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SLCO1B1 Polymorphism is not associated with Risk of Statin-Induced Myalgia/Myopathy in a Czech Population

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Background: Gene *SLCO1B1*, encoding solute organic anionic transport polypeptide OATP1B1, belongs to the group of candidates potentially influencing statin treatment safety. OATP1B1 regulates (not only) the hepatic uptake of statins. Its genetic variation was described as an important predictor of statin-associated myopathy in a cohort of patients treated with a maximum dose of simvastatin. However, the impact of *SLCO1B1* gene polymorphism on this risk in patients treated with other statins or lower doses of simvastatin needs to be assessed. Therefore, we performed the present study.

Material/Methods: *SLCO1B1* tagging rs4363657 polymorphism was analyzed in 2 groups of patients with dyslipidemia (treated with simvastatin or atorvastatin, 10 or 20 mg per day), subgroup with statin-induced myalgia (N=286), and subgroup (N=707) without myalgia/myopathy, and in 2301 population controls without lipid-lowering treatment.

Results: Frequency of the individual genotypes in patients with myalgia/myopathy (TT=62.3%, CT=34.5%, CC=2.8%) did not significantly differ (both P values over 0.19) from that in patients without muscle symptoms (TT=61.4%, CT=32.9%, CC=5.7%) or from the population controls (TT=63.9%, CT=32.5%, CC=3.6%). Null results were also obtained for the dominant and recessive models of the analysis.

Conclusions: In Czech patients treated with low statin doses, there is no association between *SLCO1B1* gene polymorphism and risk of myalgia/myopathy.

MeSH Keywords: Hydroxymethylglutaryl-CoA Reductase Inhibitors • Muscular Diseases • Polymorphism, Genetic

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2079 3 — 24

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Background

Dyslipidemia (together with smoking, diabetes, obesity, and hypertension) is a common risk factor of cardiovascular disease. Lowering plasma lipid levels reduces the risk of vascular events significantly.

Statins are widely used drugs for treatment of high plasma total and LDL cholesterol levels. Statins inhibit the key enzyme of cholesterol synthesis, 3-hydroxy 3-methylglutaryl coenzyme A reductase, and effectively reduce the dyslipidemia and global cardiovascular risk [1].

Statin use is associated with a number of undesirable side effects, myopathies and myalgias being most frequent and clinically important [2]. The frequency of statin-associated myopathy is reported to be 1–2% in clinical trials, but reaches 15–20% in everyday clinical practice. Because of the increasing number of patients treated with statins (almost 50% of individuals older than 65 years in the US are on statins), the number of patients at risk of statin-associated myopathy may reach the millions in Western countries [3].

There are significant interindividual differences in statins tolerability and it is likely that these differences have a genetic background [4]. One of the possible candidates contributing to the development statin-associated myopathy may be common variants within the solute carrier organic anion transporter *SLCO1B1* [5].

SLCO1B1 (alternative former name *SLC21A6*, OMIM acc. No. 604843), encoding organic anionic transport polypeptide OATP1B1, mediates absorption of various drugs (including statins) by hepatocytes, and its polymorphisms (rs4363657 and rs4149056) influence the clearance of statins from circulation [6,7]. OATP1B1 is a 691-amino acid transmembrane receptor, a member of the organic anion transporter family, which is expressed exclusively in the liver. Intronic rs4363657 variant, originally detected by the SEARCH group, is in almost complete linkage disequilibrium with rs4149056. For alleles at this position, 2 common alleles are c.521T and c.521C, Val174 and Ala174; and 2 rare alleles are c.521A, Glu174 and c.521G, Gly174). The SEARCH investigators demonstrated that carriers of the minor C allele had higher plasmatic concentrations of statins in comparison with common TT homozygotes. This explained the observed substantial increase in the risk of SAM in subjects treated with simvastatin (80 mg daily) who were followed within the SEARCH project. Thus, it was concluded that the *SLCO1B1* gene polymorphism is a significant risk factor increasing by 4.5-fold the risk of statin-associated myopathy per single C allele. However, in the SEARCH study, only 85 patients with SAM and 90 controls were included, all of them taking a maximum dose of simvastatin 80 mg a day [6,7].

Thus, we studied the impact of *SLCO1B1* gene variant on the risk of SAM development in a large population of Czech patients treated with lower doses of commonly used statins.

Material and Methods

Patients with myalgia/myopathy

During the enrollment period, between April 2010 and July 2014, adult patients (N=286) treated with statins who developed statin-associated myopathy were identified and their charts were collected at the Lipid Clinics of the 3rd Department of Internal Medicine of the 1st Faculty of Medicine, Charles University and at the Institute for Clinical and Experimental Medicine, Prague, the Czech Republic. Definition of statin-associated myopathy was based on the criteria described elsewhere [2]. Basic characteristics of the patients are summarized in Table 1.

Control patients on statin treatment

During the same time period and at the identical clinics, 707 patients with primary dyslipidemia on statin treatment but without myalgia were included.

For both groups, patients taking low doses of simvastatin (41%) or atorvastatin (59%) of 10 (~90% of individuals) or 20 mg/day were considered eligible for the study [8,9]. Patients treated with fluvastatin and rosuvastatin were not included in the study, as pharmacokinetics of these statins seems not to be markedly influenced by OATP1B1 [6,10]. Basic characteristics of the control patients are summarized in Table 1.

Control general population

The control group was selected from the original Czech post-MONICA cohort of 2559 individuals, (1191 males and 1358 females) [11,12]. Only subjects from this general population sample without lipid-lowering treatment and/or dietary interventions were included to our study (N=2301; average age 48.2±10.8 years). Basic characteristics of the control population are summarized in Table 1.

All participants of the study were of Caucasian ethnicity.

Written informed consent was obtained from all the study participants prior to any study-related procedure. The local ethics committee approved the conduct of the study, respecting the rules of the Declaration of Helsinki of 1975.

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Table 1. Basic characteristic of analyzed individuals.

	Patients		Population control
	With myopathy	Without myopathy	
N	286	707	2,301
% of males	36.3	34.1	45.6
Age	63.5±13.2	60.2±14.1	48.2±10.8
Plasma cholesterol (mmol/l)	7.2±1.6	7.5±1.8	5.8±1.1
Diabetes (%)	22.5	20.1	6.9
Smoking (%)	28.7	28.1	27.2
Obesity (%)	31.2	32.9	29.9

Genotype analysis

The DNA was isolated using the standard salting-out method from 3 milliliters of whole EDTA blood. Rs4363657 variant was genotyped using the nested polymerase chain reaction (PCR) and restriction analysis as described in details before [13].

Analysis of plasma lipids

The lipoprotein parameters in fasting plasma samples were assessed using autoanalyzers and conventional enzymatic methods with reagents from Boehringer Mannheim Diagnostics and Hoffmann-La Roche in CDC Atlanta-accredited local laboratories.

Statistical analysis

The Hardy-Weinberg test (*http://www.tufts.edu/~mcourt01/Documents/Court%20lab%20-%20HW%20calculator.xls*) was applied to confirm the independent segregation of the alleles. Chi-square test (*http://www.physics.csbsju.edu/cgi-bin/stats/contingency_form.sh?nrow=2&ncolumn=3*) was used for the analysis of the differences between genotypes.

ANOVA for adjustments (BMI, age, smoking) was used for statistical analysis of the association between the SNP and plasma lipids (in the control population only).

Results

The call rates (% of the successfully analyzed genotypes) were 98.5% for controls, 98.3% for patients presenting with statin-associated myopathy, and 97.2% for patients without any undesirable side effects of statins. Within all 3 groups, genotype distributions were within the H-W equilibrium (P=0.23 for patients with myalgia/myopathy P=0.21 for patients without myalgia/myopathy, and P 0.33 for controls). Minor allele frequency within the controls (19.9%) was similar to the frequencies found in other Caucasians and is among the highest in Europe [14,15].

We did not detect an association (all P values over 0.52, adjustment for BMI, smoking and age did not influence the results noticeably) between the *SLCO1B1* polymorphism and plasma lipids in controls (Table 2). This suggests that the possibility that patients with a distinct genotype would be more likely to receive a statin is rather unlikely.

Using the codominant model (TT *vs.* TC *vs.* CC) for the analysis, we did not detect different frequencies of the *SLCO1B1* genotypes between the patients who developed statin-associated myopathy (P<0.67) and population controls. Similarly, no differences were found between the patients who developed statin-associated myopathy and the patients on statins but without a history of statin-associated myopathy (P<0.19). The same null results were obtained when either the dominant or the recessive models were used (all P values over 0.08, without correction for multiple testing) for comparison. For more details for frequencies and corresponding ORs and 95% CI, see Table 3.

Discussion

Statins are definitely the most commonly prescribed lipid-lowering drugs today. Despite the relative low risk of undesirable side effects of statins, the very high statin prescription rate results in an increasing absolute number of patients presenting with adverse reactions.

In our study, the relatively high frequency of statin-associated myopathy among the patients compared to the literature can be explained by the fact that the study sites serve as tertiary centers for management of dyslipidemia and, thus, there might be overrepresentation of patients prone to adverse effects.

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Table 2. *SLCO1B1* polymorphism (s4363657) and plasma lipids in control population.

	TT	TC	CC
Males			
N	667	332	44
TC	5.76±1.08	5.70±1.04	5.74±1.04
LDL-C	3.66±0.94	3.63±0.94	3.73±0.95
TG	1.99±1.34	1.87±1.09	1.74±0.81
HDL-C	1.23±0.35	1.24±0.34	1.22±0.34
Females			
N	782	404	38
TC	5.77±1.15	5.79±1.18	5.60±1.08
LDL-C	3.61±1.02	3.62±1.07	3.49±0.98
TG	1.43±0.78	1.50±0.87	1.38±0.94
HDL-C	1.51±0.37	1.48±0.36	1.48±0.35

All values are in mmol/l. All P values were higher than 0.56 for the codominant model of the analysis. Adjustments for BMI, smoking and age did not influence the results noticeably.

Table 3. Genotype (for rs4363657) distributions within the analyzed groups. No significant differences between patients with myalgia/myopathy (M/M) and two control groups were detected in any model of the analysis (recessive, codominant or dominant).

	Controls		Patients with (+) MM		Patients without (–) MM		OR (95% CI) C *vs.* +MM	OR (95% CI) +MM *vs.* –MM
	N	%	N	%	N	%		
T/T	1449	63.9	176	62.6	422	61.5	1.00	1.00
T/C	736	32.5	97	34.5	226	32.9	1.08 (0.83–1.41)	1.02 (0.77–1.38)
C/C	82	3.6	8	2.9	38	5.5	0.78 (0.37–1.63)	0.51 (0.23–1.10)

Undesirable side effects of statins (most importantly myalgia/myopathy) have a significant genetic component [2] and genes for CYP2C8, UGTs, and RYR2 have been suggested to be partially responsible for SAM development.

Another promising candidate gene for predicting risk of statin-induced muscle damage is the *SLCO1B1* gene and its tagging variants. Interestingly, the frequency of the minor allele (associated with low activity) varied markedly between ethnicities [16] with highest frequency observed in Caucasians (~17%) and lowest (~3%) in Africans.

Studies focused on the rs4363657 and rs4149056 variants within the *SLCO1B1* gene have addressed 2 major questions. Firstly, is there an association between this variant and statin treatment efficacy? Secondly, does the risk of statin-associated myopathy depend on the SLCO1B1 genotype? Our study focused on the second question.

The first study on this topic [5] described the carriers of 1 minor risky C allele as having 4.5 times higher risk of development of myopathy once treated with maximum doses of simvastatin (80 mg per day). However, treatment with such a high dose cannot be considered usual standard of care, as shown by reports from a real-world setting [17]. Subsequent studies have analyzed patients on other statins at significantly lower doses. This heterogeneity of the studies makes it difficult to directly compare published results. There are even studies analyzing the SLCO1B1 variants in patients on rosuvastatin [18], despite the fact that metabolism of this statin is not mediated through this protein [10].

We have searched the literature published on the topic so far and have identified some confirmatory studies. Most of them (reviewed by [3]), but not all [19], suggest a possible association between *SLCO1B1* variants and statin-associated myopathy/myalgia.

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The results from the go-DARTS study [20] confirm the original finding of positive association of the minor *SLCO1B1* allele with higher susceptibility to statin intolerance (defined by serum parameters, discontinuation, and switching or dose reduction).

A very small study (25 patients with severe myopathy) described possible risk of myopathy based on *SLCO1B1* in patients on simvastatin, but not in patients receiving atorvastatin [21].

In contrast, the authors of the Rotterdam study documented exactly the opposite, reporting that atorvastatin users were at greater risk of needing to switch statins and/or adjust the dose [22].

A positive association between *SLCO1B1* and SAM was described in a heterogeneous group of patients randomized to low doses and subsequently titrated to maximal doses of atorvastatin, pravastatin, and simvastatin [23]. Moreover, the same gene polymorphism has been implicated as a significant risk factor of cerivastatin-induced rhabdomyolysis, increased frequency of which led to its withdrawal from the market [24].

In our study, we did not detect an association between *SLCO1B1* variant and statin-associated myopathy. There are some plausible explanations for this observation. First, despite many guidelines on treatment of dyslipidemia and the use of statins, we still lack a single clear and universally accepted definition of statin-associated myalgia/myopathy. Therefore, studies on the topic published so far have used rather heterogeneous criteria for assessment of SAM, which makes comparison of the results difficult [2,3]. Further, there are 6 commonly used statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin), with substantial differences in their pharmacokinetics. This in turn leads to conflicting results of genetic studies on the susceptibility to SAM, because a particular genetic polymorphism may influence transport or metabolism of a particular statin, while others remain less affected or even unaffected. Secondly, because SAM seems to be at least partly dose-dependent, dosage is an important modulator of SAM development. Our patients had been on low doses of 2 statins – atorvastatin or simvastatin. Therefore, slowing the metabolic rate increases the average concentration of the statins in plasma could still lead to submaximal (and safe) final levels of the drugs in these patients. Importantly, it has not been postulated at which concentration of statins myalgia/myopathy is triggered in plasma. Thirdly, we detected higher frequency of the minor "risky" allele in our Slavonic population, suggesting possible genetic differences between populations, and it cannot be excluded that the interaction between *SLCO1B1* and some other gene(s) (e.g., apolipoprotein E or RYR2 receptor) (2) might be more important. Patient adherence/compliance to therapy is another factor, which can significantly shift the outcome in a negative direction. Another crucially important issue is the statistical power of the published studies. Because statin-induced muscle problems are not very common, anywhere between several dozen to several hundred affected individuals usually have been examined. Due to their lower number of subjects, the published studies could be prone to false-positive results. Lastly, but not least, some publication bias also needs to be taken into account because it is likely that some negative findings were not published.

Despite the fact that original studies on the effect of *SLCO1B1* and SAM are rather heterogeneous and usually small (thus enhancing the risk of false-positive/negative results), there have been more reviews than original papers published on this topic [3,4,16,25]. Furthermore, statins are not the only risk factor associated with myopathy, and there have been no studies focusing on possible interactions with sex, other drugs used, and other known risk factors of SAM. The published studies also do not allow (except for the maximum doses of simvastatin) classifying the risk for different statin types and doses. Thus, it is actually impossible to make a final recommendation on SLCO1B1 and statin-induced myalgia/myopathy.

Conclusions

In Czech dyslipidemic patients treated with low statin doses, there is no effect of *SLCO1B1* tagging polymorphism on the risk of statin-associated myopathy.

Conflict of interest

The authors declare that they have no conflicts of interest.

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