

INVITED COMMENTARY

Gene–nutrient interactions: an important area for consideration

In this month's issue, Loktionov and colleagues (Loktionov *et al.* 1998) report a study further investigating the effect of drinking black tea on blood lipids and coagulation factors. The study presents a reanalysis of a previously reported study which showed negative responses of both blood lipid and coagulation factors to a 4-week period of drinking black tea in adult volunteers (Bingham *et al.* 1997). In the present study, data have been reanalysed according to the subjects' apolipoprotein E (ApoE) genotype, with subjects allocated into three main groups according to the presence or absence of the isoforms E2, E3 or E4; E3/E3 (*n* 39), E2/E3 (*n* 6) and E4+ (*n* 12). Consistent with the original findings for the group as a whole (*n* 57), total- and LDL-cholesterol values showed no response to 4 weeks of black tea drinking in any of the main genotypic groups. However, there was a small decline in HDL-cholesterol in the E3/E3 group and also in triacylglycerol in the E2/E3 group, after 4 weeks of drinking black tea.

Of greater interest was the observation, based on measurements made during the placebo period, of a relationship between activity levels of the blood coagulation factor PAI-1 and ApoE genotype, with PAI-1 activity levels being highest in the apo E4 group, intermediate in the E3/E3 group and lowest in the apo E2/E3 group. These genotypic differences were fairly marked with levels in the E2/E3 group being 40% lower than in the E4+ group. The E2/E3 group also showed a significant reduction in PAI-1 activity levels after 4 weeks of black tea. There was a similar but non-significant trend seen in the E4+ group, but this response was not evident in the E3/E3 group.

Although the number of subjects studied by Loktionov *et al.* (1998) was small and the findings require confirmation within a larger study population, they are of significance for a number of reasons. As discussed by the authors, subjects with an E4 isoform have higher, and those with E2 lower, risk of coronary heart disease. This is usually attributed to the higher levels of cholesterol and triacylglycerol frequently observed in E4 subjects (also confirmed in the present study). However, this is the first time that an association between ApoE genotype and activity levels of PAI-1 have been reported. Since PAI-1 is a risk factor for CHD, the elevated levels in the E4+ group could provide an additional explanation for their increased risk of CHD and may be independent of any effect of blood lipid levels.

The fact that the E2/E3 group also showed a notable and significant reduction in PAI-1 activity with drinking black tea, which greatly exceeded that shown by the other genotypic

groups, indicates that individuals with this genotype may be hyper-responders to dietary manipulations which can alter PAI-1 levels. This illustrates the important principle of genetic heterogeneity in determining response to dietary change, a factor frequently ignored in attempts to explain the variability in individual responses to altered diets. Because subjects in the E2/E3 group represented less than 10% of the study population, the effect of drinking black tea in this subgroup was masked when data were analysed for the group as a whole and was only evident once the data were grouped according to apoE genotype. The rationale for sub-analysis according to apoE genotype in the present study was clear in that variation in the apoE gene has long been recognized as a risk factor for CHD. As more information is acquired on other candidate risk-factor genes, there is likely to be greater emphasis on the need for measurement of genetic variation in dietary intervention studies.

Future prospective studies involving altered diets, including those involving the use of supplements, beverages, alcohol etc., should incorporate, as a matter of routine, collection and storage of buffy coat preparations which will allow for future genotype analysis. An advantage of the present study which involved only a requirement of subjects to take a specific beverage is that compliance is likely to have been high and less variable than is the case with other dietary studies. In studies where the nature of the interventions are more complex, there is greater room for inter-individual variability and it is clear that much larger sample sizes may be required to distinguish the contribution made by genetic variation.

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