

Influence of Apolipoprotein E Polymorphism on Postprandial Inflammation

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Background: Apolipoprotein E has a particularly important function in plasma as the facilitator of cholesterol and lipid transport and as a modulator of inflammatory response. There exists three isoforms – ApoE2, ApoE3, and ApoE4 – with ApoE3 being the most common. The less prevalent isoforms are associated with various metabolic diseases including atherosclerosis and diabetes. In particular, ApoE4's inflammation is a result of macrophage dysfunction and increased macrophage endoplasmic reticulum stress, possibly due to the misfolding of the ApoE4 protein. Whereas, ApoE2's inflammation is mediated by defective clearance of triglyceride-rich lipoproteins, leading to increased lipid uptake by leukocytes and their resultant activation.

Aims: We wanted to compare the influence of apoE polymorphisms on fasting and postprandial circulating leukocyte levels and activation in humans, and to determine the function of their macrophages *in vitro*.

Methods: Age and weight-matched subjects were recruited from the Princeton Cholesterol Studies. Subjects on lipid-lowering drugs were excluded. Fasting blood samples were drawn then each subject was fed a standardized breakfast of 2 Sausage McMuffins with Egg and a hash brown. Another blood sample was drawn three hours later. Serum triglycerides and cholesterol were measured colorimetrically. Both plasma concentrations and lipid content of monocytes and neutrophils were determined by flow cytometry. Peripheral blood monocytes isolated from each subject were differentiated into macrophages to assess efferocytosis and susceptibility to apoptosis *in vitro*.

Results: Three ApoE3 subjects and three ApoE4 subjects were successfully enrolled. All subjects responded to the high fat meal with elevated postprandial serum triglyceride and unchanged total serum cholesterol; however, the leukocytes of both E3 and E4 subjects did not exhibit significantly increased lipid uptake. All three E4 subjects showed an increase in activated neutrophils and in total monocyte concentrations postprandially; and only one showed an increase in activated monocytes. The E4 subjects' macrophages also tended to be less efficient at efferocytosis and more susceptible to apoptosis.

Conclusion: The impaired macrophage function and viability suggests that the apo E4 polymorphisms have similar effects in humans as in mice. Further testing is needed on a much larger scale in order to cement the mechanism underlying the relationship between ApoE gene polymorphisms and metabolic disease risk.

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