**Apolipoprotein E and coronary artery disease: the debate is still on**

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Apolipoprotein E (Apo E) is quite a fascinating lipoprotein. As reported by Zou et al. in this issue of the *Journal of Geriatric Cardiology*, Apo E has three isoforms, ε2, ε3, and ε4, differing from each other by the polymorphisms found in the amino acid residues at sites 112 and 158. Apo E and its three isoforms, with ε3 being the most common, is like a Pandora’s box of sorts, where upon investigation, interesting correlations to some very prominent modern diseases have been found. For example, there was evidence that the presence of one ε4 allele in their Apo E gene increased the risk for type-2 Alzheimer’s disease and two ε4 alleles would increase further this risk. Also intriguing is the subject of this paper by Zou et al.: the relationship between Apo E isoform ε2 and the presence of coronary artery disease (CAD).

In this study, which featured 91 patients (55 with CAD and 36 controls) in their mid to late 60’s, Zou et al. found a positive correlation between the lack of the ε2 allele and the presence of CAD. This was determined through PCR amplification and the presence of two HhaI restriction sites located at 112bp and 158bp. Their results found that out of all the combination of alleles found, those people with CAD showed a total ε2 frequency of 13.6% whereas the ε2 frequency in the control group was 21.0%. This finding, if true, could help to put another puzzle on the genetic map of CAD. This approach is revolutionary by providing a personalized, genotype-dependent adaptation of drug therapy. This approach is able to take into account the variability of drug response at an individual genetic level for a higher chance of success. This approach differs from the current way of management by giving medications to ALL patients whether they respond or not.

However, there are some important questions which need to be clarified. The main question is whether Apo E isoform ε2 does indeed result in decreased level of LDL or in the contrary, that ε2 actually is a cause of CAD. There has been evidence for the latter, as Zou et al. referenced in their paper. So far, the cause-effect relationship between Apo E and CAD is far from clear. Zou et al. speculates that due to Apo E’s function in systemic and local transport of excess cholesterol from the bloodstream to the liver and the difference in affinity for LDL evidenced between the three isoforms, that the presence of ε2 may result in decreased cholesterol. This decrease could be due to delayed clearance of chylomicron remnants from the blood associated with the ε2 allele associated with up-regulation of LDL receptor activity. However there have been studies that suggested the opposite: Orth et al. studied the concentration of chylomicron remnants and its association with CAD. They found that chylomicron remnants were paradoxically lower in patients with CAD than in the control group. This contrasts with Zou et al. and their suggestion that chylomicron remnants up-regulate LDL receptor activity. So, as it can be seen, the current understanding of the relationship between Apo E and CAD is far from being final.

There is little doubt that there are some possible correlations between apolipoprotein E, with its three isoforms and CAD. Their relationship, once clarified, will help tremendously the development of more effective therapies for CAD. However, more studies must be done in order to prove such a cause-effect relationship. The study by Zou et al. is a step in the right direction. Larger, multi-centered, randomized, double blind trials must be done in order to find an answer to this provocative question and its revolutionary therapeutic implication. The future is still obsessively challenging.

**References**