Response to the Letter by Singh et al Regarding “Apolipoprotein Isoform E4 Does Not Increase Coronary Heart Disease Risk in Carriers of Low-Density Lipoprotein Receptor Mutations”

In our article, we show less increased coronary heart disease (CHD) risk in familial hypercholesterolemia (FH) patients with a low-density lipoprotein receptor (LDLR) mutation and with the APOE4/E4 genotype.1 We give several possible explanations, including decreased trapping at the surface of hepatocytes when fewer LDL receptors are available. These scenarios could have been accompanied by higher serum ApoE levels, compared with the earlier described lower ApoE levels in APOE4/E4 genotyped individuals.2 However, in the present study, we did not measure serum ApoE levels. ApoE levels could have given a clue for the biological explanation for the inversed relationship between APOE4/E4 and CHD risk in FH patients with an LDLR mutation. On the other hand, in most studies, serum ApoE levels correlate strongly with serum lipid levels. We could not detect effects of APOE genotypes on lipid levels within the groups with and without LDLR mutation.

Analyses of a potential role of other members of the APOE/APOC1/APOC2/APOC4 gene cluster is, in our opinion, beyond the scope of this study. Moreover, a recent fine-mapping study of this region after genome-wide association study results concluded that of the above-mentioned genes the APOE4-defining polymorphisms had the strongest effect on serum lipid levels.3

In conclusion, we did not measure serum ApoE levels, so we cannot rule out that these are an intermediate trait in the relationship between APOE genotype, LDLR mutation, and CHD risk. We agree that this would be interesting to test in a follow-up study to further unravel the molecular biological mechanisms underlying this relationship.

Disclosures

None.

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