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PHYTOSTEROL SUPPLEMENTATION IN MANAGEMENT OF DYSLIPIDAEMIA IN STATIN REFUSAL

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ABSTRACT

Background: Statins are most important lipid-lowering drugs. However, many patients discontinue the statin therapy because of side effects or refusal of further statin treatment. Phytosterol supplements in addition to lifestyle changes may represent an alternative to these patients.

Methods: 94 participants (42 men, 52 women) with history of statin refusal took 800 mg of phytosterol twice a day. Primary end point was change in LDL concentration in 4, 8 and 12 weeks.

Results: LDL concentration declined significantly to 3.49 ± 0.858 in week 8 ($p < 0.05$) and 3.33 ± 0.955 mmol/l in week 12 ($p < 0.05$). Total cholesterol decreased accordingly. One participant did not complete the trial due to intolerance of phytosterol. 26.9% subjects reached their target values of LDL.

Conclusions: Statins remains the most important lipid-lowering drugs. Phytosterol supplementation may help to reduce LDL concentration in patients with statin intolerance or refusal.

KEYWORDS : phytosterol supplementation, LDL, cholesterol, statin intolerance, statin refusal

Background:

Elevated plasma cholesterol concentration is one of most important risk factor of cardiovascular mortality and morbidity [1]. Therefore pharmacological and nonpharmacological approaches of lowering the plasma cholesterol carry fundamental role in preventive cardiology. European Society of Cardiology guidelines for management of dyslipidaemia recommend to treat if LDL cholesterol as exceeds 3.0 mmol/l in low risk individual, 2.5 mmol/l in high risk and 1.8 mmol/l in very high risk individual. If these targets cannot to be reached in a particular individual, than lowering the LDL concentration as much as possible is recommended [2]. Statins are preferred lipid lowering drugs for their effectivity in preventing of cardiovascular events. Their ability to reduce cardiovascular morbidity and mortality is not matched by any other hypolipidaemic drug [3,4]. Serious adverse effects of statin therapy like rhabdomyolysis are feared by both clinicians and patients, but are very rare and statins are considered to be safe [5, 6]. Mild side effects like muscle pain, headache or elevated liver enzymes are usually benign and fully reversible [5]. However, more than 50% of patients with dyslipidaemia in United States discontinue the lipid-lowering therapy in 5 years [7]. Even worse compliance was shown by population based study in Israel which included more than 200 000 patients, where about 75 % first-time statin treated patients discontinued the therapy by 2 years [8]. The reasons for statin discontinuation might be non-compliance, intolerance, fear of side effects or cost of the treatment. One of the alternative strategies for treatment of individuals who discontinue or refuse the statin treatment might be phytosterols (plant sterols and stanols) supplementation. Metaanalysis of various phytosterol supplementation studies demonstrated their dose dependent lipid-lowering potential [9]. The mechanism mediating their lipid-lowering effect is most likely the inhibition of intestinal cholesterol absorption, however, several other possible ways of action were studied. They included competition with cholesterol for solubilisation in micelles, crystallization with cholesterol forming insoluble mixed crystals and interference with the hydrolysis process by lipases and cholesterol esterases. Plant sterols also might interfere with transport-mediated processes of cholesterol uptake [10]. Regardless of its potential, phytosterol supplementation plays only marginal role in today's clinical practice. Therefore, we focused on effects of high dose phytosterol supplementation in patients who does not tolerate statins or refused the statin therapy in clinical practice of general practitioners.

Methods:

Participants: We recruited volunteers from private offices of general practitioners in Slovakia. Inclusion criteria were dyslipidaemia based on criteria by latest ESC/ESH guidelines for management of dyslipidaemia [2] and documented history of statin refusal. Dyslipidaemia was diagnosed if LDL exceeded 3.0 mmol/l in low risk patients, 2.5 mmol/l in high risk and 1.8 mmol/l in very high risk subject. Patients with documented statin refusal were informed about benefits of statin treatment by their general practitioners and refused it before this study was conducted and before general practitioner was contacted by investigators. Their refusal were documented by informed consent. Subject with history of myocardial infarction or instable angina in past 12 months were excluded because they should take 80 mg of atorvastatin regardless of their LDL levels. We also excluded the patients after stroke or with documented ischemic heart disease or diabetes. Exclusion criteria were also current oncologic disease, malabsorption syndrome (Crohn's disease, celiac disease, chronic pancreatitis), not compensated hypothyreosis, cirrhosis, pregnancy, breastfeeding, drug or alcohol abuse and manifested psychosis. Military or law-enforcement employees were also excluded. Medical history of each subject was obtained from medical records and using questionnaire. All subject signed informed consent.

Study design: Volunteers were to took food supplement containing 800 mg of phytosterol (Zerochol®, Innoceutics, Belgium) twice a day for period at least 12 weeks. These supplements were provided to partients by manufacturer (Innoceutics, Belgium). Plasma total, LDL and HDL cholesterol and triacylglycerol concentrations were measured at the baseline, 4 weeks, 8 weeks and 12 weeks of supplementation therapy. Patients also self-reported any possible side effects of used food supplement. Cholesterol, TAG, LDL and HDL concentrations were determined by an enzymatic colorimetric method (Cobas Mira Plus, Roche Diagnostics GmbH, Montclair, NJ, USA). Blood samples for lipoprotein measurement were obtained after at least 12 hour of fasting. After the blood sampling, the samples remained for 30 minutes at room temperature and subsequently supernatant was separated by centrifugation for 10 minutes at 3,000 rpm. Food and physical activity questionnaire was used to exclude volunteers with significant diet or lifestyle changes during the study. The authors declare that the study was approved by the local Ethics Committee and was conducted in accordance with Declaration of Helsinki.

Statistical analysis: The descriptive data were provided as a mean values ± standard deviation. The Kolmogorov-Smirnov test was used to verify the normal distribution of parameters. Mean values of lipid parameters between study visits were compared using one-way analysis of variance (ANOVA) and Dennett's and Tukey's Multiple Comparison Test (as post-tests). A difference with the P-value of less than 0.05 was considered as statistically significant.

Results:

We recruited 94 patients (42 men, 52 women) with dyslipidaemia with prior statin intolerance or refusal from 28 general practitioners offices. Mean age of volunteers was 54,5 ± 12,20 and mean BMI was 28,8 ± 3,75. 45 patients had arterial hypertension and 19 patients smoked. 14 of all smokers had also arterial hypertension. 1 patient was excluded from final analysis because of discontinuation of supplementation after 4 weeks of treatment due to intolerance (diarrhea). No other adverse effects of phytosterol supplements were observed. Total cholesterol and mean LDL concentration dropped significantly in week 8 and 12 of supplementation therapy (tab 1., fig. 1, fig. 2). Mean TAG concentration also declined by weak 12, but this decrease was not statisticaly signifficant (tab. 1). We also observed mild increase of HDL concentration. However, this increase was not statistically significant (tab 1). 25 of 93 volunteers (26.88 %) reached the target values recommended by ESC/ESH guidelines for management of dyslipidaemia.

Discussion:

This study focused on the potential and efficiency of phytosterol supplements in treating the dyslipidaemia patient with history of statin intolerance or patients who refused to take statins despite the recommendations. Phytosterol supplementation represented 800 mg twice a day (1600 mg daily dose) in phytosterol food supplement tablets (Zerochol®, Innoceutics, Belgium). Phytosterol tablets significantly improved total cholesterol and LDL in 3 months. Mean LDL decreased by 17.37% of its basal concentration. This result is more optimistic than 10 % decrease observed than previous study using similar dose of plant sterols per day [9,11]. Despite this decrease, mean LDL remained over 3.0 mmol/l. 26.88 % of volunteers reached the LDL target values recommended by 2014 ESC/ESH guidelines for management of dyslipidaemia. From early statin trials we know that 20 mg of atorvastatin lead to 35% reduction and 40 mg of pravastatin to 23 % reduction of LDL in 52 weeks [12]. Based on our findings and findings of previous phytosterol studies we can conclude that the effectivity of phytosterol supplementation is inferior to statins. In our study TAG concentration and HDL concentration remain unchanged. This is consistent to finding of previous studies [9,10,11].

Despite well-known benefits of statins in primary cardiovascular prevention [3,4] more than one half of dyslipidaemia patients discontinue the statin therapy [7,8]. In population based study in Israel with data on more than 200 000 patients even about 75 % first-time statin treated patients discontinued the therapy in 3 years [8]. This discontinuation rates are much higher than can be explained by possible side effects, whereas their prevalence is believed to be much lover [5,6]. Most common side effect is myopathy presented as muscle pain or weakness and is reported in about 10% of statin treated individuals [6]. Significant amount of patients with dyslipidaemia in clinical practice refuse the statin treatment. Reason might be fear of possible side effects. Exact proportion of these patients in offices of general practitioner is yet to be determined. Although limited lipid-lowering efficiency of phytosterol supplementation therapy, it may provide benefit in individuals who cannot or whish not to be treated by statins. From statin trials we know that 10% decrease of LDL concentration leads to decrease of incidence of coronary heart disease by 20% over 5 years [13]. Large meta-analysis of more than 60 prospective studies suggest that 10% LDL concentration reduction decrease the cardiovascular mortality by 10% and all-cause mortality by 13%. This paper also stated than subjects with LDL concentration 1 mmol/l lower than mean concentration LDL levels reduce ischemic heart disease-related death by 50% from 40 - 49 years, 40% from 50-59 years, 30% from 60-69 years, and 20% from 70-79 years [16]. Based on these findings, we can conclude that effect of phytosterol supplement observed in our study may provide similar or even better benefit because of drop in LDL concentration exceeds 10%. Statin also changes distribution of LDL particles reducing amount of atherogenic small dense LDL subpopulation [14]. Same effect was also demonstrated using 4 g of phytosterol per day by Sialvera et al. [15].

Nevertheless phytosterol supplementation lacks data from studies with mortality or morbidity endpoints, so we can only hypothesize of their possible benefits. In animal model phytosterol demonstrated possible antiatherogenous effects besides lowering of LDL. Rabbits fed with atherogenous diet and phytosterol supplements had lover coronary atherosclerosis than control animals despite insignificant difference in plasma LDL concentration [17].

Phytosterol supplements are considered to be very safe and are usually well tolerated. Is believed that phytosterol dose up to 2 g per day possess no health risk at all [11]. Only one volunteer in our study discontinued the supplementation because of side effects. The volunteer experienced mild diarrhea which disappeared after he stopped the supplementation.

In this study, lipoprotein concentrations were measured 12 weeks since start of supplementation. Miettinen et al. demonstrated that after adding high doses of phytosterol to diet cholesterol concentration reaches plato in 12 weeks and remained on this level for at least one year [18]. Therefore we supposed that 12 weeks are sufficient to determine the effect of therapy.

Conclusion:

Adding of foot supplement containing 1600 mg of phytosterol to diet leads to significant reduction in total cholesterol and LDL concentration in 8 and 12 weeks. However their effect is inferior to effect of statins. Statins represents mainstay in management of dyslipidaemia and should be recommended to all patients which meats indication criteria for primary or secondary cardiovascular prevention. Phytosterol supplements added to lifestyle and diet changes might help to reduce cholesterol and LDL levels in patients with statin intolerance or patients who are refusing the statin treatment despite of proper recommendation. Major drawback of statin supplementation is lack of data from studies with hard endpoints, so its efficiency on reducing cardiovascular risk is yet to be determined.

Abbrevations:

BMI – body mass index, CK – creatin kinase, ESC/ESH – European Society of Cardiology/European society of Hypertension, HDL – high density lipoprotein, LDL – low density lipoprotein, TAG – triacylglycerol

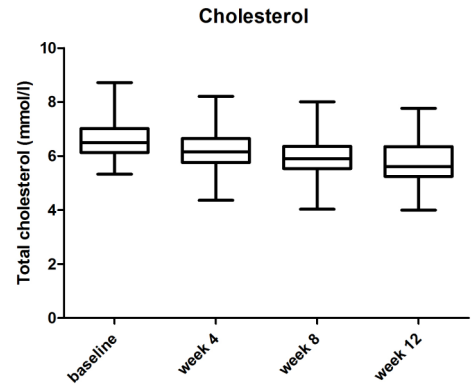
Competing interest:

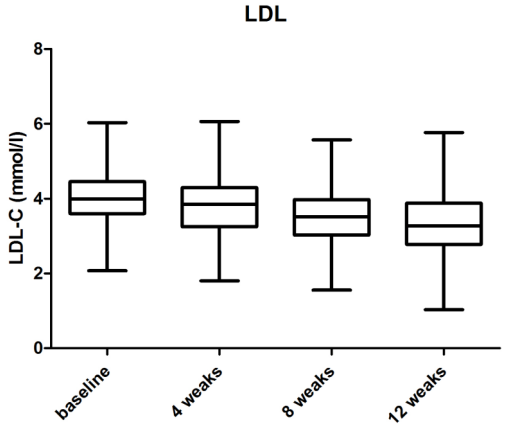
The authors declare that they have no competing interest.

Table 1: Effect of supplementation on lipid parameters

	Baseline	Week 4	Week 8	Week 12	P [ANOVA]
Cholesterol (mmol/l)	6.64 ± 0.757	6,23 ± 0.702*	5.97 ± 0.730*	5.793 ± 0.814*	< 0.0001
LDL (mmol/l)	4.03 ± 0.887	3.79 ± 0,891	3.49 ± 0.858*	3.33 ± 0.955*	< 0.0001
HDL (mmol/)	1.35 ± 0.413	1.39 ± 0.401	1.42 ± 0.418	1.46 ± 0.457	> 0.05
TAG (mmol/l)	2.31 ± 1.42	2.13 ± 1.34	1.98 ± 1.01	1.91 ± 0.960	> 0.05

* mean concentration is significantly different from baseline mean concentration ($p < 0.05$)





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