Interactions between age and apoE genotype on fasting and postprandial triglycerides levels

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ABSTRACT

Objective: The influences of genetic determinants on the magnitude of postprandial lipaemia are presently unclear. Here the impact of the common apolipoprotein (apo)E epsilon mutation on the postprandial triglyceride (TG) response is determined, along with an assessment of genotype penetrance according to age, body mass index and gender.

Methods and results: Healthy adults ($n = 251$) underwent a postprandial investigation, in which blood samples were taken at regular intervals after a test breakfast (0 min, 49 g fat) and lunch (330 min, 29 g fat) until 480 min after the test breakfast. There was a significant impact of apoE genotype on fasting total cholesterol (TC), ($P = 0.027$), LDL-cholesterol (LDL-C), ($P = 0.008$), and %LDL$_3$ ($P = 0.001$), with higher and lower levels in the E4 and E2 carriers respectively relative to the E3/E3 genotype. Reflective of a higher fasting TG ($P = 0.001$), a significantly higher area under the curve for the postprandial TG response (TG AUC) was evident in the E4 carriers relative to the E3/E3 group ($P = 0.038$). In the group as a whole, a significant age × genotype interaction was observed for fasting TC ($P = 0.021$). In the participants >50 years there was a significant impact of genotype on TC ($P = 0.005$), LDL-C ($P = 0.001$) and TAG AUC ($P = 0.028$).

Conclusions: It is possible that an exaggerated postprandial lipaemia contributes to the increased coronary heart disease risk associated with carriers of the E4 allele; an effect which is more evident in older adults.

1. Introduction

From the earliest observations nearly 50 years ago [1], numerous case–control studies [2,3] and more recent prospective analysis of US and Danish cohorts [4,5] have established non-fasting triglycerides (TG) levels as an important determinant of coronary heart disease (CHD) risk. Elevated circulating TG-rich lipoproteins (TRL) can result in a number of atherogenic effects including sequestration of cholesterol into the developing plaque, are often associated with decreased levels of HDL-cholesterol (HDL-C), reduced particle sizes of LDL and HDL [6–8] and have also been linked with increased pro-thrombosis and endothelial dysfunction [8].

Individuals living in western societies, who consume regular meals and snacks, are thought to spend up to 18 h in the postprandial state. The postprandial TG response has been shown to be influenced by various factors including test meal size and composition (including fat content and fatty acid profile), the habitual diet, lifestyle factors (including alcohol intake and physical activity) plus physiological determinants such as body weight, gender and age [9]. Furthermore, using a candidate gene approach, numerous common single nucleotide polymorphisms (SNPs) have been identified as potentially in part responsible for the heterogeneity in the postprandial response to dietary fat, as summarised in several recent reviews [9,10]. Perhaps the most well described of these is the apolipoprotein E (apoE) genotype. ApoE plays a central role in lipoprotein metabolism; it is a structural component of TRL (such as VLDL and chylomicrons) and HDL and also acts as a high affinity ligand for the receptor mediated endocytosis of TRL remnants by the liver and other tissues [11–13]. It is also thought to be a cofactor in VLDL synthesis, the catabolism of VLDL to LDL, and also has

roles in cellular cholesterol efflux, and reverse cholesterol transport [14–16].

The apoE2 isoform of the protein has been associated with an exaggerated postprandial lipaemic response which is attributable to its relatively low affinity for the LDL-receptor when compared to the E3 and E4 isoforms [17,18]. However, there are large study inconsistencies regarding the relative effect of the E4 allele, consequently the impact of apoE genotype on the postprandial lipaemic response in healthy subjects remains controversial. A lack of a significant difference reported by some studies is undoubtedly due to a lack of study power, where small subject numbers in the rare allele groups may result in a lack of significance despite a 'real biological' difference being present. Furthermore, emerging evidence indicates that the penetrance of the apoE genotype on CHD risk may be dependent on factors such as age, gender and body mass index (BMI) [19], so that the population under study may have important relevance to the findings. Here we report on the impact of the apoE epsilon (E2, E3, E4) polymorphisms on postprandial lipaemia and examine age × genotype, gender × genotype, and BMI × genotype interactions in healthy UK adults.

2. Subjects and methods

2.1. Subjects

Subjects included in the current analysis were pooled from the baseline data of six individual studies designed to investigate the impact of various dietary interventions on postprandial TG, NEFA, glucose and insulin responses. At the time of the postprandial investigation, all subjects were following their habitual diet and had not commenced the relevant dietary intervention. Volunteers were aged between 20 and 70 years, with a BMI between 19 and 32 kg/m^2, fasting TC < 8.0 mmol/l and fasting TG < 4.0 mmol/l. A full list of inclusion and exclusion criteria has been previously reported [20]. The studies were approved by the University of Reading Ethics and Research Committee and the West Berkshire Health Authority Ethics Committees and all participants provided informed written consent prior to commencing the study.

2.2. Postprandial methodology

The day before their postprandial assessment participants were asked to refrain from alcohol or organized exercise regimens, and were provided with a relatively low fat (<10 g fat) evening meal (in order to standardise short-term fat intake). After a 12-h overnight fast, an indwelling cannula was inserted into the antecubital vein of the forearm, and a fasting blood sample taken. As this was a sequential meal protocol, two meals were provided: a standard test breakfast at $t = 0$ min (croissants with butter and jam, cornflakes and semi-skimmed milk and a glass of orange juice) followed by a lunch at $t = 330$ min (cheese sandwiches, crisps and a chocolate bar), with blood samples taken at 30–60 min intervals until 480 min after the test breakfast (see Fig. 1). The nutritional content of the test breakfast was 3.9 MJ energy, 111 g carbohydrate, 19 g protein and 49 g fat, which comprised 29.6 g saturated fatty acids (SFA), 12.2 g monounsaturated fatty acids (MUFA), 1.6 g PUFA and 2.5 g trans-fatty acids. The nutritional content of the test lunch was 2.3 MJ energy, 63 g carbohydrate, 15 g protein and 29 g fat which contained 14.3 g SFA, 7.1 g MUFA, 3.0 g PUFA and 2.9 g trans-fatty acids. This nutritional information was derived using food nutrient data from McCance and Widdowson's Food Composition Tables, supplemented with a food fatty acid content database (Foodbase2000, London, UK).
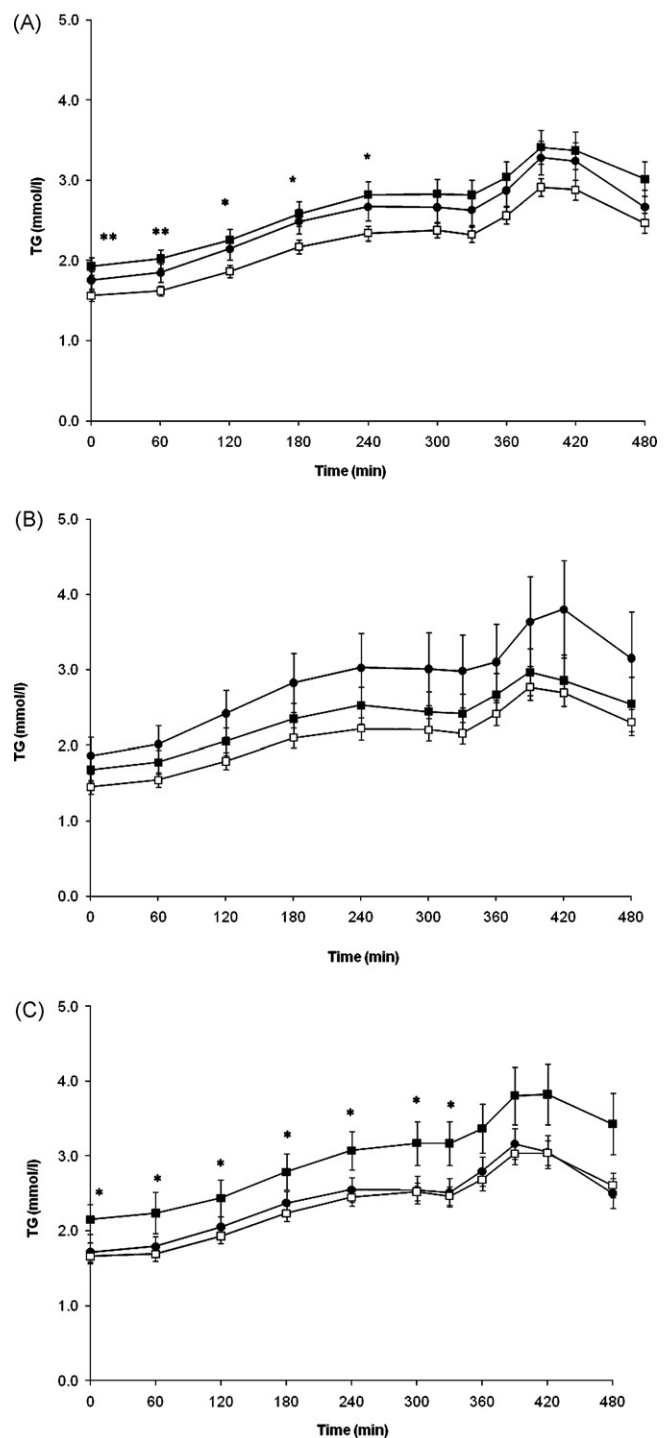
Fig. 1. Mean (±SEM) postprandial TG response in the apoE2 carriers (E2/E2 and E2/E3, black circles), homozygous E3/3 (open squares) and E4 carriers (E4/E4 and E4/E3, black squares) after consumption of a test breakfast (49 g fat) at 0 min and a test lunch (29 g fat) at 330 min. Data is presented as (A) the group as a whole (E2 carriers $n = 44$, E3 $n = 142$ and E4 carriers $n = 65$), (B) ≤50 years subgroup (E2 carriers $n = 11$, E3 $n = 65$ and E4 carriers $n = 30$) and (C) >50 years subgroup (E2 carriers $n = 33$, E3 $n = 77$ and E4 carriers $n = 35$). **$P ≤ 0.01$ and *$P ≤ 0.05$ denote differences in TG concentrations between the E4 carriers and E3/3 groups at specified time points.

2.3. Blood handling

Baseline and postprandial venous blood samples were collected into EDTA tubes for the analysis of lipids and insulin and a fluoride oxylate tube for glucose analysis. All samples, except those