

Influence of Apolipoprotein E Geno-Type on the Response to Simvastatin Treatment in Patients with Hyper-Cholesterolemia

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Summary

The genetic variation of the apolipoprotein E (apo E) locus has a significant impact on the lipoprotein profile and on the expression of disorders in lipoprotein metabolism. Moreover, in hyperlipidemic subjects, the response to dietary change and to therapy with hypolipidemic agents may be influenced by apo E genotype. The aim of the present study was to compare the response to therapy with the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor simvastatin between hypercholesterolemic patients with distinct apo E genotypes. 53 male and female patients with heterozygous familial hypercholesterolemia were included in the study. Simvastatin was taken in a daily dose of 10 mg for 12 weeks. Patients that carry the apo E 4 allele (genotypes E 3/4 and E 4/4) were less responsive to simvastatin treatment than subjects with the genotypes E 3/3, E 2/3, and E 2/2 with respect to total and LDL-cholesterol. No differences were found regarding HDL-cholesterol.

Introduction

In hyperlipidemic patients, the response to lipid-lowering therapy including diet and hypolipidemic agents shows considerable individual variation. It can be assumed that at least some of this variability is due to

mutations at specific gene loci. Potential gene loci include apolipoprotein E (apo E). In humans, apo E is coded by three different alleles at a single locus on chromosome 19, whose products (apo E 2, apo E 3, apo E 4, respectively) give rise to six apo E phenotypes (1).

It has been established that genetically determined apo E polymorphism is one of the major factors affecting plasma lipoprotein levels and postprandial response of lipoproteins (2, 3). Moreover, apo E genotype appears to modulate the association between plasma lipoproteins and lifestyle-related factors (4, 5). An increased prevalence of apo E 4 was found in angiographically verified coronary patients (6). Several studies have indicated that subjects that carry the apo E 4 allele are more responsive to dietary modification with respect to LDL-cholesterol changes than are subjects who carry the apo E 3 and apo E 2 allele. The opposite seems to be true regarding the responsiveness to therapeutical interventions with HMG-CoA reductase inhibitors, but practical implications remain to be explored (7, 8).

The objectives of the present study were to compare the response to therapy with the HMG-CoA reductase inhibitor simvastatin between both male and female hypercholesterolemic patients with different apo E genotypes.

Materials and Methods

The study group consisted of 53 patients (21 men and 32 women, mean age 53 and 57 years, respectively) with heterozygous familial hypercholesterolemia. Subjects visited the Department of Internal Medicine IV of the University of Leipzig. All patients had received dietary advice about prudent diet, and were stabilized on this regimen when therapy with the HMG-CoA reductase inhibitor simvastatin (daily dose of 10 mg for 12 weeks) was introduced.

Blood samples were taken after an overnight fast. Apo E genotyping was carried out by means of analyzing polymerase chain reaction products performed by restriction fragment-length polymorphism analysis. The amplification products were digested with the restriction endonuclease *Hha* I, and the digested samples were electrophoresed through a polyacrylamide gel (9, 10). Multiple regression models were built to analyze the association between genotypes and lipids/lipoproteins as well as to predict mean changes of lipoprotein values for several genotypes.

Results

Predicted values of percent changes of serum total cholesterol, LDL-cholesterol, and HDL-cholesterol for different apo E genotype groups are presented in Table 1. After 3 months simvastatin therapy, the decrease in

Table 1. Predicted percent changes of total cholesterol, LDL-cholesterol, and HDL-cholesterol after simvastatin therapy in dependence on apo E genotype

	Apo E genotype	Changes of concentration (%)	95 % Confidence interval
Total cholesterol	E 2/2 and E 2/3	- 26.5	- 56.6; 3.9
	E 3/3	- 21.9	- 51.3; 7.2
	E 3/4 and E 4/4	- 10.0	- 40.7; 20.6
LDL-cholesterol	E 2/2 and E 2/3	- 35.9	- 76.1; 4.3
	E 3/3	- 30.5	- 69.3; 8.4
	E 3/4 and E 4/4	- 12.2	- 53.5; 29.1
HDL-cholesterol	E 2/2 and E 2/3	- 1.8 *	- 42.9; 39.6
	E 3/3	- 0.9 *	- 40.9; 39.0
	E 3/4 and E 4/4	2.8 *	- 38.8; 44.4

* non significant

serum total cholesterol and LDL-cholesterol among the apo E genotype groups was different, being greater in patients with the genotypes apo E 2/2, E 2/3, and apo E 3/3 in comparison with the genotypes apo E 3/4 and apo E 4/4. No differences were found with respect to HDL-cholesterol.

Conclusions

The results of the present study indicate that the apo E genotype appears to affect not only plasma lipoprotein profile and postprandial response of lipoproteins but also the degree of total and LDL-cholesterol responsiveness to HMG-CoA reductase inhibitor therapy. It is known that apo E 4 has a higher affinity for the apo E receptor in comparison with apo E 3 and apo E 2. For this reason it could be postulated that apo E 4 may result in a more rapid uptake of triglyceride rich particles including cholesterol by the liver, resulting in the observed diminished responsiveness to therapeutical intervention in patients with the genotypes apo E 3/4 and apo E 4/4.

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