Austin Journal of Cardiovascular Disease and Atherosclerosis

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Austin Publishing Group

Research Article

Apolipoprotein E Polymorphism is not Associated with Statin Induced Myalgia/Myopathy

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Received: November 25, 2014; **Accepted:** February 17, 2015; **Published:** February 19, 2015

Abstract

Statin treatment is the most commonly used way to lower plasma cholesterol levels and prevent cardiovascular disease. The variability of the lipid response seems to be dependent on *APOE* variant and carriers of *APOE4* allele are less responsive to statins than others. As the potential mechanism of such effect is unclear, we hypothesise, that *APOE4* carriers could be more prone to the statin side effect, leading to the lower compliance, causing the false effect of lower efficacy. We have successfully genotyped 621 adult patients treated with statins (166 with myalgia/myopathy) and 667 population controls. As expected, carriers of the *APOE4E3* and *APOE4E4* genotypes were more common among the patients (25.0% vs 16.6%, P < 0.0005). However, the frequencies of the individual *APOE* genotypes were identical within the groups of patients on statins with and without the myalgia/myopathy (P = 0.99 for codominant model of the analysis). We conclude that it is very unlikely that the lower efficacy of statins in patients with *APOE4* allele is a consequence of the higher risk of statin induced side effects in these patients.

Keywords: Apolipoprotein E; Polymorphism; Cholesterol; Treatment; Statin; Myopathy/Myalgia

Introduction

High levels of plasma total- and/or LDL - cholesterol are an independent risk factor for cardiovascular disease [1].

As majority of the patients do not respond sufficiently to the lifestyle interventions (most commonly some dietary restrictions and enhanced physical activity), the pharmacological treatment is the usual way to achieve recommended target lipid levels, and statins (inhibitors of the 3-hydroxymethyl glutaryl coenzyme A reductase, the key enzyme in the biosynthesis of the cholesterol) are the drugs of first choice in this case [2]. High interindividual response variability among individuals treated with the equipotent doses was observed [3], and it has been estimated that up to 70% of the effect of statins is attributable to genetic variation [4] with many other important confounders - e.g. sex, age, physical activity, alcohol intake, or type of diet consumed.

The effect of the common variants within the apolipoprotein E (*APOE*, gene ID 348, OMIM acc. no. 107741) on plasma cholesterol are consistent over all so far analysed populations. Carriers of the *APOE4* (Cys112 → Arg, rs429358) allele have higher total cholesterol levels, while *APOE2* (Arg158 → Cys, rs7412) allele carriers have lower cholesterol in comparison to the most common *APOE3E3* homozygotes [5].

Because of these facts, many pharmacogenetic studies focused on the potential impact of the common *APOE* variants on statin treatment efficacy.

Despite some inconsistency among the studies (almost half of the studies found no effect), *APOE4* carriers seems to have poorer response to statin treatment and individuals with the *APOE2* allele appear to profit more from the treatment (rewieved by [6]).

These differences could have (so far unknown) physiological background or, more simply, could reflect the association between the *APOE* genotype and statin induced undesirable effects, going hand in hand with lower compliance to statin therapy. A large meta-analysis of almost 80 000 patients, provide the results that statin treatment is associated with low, however, not negligible risk of undesirable side effects [7]. The most frequent side effect in statin treated patients is myopathy [8] that occurs in different forms (myalgia, myositis, rhabdomyolysis) in 3 - 10% of patients. A significant contribution of genetic background to individual susceptibility for undesirable effects of statins is certain [4].

There has been so far also just one published study focusing on the possible effect of the *APOE* on the statin compliance [9]. Among almost 800 patients treated with statins, individuals carrying the *APOE4* allele were under more than double risk to discontinue their drug use. One reason for this fact could be the lower effectiveness associated with this allele. Another possibility could be a different susceptibility to side effects in *APOE4* carriers. However, to our knowledge there is no direct study on the topic of adverse effects of statins and *APOE* polymorphism published.

We have analysed *APOE* variant in a group of the patients treated with statins, with part of them developing the myopathies.

Materials and Methods

Patients with primary dyslipidemia indicated to statin treatment were retrospectively selected from databases of Lipid Clinics of the 3rd Department of Internal Medicine of the 1st Faculty of Medicine, Charles University and the Institute for Clinical and Experimental

Citation: Hubacek JA, Schwarzova L, Zlatohlavek L, Adamkova V, Ceska R and Vrablik M. Apolipoprotein E Polymorphism is not Associated with Statin Induced Myalgia/Myopathy. Austin J Cardiovasc Dis Atherosclerosis. 2015;2(1): 1009.

Table 1: Basic characteristic of analyzed individuals.

	Patients		Population control
	With myalgia/myopathy	Without myalgia/myopathy	
N	166	455	667
% of males	38.6	43.3	40.3
Age (years)	62.9 ± 13.1	60.5 ± 13.8	62.0 ± 3.5
Total cholesterol (mmol/l)	7.1 ± 1.6	7.4 ± 1.8	5.8 ± 1.0
Diabetes (%)	22.3	19.9	17.7
Smoking (%)	29.6	28.3	16.2
Obesity (%)	31.6	32.7	45.1

No significant differences have been detected between the patients with and without myalgia/myopathy.

Table 2: Distribution of the apolipoprotein E genotypes in analyzed groups.

APOE	Patients with myopathy/myalgia		Patients without myopathy/myalgia		Controls	
genotype	N	%	N	%	N	%
Total	166		455		667	
E2/E2	1	0.6	7	1.5	3	0.5
E3/E2	9	5.4	20	4.4	81	12.1
E3/E3	111	66.9	306	67.3	461	69.1
E4/E3	38	22.9	102	22.4	103	15.4
E4/E4	4	2.4	11	2.4	8	1.2
E4/E2	3	1.8	9	2.0	11	1.7

Both groups of patients significantly differ from the controls (P = 0.005 and P = 0.0005). Distribution of the *APOE* genotypes was almost identical within the patients treated with statins with and without the myalgia/myopathy (P = 0.99, if E2/E2 + E3/E2 vs. E3E3 vs. E4/E3 + E4/E4 were compared).

Medicine, Prague, the Czech Republic [10]. Six hundred thirty eight adult patients were included, average age 58.5 ± 12.6 years (261 males) (for more details, see Table 1). Patients taking simvastatin (45.6%), atorvastatin (42.0%) and lovastatin (12.4%) in doses of 10 (~90% of individuals) or 20 mg/day were enrolled in the study. We did not include subjects on combination lipid-lowering therapy (e.g. statin-fibrate, statin-ezetimibe ...). The individuals fulfilling the clinical and laboratory criteria of familial hypercholesterolemia were not included in the study. Criteria for the definition of statin induced adverse effect (myalgia/myopathy) were used as described in details elsewhere [8] and were based on self reported muscle problems resolving with the interruption of therapy, elevation of CK over 5x upper normal limit and family history of myalgia/myopathy.

As a population control group, a subset of the Czech post-MONICA study (675 individuals, upper age quartile of the entire population) was used [11] (Table 1).

All participants of the study were of Caucasian ethnicity from the Central European Czech population. Written informed consent was obtained from all the study participants and the local ethics committee approved the design of the study according to the Declaration of Helsinki of 1975.

Three millilitres of whole blood collected into EDTA tubes for DNA isolation were stored at -20˚C. The DNA was isolated using the standard salting out method [12]. *APOE* gene fragment with two polymorphisms was genotyped using PCR – RFLP method as described in more details elsewhere [13].

The Hardy-Weinberg test was applied to confirm the independent segregation of the alleles. Genotype frequencies between the examined groups were compared individually (using www tool http://www.physics.csbsju.edu/cgi-bin/stats/contingency_form.sh?nrow=2&ncolumn=3) for each polymorphism in 6x2 table and each genotype with the rest of the group in 2x2 table. Distinct combinations pooling together i) carriers of the *APOE2/E2* and *APOE2/E3* genotypes ii) *APOE4/E3* and *APOE4/E4* genotypes and iii) *APOE3/E3* homozygotes (in this case *APOE2/E4* heterozygotes were omitted and 3x2 table was used for the analysis) have been used.

As there have been no significant differences in age, gender, and prevalences of obesity, smoking and diabetes between the patients with and without statin induced myalgia/myopathy, no adjustments have been performed.

Results and Discussion

Hardy-Weinberg test confirmed independent segregation of individual alleles in both groups. The call rate for the *APOE* polymorphism was very high in both groups – 97.3% for the patients and 98.8% for the controls resulting with 166 patients with myopathy/myalgia, 455 patients without myopathy/myalgia and finally with 667 controls.

In the control population, the APOE allelic (E2 = 7.3%, E3 = 82.9% and E4 = 9.7%) and genotype frequencies were fully comparable with the so far published frequencies obtained in other Caucasian populations [14]. No gender differences in genotype frequencies were observed either in the patients or in controls (data not shown in details).

As expected the carriers of the APOE4 allele were significantly

more prevalent in the patients (as patients on statins have higher plasma lipids) than in the controls (25.0% vs. 16.6%, P < 0.0005) (Table 2). Within the patients treated with statins, the frequencies of the individual genotypes were almost identical (P = 0.99 for codominant model of the analysis) in a subgroup with and without myopathy/myalgia (Table 2). Also other models of the analyses (dominant or recessive) reveal no significant differences (not shown in details). This result almost excludes the possibility, that variants within the apolipoprotein E gene could be significant predictors of statin induced myalgia/myopathy.

Thus our theory that *APOE4* carriers have lower compliance, due to the higher frequency of undesirable side effects than others, seems not to be valid. A large number of gene polymorphisms has been implicated as potentially causal in the development of adverse effects of statins [8,15]. However, most studies assessing impact of genetic background on statin induced adverse effects suffer from the lack of sufficient power (some of them reviewed by [16]). Major issues concern the insufficient number of patients included (as a consequence of the relative low frequency of this condition) and substantial heterogeneity of concomitant treatment as well as study population selection. The interest of medical community in the understanding of the genetic determination of statin adverse effect is obvious. Compared to common biochemical assays analysis of the genetic information yields steady results at relatively low cost and a very robust reproducibility.

In our pilot study, we have detected identical distribution of the common six *APOE* genotypes between the patients treated by statins with and without myalgia/myopathy. Despite the relative low number of included individuals, there is little reason to consider the use of *APOE* genotyping as a predictor of statin induced myalgia/myopathy.

6. Acknowledgement

This study was supported by projects No. NS 11307-5 (IGA MH CR) and by the project (Ministry of Health, Czech Republic) for development of research organization 00023001 (Institute for Clinical and Experimental Medicine, Prague, Czech Republic) – Institutional support.

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Austin J Cardiovasc Dis Atherosclerosis - Volume 2 Issue 1 -2015
ISSN: 2472-3568 | www.austinpublishinggroup.com

Citation: Hubacek JA, Schwarzova L, Zlatohlavek L, Adamkova V, Ceska R and Vrablik M. Apolipoprotein E Polymorphism is not Associated with Statin Induced Myalgia/Myopathy. Austin J Cardiovasc Dis Atherosclerosis. 2015;2(1): 1009.