriguing finding in the context of previous

Table 3 – Safety parameters.

Parameter	Baseline	4 weeks	8 weeks	*P* value[a]
Blood biochemistry				
Total cholesterol, mmol/L	4.45 (1.24)	4.05 (0.62)	4.23 (0.57)	0.259
Triglycerides, mmol/L	2.25 (1.39)	1.72 (1.16)	1.87 (0.95)	0.023
HDL-cholesterol, mmol/L	1.33 (0.27)	1.32 (0.27)	1.37 (0.23)	0.844
LDL-cholesterol, mmol/L	2.25 (0.95)	1.99 (0.54)	2.02 (0.58)	0.305
Glucose, mmol/L	5.34 (0.77)	5.35 (0.77)	5.46 (0.67)	0.810
Creatine kinase, U/L[b]	107 (85–275)	176 (97–214)	178 (92–216)	0.231[c]
AlAT, U/L	29.82 (11.69)	29.36 (8.87)	31.27 (12.91)	0.796
AsAT, U/L	34.27 (13.99)	32.64 (11.29)	35.36 (19.03)	0.648
GGT, U/L	65.81 (74.83)	58.18 (61.60)	46.18 (38.36)	0.286
AP, U/L	89.91 (15.16)	86.64 (19.72)	82.00 (13.52)	0.338
Conjugated bilirubin, μmol/L	3.85 (1.55)	4.03 (1.45)	3.54 (1.31)	0.538
Unconjugated bilirubin, μmol/L	7.28 (2.37)	7.48 (2.22)	6.98 (2.28)	0.624
Creatinine, μmol/L	73.18 (17.93)	71.64 (19.97)	73.00 (22.62)	0.292
GFR, mL/min	96.30 (25.61)	100.70 (30.35)	98.30 (28.90)	0.275
Potassium, mL/min	4.59 (0.74)	4.84 (0.72)	4.49 (0.28)	0.333
TSH, mU/L ($n = 10$)	1.57 (1.25)	–	2.07 (1.44)	0.059
25-OH-Vitamin D, ng/L ($n = 10$)	24.17 (6.71)	–	23.48 (8.27)	0.571
hs-CRP, mg/L[b]	1.17 (0.97–2.47)	1.53 (0.99–3.61)	1.86 (0.83–4.70)	0.477[d]
Hematology				
Red blood cells, $\times 10^{12}$/L	4.86 (0.20)	4.79 (0.36)	4.79 (0.36)	0.599
White blood cells, $\times 10^{9}$/L	11.03 (12.10)	7.65 (2.47)	7.50 (1.92)	0.390
Platelets, $\times 10^{9}$/L	248.91 (37.70)	261.55 (34.45)	244.55 (37.32)	0.110
Hemoglobin, g/L	144.27 (8.84)	140.55 (11.64)	140.91 (13.19)	0.235
Electrocardiography				
Sinus rhythm, *n* (%)	9 (81.8)	9 (81.8)	9 (81.8)	1.000
Heart rate (bpm)	71.91 (14.87)	63.18 (9.05)	67.64 (8.42)	0.097
PR (ms) ($n = 9$)[e]	169.89 (30.23)	175.78 (36.49)	174.67 (30.97)	0.516
QRS (ms)	106.27 (24.46)	107.27 (24.73)	106.55 (23.24)	0.779
QT (ms)	407.27 (41.69)	427.45 (33.36)	412.00 (29.85)	0.125
QTc (ms)	382.82 (43.52)	394.27 (34.04)	371.64 (25.874)	0.217

Values are mean (standard deviation) unless otherwise indicated.
LDL, low density lipoprotein; HDL, high-density lipoprotein; AlAT, alanine amino transferase; AsAT, aspartate amino transferase; GFR, glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; AP, alkaline phosphatase; hs-CRP, high sensitivity C-reactive protein; TSH, thyroid stimulating hormone; PR, PR interval; QRS, QRS complex; QT, QT interval; QTc, corrected QT interval.
[a] Repeated measures ANOVA.
[b] Median and interquartile range.
[c] Friedman's test.
[d] Median and interquartile range, comparisons performed with logarithmically transformed values.
[e] In patients with sinus rhythm ($n = 9$).

Table 4 – Summary of the patient case with liver enzyme elevations.

	Baseline	4 weeks	+1 day FU	+7 days FU	Reference limits
AlAT	31.00	473	313	62	<41 U/L
AsAT	27.00	189	82	34	<37 U/L
GGT	28.00	282	250	154	<61 U/L
AP	62.00	151	134	90	<117 U/L
Total bilirubin	6.00	5.60	–	6.20	<19 μmol/L
Conjugated bilirubin	2.00	1.70	–	–	<3.4 μmol/L
Unconjugated bilirubin	4.00	3.90	–	–	– μmol/L
CK	166	191	–	–	190 U/L
Creatinine	130.00	113	–	–	30–106 μmol/L
GFR	50	58	–	–	>90 mL/min
Potassium	4.70	4.90	–	–	3.50–5.30 mmol/L)
25-OH-vitamine D	21.81	–	–	–	30–100 ng/mL
hs-CRP	1.60	2.49	–	–	<1.0 mg/L

FU, follow-up; AlAT, alanine amino transferase; AsAT, aspartate amino transferase; GGT, gamma-glutamyl transpeptidase; AP, alkaline phosphatase; CK, creatine kinase; GFR, glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein.

Table 5 – Physical tests (n = 11).

	Baseline	4 weeks	8 weeks	P value
Dynamometry				
Right arm, maximum (kg)	39.73 (20.80)	38.36 (20.09)	40.36 (22.77)	0.425
Right arm, average (kg)	35.94 (20.21)	35.88 (18.94)	36.09 (20.03)	0.985
Left arm, maximum (kg)	35.18 (20.83)	36.45 (20.97)	39.36 (18.60)	0.047
Left arm, average (kg)	33.09 (20.31)	34.73 (20.17)	36.91 (18.09)	0.102
Exercise test				
Load (watts)	106.82 (37.23)	–	100.00 (29.58)	0.192
Peak pulse (bpm)	107.36 (18.05)	–	108.73 (15.14)	0.728
Peak SBP (mmHg)	172.18 (17.53)	–	160.00 (23.18)	0.087
Peak DBP (mmHg)	89.82 (6.13)	–	94.73 (17.60)	0.443
ST depressions (mm)	2.23 (1.77)	–	1.96 (1.10)	0.433
Heart rate/ST index (bpm/mm)	1.00 (1.02)	–	1.24 (1.03)	0.609

SBP, systolic blood pressure; DBP, diastolic blood pressure.

reports suggesting vitamin D deficiency as a risk factor of statin induced muscle symptoms [14–16].

Contrary to our expectations, we did not observe reduction of CK levels. Moreover, there appeared to be some increase of CK levels during 8 weeks, which was not significant, but clinical relevance cannot be ruled out. It should be noted that the distribution of CK in the study sample was negatively skewed and non-parametric Friedman's test for repeated measures was therefore applied. Thus small sample size in combination with lower power of the non-parametric tests leaves high probability of type 2 statistical error. Irrespectively, we recommend to closely monitor CK levels in future studies of polyprenols alone or in combination with CoQ10, especially in patients with CK levels in the range of 5–10 times above the ULR. Having said that, we found no evidence of worsened muscle symptoms in patients with increase of CK levels, and there was no correlation of CK changes with regression of muscle symptoms. Clearly, if confirmed, the significance and mechanisms of CK changes with polyprenols should be further investigated.

The study has several limitations. Our attempt to develop very stringent criteria to select ''true'' SIM patients lead to a small sample size, which limits the power of the study. These patients were selected at the Latvian Center of Cardiology, among thousands of patients during 18 months. The challenge was to find patients meeting inclusion criteria, and there were very few cases where patients could not be included because of the exclusion criteria. This reiterates previous observations that the true prevalence of statin induced myopathies is much lower than commonly perceived.

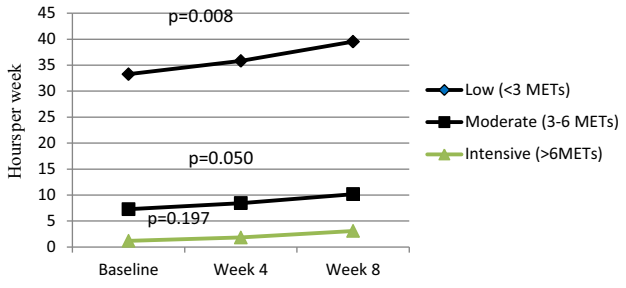

Fig. 3 – Self-reported physical activities in hours per week (n = 11).

Another limitation was the fact that only 11 of the 14 patients completed the study. In investigators' opinion only one case of discontinuation, however, was likely related to the study supplements as discussed above. Two other patients withdrew from the study due to clearly personal reasons unrelated to the study and had no record of poor tolerability or non-compliance. Nevertheless, an attrition or observer bias cannot be ruled out. It should also be noted that the patient sample was rather heterogeneous. For instance, the statins and doses varied. We did not attempt to switch patients to a unified treatment as patients had various experiences with other statins and/or doses. This may be regarded also as a strength of the study, because every patient was receiving maximum tolerated dose of the statin, which was previously individually tailored. In terms of cardiovascular risk the sample was less heterogeneous as they all had established coronary heart disease, although not all had the history of myocardial infarction or revascularization.

The current study was designed before the publication of several important position papers on the statin intolerance [3,4,17]. We therefore did not calculate statin myalgia clinical index score recommended by the European Atherosclerosis Society and supported by the International Lipid Expert Panel [3,4,17]. In the future research of polyprenols this score should be used for selection and characterization of the patients at the study entry.

This was an open-label, non-controlled, single center study, and all the results should be therefore interpreted with caution. Thus, the placebo effect and potential observer bias cannot be ruled out. Nevertheless the clinical efficacy surpassed the expectations of the investigators and was appreciated by several patients. Seven of them expressed willingness to continue the study agents after the completion of the study, as they are available as food supplements. Importantly, 4 patients were ready to increase the dose of statin at the end of the study.

The results should be put into context of the fact that all patients received only combination of polyprenols and CoQ10, which does not allow distinguishing the effects of either of the two agents. The design of the study was planned before the publication of an important meta-analysis of randomized trials, which did not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy

[9,18]. Another systematic review and meta-analysis, however, demonstrated a significant reduction in plasma CoQ10 concentrations in patients treated with statins [19]. There is a rational therefore to further investigate role of CoQ10 in statin-induce myopathy, probably with higher doses [20,21]. When our study was designed there was evidence that patients with statin-induced myopathy would benefit from CoQ10 in two studies [21,22] which was not confirmed in other studies [23–25]. Hence, this was planned as a pilot study to test if the combination is safe and if there is a signal of clinical efficacy. Based on the current findings there is a rational to perform randomized double-blind placebo controlled prospective parallel group study where monotherapy of polyprenols and combination of polyprenols with CoQ10 are tested against each other and placebo to clarify the role of polyprenols in alleviation of the statin induced muscle symptoms.

5. 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. Significant improvement of SIM symptoms observed in this study provides the rationale for a larger, double-blind controlled study with polyprenols.

Conflicts of interests

Ilona Vanaga and Ugis Kletnieks are employees of Pharma and Chemistry Competence Center of Latvia, Ltd. and ''Silv EXPO'' Ltd.

Funding

The study was sponsored by Pharma and Chemistry Competence Center of Latvia, Ltd. Grant No. L-KC-11-0001 with the co-financing of the European Regional Development Fund. Project P29: ''The conifer isoprene alcohol biological activity studies in pathology models''.

REFERENCES

[1] Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). Eur Heart J 2012;33:1635–701.
[2] Reiner Ž, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J 2011;32:1769–818.
[3] Stroes E, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy – European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015;36:1012–22.
[4] Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the statin muscle safety task force: 2014 update. J Clin Lipidol 2014;8:558–71. EAS Paper.
[5] Thompson PD, Clarkson PM, Rosenson RS. National Lipid Association Statin Safety Task Force Muscle Safety Expert Panel. An assessment of statin safety by muscle experts. Am J Cardiol 2006;97(8A):69C–76C.
[6] Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clin Ther 2008;30:2167–79.
[7] Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients – the PRIMO study. Cardiovasc Drugs Ther 2005;19:403–14.
[8] Krum H, McMurray JJ. Statins and chronic heart failure: do we need a large-scale outcome trial? J Am Coll Cardiol 2002;39(10):1567–73.
[9] Banach M, Serban C, Sahebkar A, Ursoniu S, Rysz J, Muntner P, et al. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. Mayo Clin Proc 2015;90(1):24–34.
[10] Taylor BA, Lorson L, White CM, Thompson PD. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. Atherosclerosis 2015 Feb;238(2):329–35.
[11] Khidyrova NK, Shakhidoyatov MK. Plant polyprenols and their biological activity. Chem Nat Compd 2002;38(2):107–21.
[12] Roschin, VI, Sultanov, VS, inventors. Method for processing vegetable raw materials. Russian patent number 8969517. 2004; 1; April 27.
[13] http://www.pvd.gov.lv/lat/lab_izvlne/registri/uztura_bagatinataji/uztura_bagatinataju_registrs [accessed 22.10.15].
[14] Ahmed W, Khan N, Glueck CJ, Pandey S, Wang P, Goldenberg N, et al. Low serum 25 (OH) vitamin D levels are associated with reversible myositis-myalgia in statin-treated patients. Transl Res 2009;153:11–6.
[15] Bell D. Resolution of statin-induced myalgias by correcting vitamin D deficiency. South Med J 2010;103(7):690–2.
[16] Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, Rysz J, Muntner P, Toth PP, et al. Analysis of vitamin D levels in patients with and without statin-associated myalgia – a systematic review and meta-analysis of 7 studies with 2420 patients. Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Int J Cardiol 2015;178:111–6.
[17] Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, et al. Statin intolerance – an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci 2015;11(1):1–23.
[18] Banach M, Serban C, Sahebkar A, Rysz J, Muntner P, Toth PP, et al. Futility of supplementation with Coenzyme Q10 for statin-induced myopathy: an updated (2015) meta-analysis of randomized controlled trials. Eur Heart J 2015;26(Suppl. 1):1047.
[19] Banach M, Serban C, Ursoniu S, Rysz J, Muntner P, Toth PP, et al. Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Statin therapy and plasma coenzyme Q10 concentrations – a systematic review and meta-analysis of placebo-controlled trials. Pharmacol Res 2015;99:329–36.
[20] Banach M, Mikhailidis DP, Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. In reply – coenzyme Q10 and statin-induced myopathy. Mayo Clin Proc 2015;90(3):420–1.
[21] Caso G, Kelly P, McNurlan MA, Lawson WE. Effect of coenzyme Q10 on myopathic symptoms in patients treated with statins. Am J Cardiol 2007;99(10):1409–12.

[22] Fedacko J, Pella D, Fedackova P, Hänninen O, Tuomainen P, Jarcuska P, et al. Coenzyme Q(10) and selenium in statin-associated myopathy treatment. Can J Physiol Pharmacol 2013;91(2):165–70.
[23] Young JM, Florkowski CM, Molyneux SL, McEwan RG, Frampton CM, George PM, et al. Effect of coenzyme Q(10) supplementation on simvastatin-induced myalgia. Am J Cardiol 2007;100(9):1400–3.
[24] Bookstaver DA, Burkhalter NA, Hatzigeorgiou C. Effect of coenzyme Q10 supplementation on statin-induced myalgias. Am J Cardiol 2012;110(4):526–9.
[25] Bogsrud MP, Langslet G, Ose L, Arnesen KE, Sm Stuen MC, Malt UF, et al. No effect of combined coenzyme Q10 and selenium supplementation on atorvastatin-induced myopathy. Scand Cardiovasc J 2013;47(2): 80–7.