The Apolipoprotein E Genotype Predicts Postprandial Hypertriglyceridemia in Patients with the Metabolic Syndrome

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Apolipoprotein E (apo E) is a constituent molecule of the triglyceride-rich lipoproteins and participates in their clearance. Polymorphisms in the apo E gene are associated with increased fasting and postprandial levels of triglycerides. We studied 66 patients with the metabolic syndrome, none of whom had diabetes. Details were recorded for cholesterol, triglycerides, apo AI, apo B, insulin, homeostasis model assessment of insulin resistance, homeostasis model assessment of insulin secretion, uric acid, 24-h uric acid urinary excretion, high-density lipoprotein cholesterol, waist to hip ratio, body mass index, and age. The patients were given a 60-g fat overload (Supracal), and measurements were made at 4 h of cholesterol, triglycerides, high-density lipoprotein cholesterol, apo AI, and apo B. Patients who did not have the E3/3 genotype had an odds ratio of postprandial hypertriglyceridemia of 6.2 (confidence interval, 1.41–16.08; \(P = 0.01\)) and an odds ratio of hyperuricemia compared with the E3/3-positive patients of 7.5 (confidence interval, 1.04–39.31; \(P = 0.02\)). This study shows that patients with the metabolic syndrome who do not have the E3/3 genotype have a greater risk of hyperuricemia and postprandial hypertriglyceridemia after a fat overload. (J Clin Endocrinol Metab 90: 2972–2975, 2005)

Patients and Methods

We studied 66 patients (52 men and 14 women) with the metabolic syndrome according to the Adult Treatment Panel III criteria: obesity (waist circumference, >1.02 m in men or >0.88 m in women), blood pressure of 130/85 mm Hg or higher, fasting glucose of 6.05 mmol/liter or more, triglycerides of 1.71 mmol/liter or more, high-density lipoprotein (HDL) cholesterol below 1.04 mmol/liter for men or below 1.3 mmol/liter for women (14). Patients with diabetes (after a 75-g oral glucose tolerance test) were excluded. Measurements were made in all patients of cholesterol, triglycerides, apo AI, apo B, insulin, homeostasis model assessment of insulin resistance (IR-HOMA), homeostasis model assessment of insulin secretion (IS-HOMA), uric acid, 24-h uric acid urinary excretion, HDL cholesterol, waist to hip ratio, body mass index (BMI), and age. The patients underwent a 60-g fat overload with a commercial preparation (Supracal, SHS International, Liverpool, UK). Only water was permitted during the process, and no physical exercise was undertaken. At 4 h, measurements were made of cholesterol, triglycerides, HDL cholesterol, apo AI, and apo B. Patients were classified as having postprandial hypertriglyceridemia if the difference in plasma triglycerides at baseline and after 4 h was 1.71 mmol/liter or more. The commercial preparation of 125 ml contains 60 g fat, of which 12 g are saturated, 35.25 g are monounsaturated, and 12.75 g are polyunsaturated. Each 100 ml contains less than 1 g lauric acid, less than 1 g myristic acid, 4.8 g palmitic acid, 1.4 g stearic acid, 27.7 g oleic acid, 9.6 g linoleic acid, less than 1 g linolenic acid, 0.5 g arachidonic acid, 0.5 g eicosanoic acid, 1.4 g behenic acid, and 0.5 g lignoceric acid.

All the patients gave informed consent to the study, which was approved by the ethics committee of Carlos Haya Regional University Hospital.

DNA analysis

Two hundred microliters of whole blood were used for DNA extraction by the salting-out method described by Miller et al. (15), modified by Queipo-Ortuno et al. (16). LightCycler technology was used for apo E genotype analysis.

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Abbreviations: Apo E, Apolipoprotein E; BMI, body mass index; HDL, high-density lipoprotein; IR-HOMA, homeostasis model assessment of insulin resistance; IS-HOMA, homeostasis model assessment of insulin secretion; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

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Statistical study

The biological variables were compared with Student’s t test; the mean ± sd are shown in the tables. The χ2 test was used for analysis of the apo E genotype distribution and the presence of hypertriglyceridemia after the overload. Logistic regression analysis was carried out with postprandial hypertriglyceridemia as the dependent variable and age, sex, genotype, IR HOMA, IS-HOMA, uric acid, and baseline triglycerides as the independent variables. The same analysis was made for hyperuricemia, with uric acid greater or less than 416.5 μmol/liter as the dependent variable, and the same independent variables as those described above together with triglycerides at 4 h and the difference between baseline and postprandial levels. In all cases the rejection level for a null hypothesis was P = 0.05 for a two-tailed t test.

Results

The distribution of the apo E genotypes was E3/3, 63.6%; E3/4, 22.7%; E3/2, 10.6%; and E4/4, 3%. Table 1 shows the distribution of the E3/3 patients compared with the other genotypes according to the presence or absence of postprandial hypertriglyceridemia. The non-E3/3 genotype was more frequent in the subjects with postprandial hypertriglyceridemia (Tables 1 and 2). These non-E3/3 subjects also had greater differences between plasma triglyceride levels at baseline and at 4 h than the subjects with the E3/3 genotype (1.70 vs. 1.20 mmol/liter difference, respectively; P = 0.04; Table 3). Those variables associated with the metabolic syndrome were not significantly different between the E3/3 and the non-E3/3 subjects, except for the plasma levels of uric acid, which were higher in the non-E3/3 subjects (416.5 vs. 368.9 μmol/liter; P = 0.05; Table 3).

Logistic regression analysis using the difference in plasma triglycerides between baseline and 4 h as the dependent variable showed the odds ratio of having postprandial hypertriglyceridemia in the non-E3/3 subjects to be 6.2 (confidence interval, 1.4–16.1; P = 0.01). The model included the variables age, sex, IR HOMA, IS HOMA, BMI, uric acid, and baseline plasma levels of triglycerides (Table 4).

The non-E3/3 subjects had an odds ratio of hyperuricemia of 7.5 (confidence interval, 1.04–39.3; P = 0.02), even after inclusion of the variables associated with the metabolic syndrome, such as age, sex, IR HOMA, IS HOMA, BMI, baseline plasma levels of triglycerides, plasma levels of triglycerides at 4 h, and difference between baseline and postprandial triglycerides at 4 h, and difference between baseline and postprandial triglycerides (Table 5).

Discussion

Subjects with the e2 allele have lower levels of cholesterol and LDL cholesterol than those with the e4 or e3 allele (17). However, the association between apo E genotypes and fasting triglyceride levels is not yet clear. The prevalence of the e2 allele is greater in patients with hypertriglyceridemia (17), and some studies suggest that carriers of the e4 allele have higher plasma triglyceride levels than E3 homozygotes (18, 19). A meta-analysis by Dallongeville et al. (9) showed that E2 and E4 heterozygotes have higher concentrations of fasting plasma triglycerides than E3 homozygotes. However, we failed to detect these differences in fasting plasma triglycerides, probably because the meta-analysis of Dallongeville included a very heterogeneous population, whereas our study was centered exclusively on patients with the metabolic syndrome.

Our study shows that patients with the metabolic syndrome, but without diabetes, who have a genotype other than E3/3 have a greater risk for postprandial hypertriglyceridemia after fat overload, even after adjusting for variables related to postprandial hyperlipidemia, such as sex, age, IR-HOMA, BMI, waist to hip ratio, uric acid, and baseline plasma triglycerides. A greater and longer-lasting postprandial hypertriglyceridemia has been detected in patients with familial combined hyperlipidemia who have the e4 allele (21).

| TABLE 1. Distribution (percentage) of the E3/3 and non-E3/3 genotypes in a group of subjects with the metabolic syndrome with and without postprandial hypertriglyceridemia, as defined in Patients and Methods |
|---------------------------------|-----------------|-----------------|-----------------|
| | E3/3 (42) | Non-E3/3 (24) |
| Tg ≥1.71 (16) | 6 (37.5) | 10 (62.5) |
| Tg <1.71 (50) | 36 (72.0) | 14 (28.0) |
| P < 0.01. Tg, Triglycerides. |

| TABLE 2. Distribution (percentage) of the E3/3, E3/4, and E3/2 genotypes in a group of subjects with the metabolic syndrome with and without postprandial hypertriglyceridemia, as defined in Patients and Methods |
|---------------------------------|-----------------|-----------------|-----------------|
| | E3/3 (42) | E3/4 E4/4 (17) | E3/2 (7) |
| Tg ≥1.71 (16) | 6 (14) | 7 (41) | 3 (43) |
| Tg <1.71 (50) | 36 (86) | 10 (59) | 4 (57) |

| TABLE 3. Distribution of the biological variables studied according to the E3/3 or non-E3/3 genotype |
|---------------------------------|-----------------|-----------------|-----------------|
| | E3/3 (42) | Non-E3/3 (24) |
| Age (yr) | 43.9 ± 9.9 | 49.3 ± 11.8 | NS |
| BMI (kg/m²) | 27.5 ± 3.5 | 28.1 ± 4.1 | NS |
| Waist to hip ratio | 0.93 ± 0.07 | 0.95 ± 0.04 | NS |
| Glucose (mmol/liter) | 5.35 ± 0.51 | 5.68 ± 1.55 | NS |
| Uric acid (μmol/liter) | 386.9 ± 43.8 | 416.5 ± 89.25 | NS |
| Cholesterol (mmol/liter) | 6.48 ± 1.11 | 6.7 ± 0.98 | NS |
| Triglycerides (mmol/liter) | 4.72 ± 4.26 | 3.89 ± 1.99 | NS |
| HDL cholesterol | 11.1 ± 0.31 | 1.09 ± 0.189 | NS |
| Apo Al (mg/dl) | 164.7 ± 37.8 | 152.6 ± 19.4 | NS |
| Apo B (mg/dl) | 157.1 ± 25.2 | 158.8 ± 18.6 | NS |
| DHA5 (ng/dl) | 1797.5 ± 1051 | 2140.6 ± 1382 | NS |
| Insulin (μU/ml) | 13.8 ± 7.1 | 12.3 ± 5.6 | NS |
| Cholesterol, 4 h (mmol/liter) | 6.5 ± 1.10 | 6.67 ± 0.93 | NS |
| Triglycerides, 4 h | 5.58 ± 4.31 | 5.6 ± 2.73 | NS |
| HDL cholesterol, 4 h | 1.11 ± 0.36 | 1.07 ± 0.18 | NS |
| Apo Al, 4 h (mg/dl) | 161.4 ± 36.9 | 151 ± 18 | NS |
| Apo B, 4 h (mg/dl) | 156.4 ± 27.1 | 155.5 ± 19.5 | NS |
| Uric acid clearance (ml/min) | 8.1 ± 2.5 | 7.2 ± 3.5 | NS |
| Excretory fraction | 6.3 ± 1.7 | 5.9 ± 1.5 | NS |
| IR-HOMA | 3.2 ± 1.8 | 3.1 ± 1.8 | NS |
| IS-HOMA | 152.3 ± 85.9 | 137 ± 80 | NS |
| Tg post (mmol/liter) | 1.20 ± 1.54 | 1.70 ± 1.16 | NS |
| Systolic blood pressure (mm Hg) | 138 ± 15 | 141 ± 20 | NS |
| Diastolic blood pressure (mm Hg) | 86 ± 12 | 84 ± 16 | NS |

DHA5. Dehydroepiandrosterone sulfate; NS, not significant; Tg post, difference between baseline triglyceride levels and 4 h after the overload.
and Japanese patients with hyperlipidemia (13), and healthy subjects with the e2 allele have higher levels of postprandial triglycerides (11). Both the e2 and the e4 alleles are related to postprandial hypertriglyceridemia in patients with diabetes (21). Our study showed that grouping the genotypes as E3/E3 and non-E3/E3 revealed important differences in postprandial hypertriglyceridemia in patients with the metabolic syndrome, but without diabetes. This suggests that carriers of both the e2 and e4 alleles have difficulty clearing postprandial triglycerides.

Changes in the apo E gene, resulting in changes in the amino acids of the protein, may cause changes in the physiological structure of the protein, leading to slower clearance of triglyceride-rich lipoproteins after a fat overload. This possibility is supported by other studies that suggest that subjects with the e2 allele have a defective interaction with the (VLDL/chylomicron) cell receptor (19), and that the defect in the clearance of triglyceride-rich lipoproteins in subjects with the e4 allele may interfere with the lipolysis of these triglyceride-rich lipoproteins (22). Both the poor interaction described for E2 and the interference in lipolysis in E4 would result in an accumulation of triglyceride-rich lipoproteins, an effect we detected in those patients who did not have the E3/3 genotype. Bergeron and Havel (23) also showed that subjects with the e4 allele on chylomycin surfaces and remnants make these particles less accessible to the hepatic remnant receptor.

TABLE 4. Logistic regression model, dependent variable (difference in level of plasma triglycerides after fat overload minus the level of fasting plasma triglycerides, classified as above or below 1.71 mmol/liter)

|        | β       | sd β    | CI      | OR     | P     |
|--------|---------|---------|---------|--------|-------|
| Age    | 0.037   | 0.03    | 0.93–10.7 | 1      | NS    |
| Non-E3 vs. E3 | 1.81    | 0.74    | 1.41–16.08 | 6.2     | 0.01  |
| Sex (2 vs. 1) | 0.23    | 0.96    | 0.19–8.21  | 1.2     | NS    |
| IR-HOMA | 0.47    | 0.33    | 0.61–2.21  | 1.5     | NS    |
| IS-HOMA | −0.005  | 0.006   | 0.98–1.01  | 0.99    | NS    |
| BMI    | −0.1    | 0.13    | 0.75–1.28  | 0.90    | NS    |
| Uric acid | −0.1    | 0.29    | 0.54–1.71  | 0.88    | NS    |
| Baseline Tg | 0.001   | 0.001   | 0.99–1.00  | 1       | NS    |

Independent variables: age, genotype, sex, IR-HOMA, IS-HOMA, BMI, uric acid, and fasting plasma triglycerides. Sex 1, Male; 2, female. CI, Confidence interval; NS, not significant; OR, odds ratio; Tg, triglycerides.

This study also showed that subjects with the non-E3/3 genotype have higher plasma levels of uric acid. Our group has previously reported a greater prevalence of the e2 allele in hyperuricemic patients and that these hyperuricemic e2 carriers have higher levels of plasma triglycerides and a lower excretion of uric acid (24). The association between levels of uric acid, triglycerides, and VLDL has been reported (25, 26), and this study suggests that there is also an association between postprandial triglycerides and hyperuricemia. Indeed, uric acid is considered a risk factor for coronary heart disease (27).

In conclusion, we showed that patients with the metabolic syndrome without diabetes who have a non-E3/3 apo E genotype are at greater risk for hyperuricemia and postprandial hypertriglyceridemia after a fat overload. Apo E genotyping may be clinically useful to rule out the future presence of severe postprandial hypertriglyceridemia in patients with the metabolic syndrome.

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