

On the Mechanisms by Which Human Apolipoprotein A-II Gene Variability Relates to Hypertriglyceridemia

To the Editor:

A recent issue of Circulation contained an interesting study by van’t Hooft et al reporting a novel functional polymorphism (a T to C substitution at position −265) in the promoter of the apolipoprotein A-II (apoA-II) gene. ApoA-II is the second quantitatively major protein component of HDL. In the above-mentioned study, the −265C allele was associated with decreased plasma apoA-II concentration, increased postprandial metabolism of large VLDL, and decreased waist circumference in healthy 50-year-old men.

Important and rather surprising advances in our understanding of the role of apoA-II have been reported recently and have mainly been produced by analyses of genetically modified mice. In line with the findings of van’t Hooft et al, these advances revealed a consistent relationship of apoA-II with non-esterified fatty acids (NEFA) and VLDL triglyceride plasma concentrations. However, whether apoA-II variability causes increased VLDL synthesis, decreased VLDL catabolism, or both remains a matter of controversy.

We recently studied human apoA-II-transgenic(Tg)-mice and control C57BL/6 mice fed a Western high-fat diet (TD 88137, Harlan Teklad) for 32 weeks. As in previous studies, fasting cholesterol, triglycerides, and NEFA concentrations were increased in human apoA-II-Tg-mice. We performed oral fat tolerance tests in these mice after oral administration of 100 μL of olive oil. The area under the curve (AUC) of triglyceride metabolism did not differ (0.85 ± 0.08 pools/h in transgenic mice versus 0.99 ± 0.12 pools/h in control mice).

In our article, we reported an association between the −265T/C polymorphism in the promoter of the human apolipoprotein A-II (apoA-II) gene and the postprandial concentration of large VLDL particles. In line with the findings of van’t Hooft et al reporting a novel functional polymorphism (a T to C substitution at position −265) in the promoter of the apolipoprotein A-II (apoA-II) gene, we proposed that the plasma triglyceride concentration in transgenic mice and control mice; P < 0.05) because triglyceride catabolism did not differ (0.85 ± 0.08 pools/h in transgenic mice versus 0.99 ± 0.12 pools/h in control mice).

These data contrast with the interpretation of van’t Hooft et al, who suggested that apoA-II polymorphism is associated with enhanced postprandial VLDL clearance. In our opinion, the effect of the human apoA-II polymorphism found in our study could also be reinterpreted as the result, at least in part, of decreased postprandial VLDL synthesis which could be due to, for example, decreased postprandial NEFA levels in plasma of individuals with the −265C allele. In this context, we would like to know whether the authors measured postprandial NEFA levels in transgenic mice and control mice.

In view of the inherent limitations of our human studies, it is not possible to rule out the possibility of decreased synthesis being a mechanism implicated in our findings. Clearly, it is more appropriate to address this question using genetically modified mice, and the preliminary data reported in the letter from Julve et al may provide an excellent starting point to resolve this issue.

Ferdinand M. van’t Hooft, MD, PhD
Giacomo Ruotolo, MD, PhD
Susanna Boquist, MD, PhD
Ulf de Faire, MD, PhD
Gösta Eggertsen, MD, PhD
Anders Hamsten, MD, PhD
King Gustaf V Research Institute
Karolinska Hospital, Stockholm, Sweden

Fernando upcoming issue


Josép Julve, PhD
Francisco Blanco-Vaca, MD, PhD
Joan Carles Escolá-Gil, PhD
Hospital Santa Creu i Sant Pau
Servei de Bioquímica
Barcelona, Spain


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Josep Julve, Francisco Blanco-Vaca and Joan Carles Escolà-Gil

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