The Effect of Age, Body Mass Index, and Fasting Triglyceride Level on Postprandial Lipemia Is Dependent on Apolipoprotein E Polymorphism in Subjects With Non–Insulin-Dependent Diabetes Mellitus

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The aim of this study was to evaluate in non–insulin-dependent diabetes mellitus (NIDDM) subjects the respective influence of apolipoprotein (apo) E polymorphism, age, gender, weight, fasting triglyceride (TG) status, and glycemic status on postprandial lipemia. Apo E genotyping was performed in consecutive NIDDM hospitalized patients in order to recruite size-adjusted groups of each apo E genotype. In 57 NIDDM including 22 E3/3 (E3), 18 E2/3 (E2), and 17 E4/3 (E4) subjects, an 8-hour vitamin A–fat loading test was performed and TG and retinyl palmitate (RP) measured. Fasting TG level correlated with the TG area under the incremental curve (AUIC) ($r = 0.512$, $P < .001$) but not with RP AUIC. Despite not different fasting and postprandial TG concentrations, E2 and E4 carriers exhibited a 2- to 3-fold higher RP AUIC than E3 carriers ($P = .01$). Multivariate analysis indicated an age × apo E interaction on postprandial TG ($P < .01$), since the unfavorable effect of E2 and E4 allele on TG AUIC was unmasked by aging. In addition, a fasting TG × apo E interaction on postprandial TG was shown ($P < .01$), and the correlation between fasting TG and TG AUIC was actually restricted to E2 or E4 carriers. Finally, the negative correlation between BMI and postprandial TG observed in the experimental group was actually restricted to E4 carriers ($r = -0.77$, $P < .001$). Our results indicate interactions between apo E polymorphism and aging, fasting TG level and BMI that may be important for analyzing postprandial TG clearance in NIDDM.

NON–INSULIN-DEPENDENT diabetes mellitus (NIDDM) is an independent risk factor for cardiovascular disease and coronary heart disease (CHD) mortality.[1] Among associated risk factors, elevated fasting triglyceride level (TG) is known to worsen the cardiovascular condition of NIDDM patients.[2,3] Zilversmit first suggested in the 1980s that postprandial accumulation in the endothelium of cholesterol from TG-rich lipoproteins (TRL) such as chylomicron and their remnants should induce accelerated atherogenesis,[4] and the question about the atherogenic properties of postprandial TRL is still debated.[5] In a recent study, postprandial concentrations of apolipoprotein (apo) B-48– and apo B-100–containing particles were shown to correlate with angiographically verified CHD in type 2 diabetic subjects.[6] Apo E is a component of plasma TRL of critical importance for their catabolism, by its interaction as a specific ligand with the low-density lipoprotein (LDL) receptor, the LDL receptor–related protein, and the very-low-density lipoprotein (VLDL) receptor.[7] Human apo E occurs as 3 main isoforms designated apo E3, E2, and E4, the 2 latter resulting from a single amino acid interchange. Such change determines the lower in vitro receptor-binding activity of apo E2 on hepatocytes, and hence its delayed in vivo catabolic rate compared to E3.[8,9] Epidemiologic studies have emphazised on the importance of apo E polymorphism as a major factor for interindividual susceptibility to CHD in nondiabetic and in NIDDM subjects. In most studies, E4 allele appeared to promote CHD,[10-12] and this association should relate to the higher cholesterol level but also to the higher TG and lower high-density lipoprotein (HDL)-cholesterol levels observed in E4 compared to E3 carriers.[13] Reports relative to the modulation of postprandial TRL kinetics by apo E polymorphism are conflicting, but recently Bergeron and Havel[14] showed a delayed clearance of apo B-48 and apo B-100 in nondiabetic subjects with apo E4/3 compared to apo E3/3 genotype. In NIDDM subjects with normal fasting TG, an enhanced retinyl ester peak was observed after a vitamin A–fat load test in apo E4/3 and apo E2/3 compared to apo E3/3 subjects in a previous study.[15] The current study was designed to analyze in a large sample of NIDDM subjects interactions between apo E polymorphism and variables known to modulate postprandial lipemia such as age, gender, body mass index (BMI), fasting TG, and glycemic status.

SUBJECTS AND METHODS

Subjects

A total of 57 NIDDM patients participated to the study. Inclusion criteria selected overweight (BMI 26 to 30) or obese (BMI > 30) patients aged 35 to 70 years, with normal TG concentration (<1.70 mmol/L) or moderately elevated TG concentration (1.70 to 5.0 mmol/L). Informed consent was obtained from all patients, and the study was approved by the local Human Studies Committee.

Apo E genotyping was performed in consecutive NIDDM patients hospitalized in the Department of Endocrinology and Diabetes, in order to constitute 3 groups of similar size, eg 18 E2/3 (E2 group), 22 E3/3 (E3 group), and 17 E4/3 (E4 group) patients. Such genotype distribution does not reflect that in our population sample (data not shown), which actually was similar to the genotype distribution previously observed in other NIDDM population samples.[16,17] The clinical and biochemical characteristics of the selected patients are summarized in Tables 1 and 2. Patients were placed on a weight-maintenance diet determined at a previous visit by the dietititian. Oral antidiabetic agents were withdrawn 10 days before the test meal, while insulin was withdrawn 48 hours before the test meal. Lipid-lowering drugs (fenofibrate 7/57) were also withdrawn 10 days before the test meal.

Study Protocol

The protocol was adapted from a previous study.[15] Briefly, after an overnight fast, baseline blood samples were drawn at 11 AM for

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Table 1. Clinical Characteristics of the NIDDM Patients in the apo E Genotype Groups

Group	All NIDDM	apo E Genotype		
		E3	E4	E2
No.	57	22	17	18
Age (yr)	55 ± 1	56 ± 2	55 ± 2	55 ± 2
BMI (kg/m^2)	32.5 ± 0.5	32 ± 1	33.5 ± 1	32.5 ± 1
Sex ratio (M/F)	20/37	10/12	4/13	6/12

glucose, insulin, C-peptide, lipids, and apolipoproteins. The patients were then given (at 11 AM) a standardized fatty meal containing 60 g fat/m^2 body surface area. Vitamin A 100,000 UI (Avibon, Rhône Poulenc Rorer Laboratories, Vitry/Seine, France) was added to the fatty meal to assess the clearance rate of chylomicrons. Thereafter, blood samples for lipid and retinyl ester measurement were drawn 2, 4, 6, and 8 hours after the test meal into tubes containing 0.1% EDTA, shielded from light with aluminium foil. Plasma was separated by centrifugation at 3,000 rpm for 15 minutes at 4°C. The chylomicron fraction was separated from the nonchylomicron fraction by ultracentrifugation[18] at 25,000 rpm for 25 minutes (Beckman L8 70M Ultracentrifuge, rotor TI 70,1, Villepinte, France).

Lipid and Lipoprotein Determination

TG and cholesterol concentrations were determined in total plasma and in the non chylomicron fraction with an automated Hitachi 717 analyzer by enzymatic methods (Boehringer Manheim, Meylan, France; kits 1 0580550 and 1 040839, respectively). HDL-cholesterol was quantitated in the supernatant after precipitation of the other lipoproteins with polyethylene glycol (Quantolip, Immunofrance, Illkirch, France). Apolipoproteins A1 and B were determined by nephelemetry using a Behring Nephelemeter Analyser (Puteaux, France; antisera OUED AC4 90073 and OSAN AC4 91153, respectively).

Retinyl Palmitate Assay

Blood samples for retinyl palmitate (RP) assay were collected in aluminium covered tubes and aliquots of whole plasma and nonchylomicron fraction were kept frozen at -80°C. On the day of the assay, samples were extracted with hexane, redissolved in ethanol, then analyzed by high-performance liquid chromatography (HPLC) with a mobile phase of methanol at a flow rate of 2 mL/min. The RP peak was quantified at 325 nm. A retinyl acetate standard was used to determine the recovery, which was 95%.

Quantitation of Postprandial Lipemic Responses

Postprandial TG and RP were measured in total plasma and in the nonchylomicron fraction, and plotted against time. The areas under incremental concentration curve (AUICs) for TG and RP were determined according to Tai's model[19] derived from the trapezoid rule.

Apo E Genotyping

Apo E genotype was identified by restriction isotyping from genomic DNA extracted from frozen leukocytes, amplified by polymerase chain reaction (PCR), and restricted with *Hha*1.[20]

Other Laboratory Measurements

Plasma glucose was analysed by glucose-oxidase (kit Boehringer Manheim for BM/Hitachi 717), insulin was determined by radioimmunoassay (Phadeseph kit, Pharmacia, St Quentin Yveline, France), and C-peptide by radioimmunoaasay (RIA)-coat (Byk-Sangtec Diagnostica Inc, France). Hemoglobin A_{1c} (HbA_{1C}) was measured by HPLC (normal values, < 5.5%).

Statistical Analysis

The analysis was performed using a statistical SPSS software, on a power Macintosh 7200/75 (Apple Computer, France). All results were expressed as the mean ± SEM for quantitative variables and as the number of subjects for qualitative variables. The quantitative variables (eg, fasting TG, age, glucose, insulin, and BMI) were studied in a bivariate procedure for the overall sample, and by estimating the Pearson's correlation coefficient for each apo E group. Relationship between postprandial lipemia on one hand, and apo E genotype and gender on the other hand, were compared by 1-way analysis of variance (ANOVA). Moreover, age was also expressed as a categorical variable by separation into 2 classes (eg < or = 55 years />55 years).

Multivariate analysis was an analysis of covariance (ANCOVA) including categorical (eg, gender, age, and apoE) and quantitative (eg, fasting TG and BMI) variables. Interactions between these variables were thus considered. The average of the dependent variable was calculated for each class of the categorical variables. Homogeneity of variances for the conditional distributions was assessed by Levene's test. The least significant difference (LSD) procedure was used for

Table 2. Biochemical Characteristics of the NIDDM Patients in the apo E Genotype Groups

Group	All NIDDM	apo E Genotype		
		E3	E4	E2
HbA_{1C} (%)	8.5 ± 0.5	8 ± 0.5	9 ± 1	8.0 ± 0.5
Glucose (mmol/L)	12.9 ± 0.5	13 ± 1	14 ± 1	11.5 ± 1
Insulin (mU/L)	14.3 ± 1.2	15 ± 2	16 ± 2	11.5 ± 2
C-peptide (nmol/L)	1.14 ± 0.1	1.3 ± 0.1	1 ± 0.1	0.95 ± 0.1
TG (mmol/L)	2.01 ± 0.11	2.04 ± 0.19	1.88 ± 0.17	2.10 ± 0.24
Cholesterol (mmol/L)	5.89 ± 0.15	5.82 ± 0.23	6.07 ± 0.26	5.80 ± 0.32
HDL-cholesterol (mmol/L)	1.21 ± 0.04	1.08 ± 0.06	1.22 ± 0.09	1.37 ± 0.07*
LDL-cholesterol (mmol/L)	3.94 ± 0.23	4.28 ± 0.5	3.95 ± 0.24	3.52 ± 0.28
apo A-1 (mg/dL)	1.37 ± 0.03	125 ± 4	140 ± 6	150 ± 6†
apo B(mg/dL)	1.34 ± 0.04	137 ± 6	145 ± 7	120 ± 7
apo B:A-1 ratio	1.02 ± 0.04	1.14 ± 0.08	1.06 ± 0.06	0.83 ± 0.07‡

*$P < .05$, E2/3 *v* E3/3.
†$P < .01$, E2/3 *v* E3/3.
‡$P < .01$, E2/3 *v* E3/3 and E4/3.

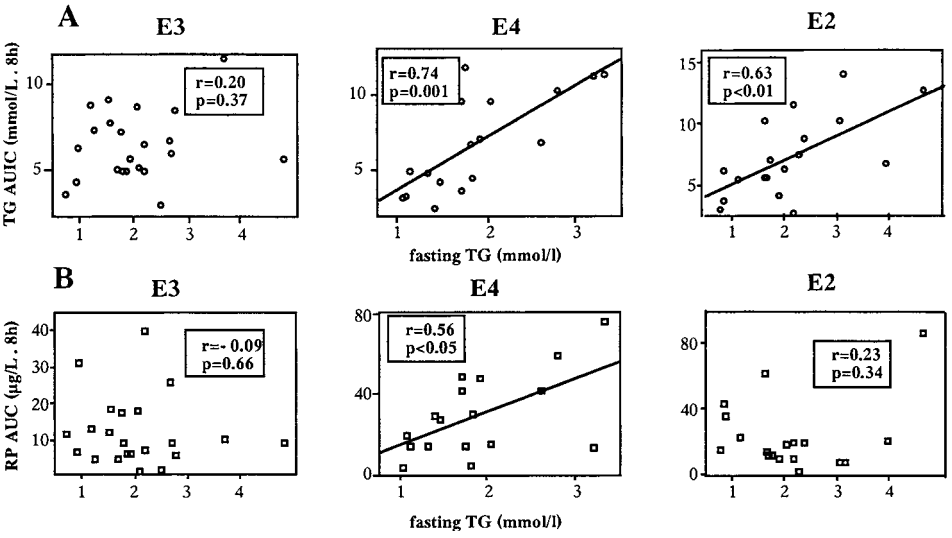

Fig 1. Association between fasting TG and postprandial (A) TG AUIC and (B) RP AUIC in groups of NIDDM subjects defined on the basis of apo E genotype.

multiple comparisons. In all statistical analyzes, the accepted level of significance was $P < .05$.

RESULTS

Factors Modulating Postprandial Lipemia

TG AUICs were not different between apo E groups in univariate analysis (E4 *v* E2 *v* E3, 6.78 ± 0.79 *v* 7.14 ± 0.81 *v* 6.39 ± 0.45 mmol/L/8 h). In contrast, RP AUICs were higher in E4 and E2 than in E3 group in total plasma (2,924 ± 488 *v* 2,248 ± 508 *v* 1,213 ± 206 µg/L/8 h, $P < .01$) and in both nonchylomicron ($P < .05$) and chylomicron fractions ($P < .01$) (data not shown). This effect of apo E polymorphism on RP AUIC was still significant in multivariate analysis including age, BMI, gender, and fasting TG level ($P < .01$).

Fasting TG correlated with TG AUIC ($r = 0.512$, $P < .001$), but not with RP AUIC (data not shown). The correlation was still significant in multivariate analysis including age, BMI, gender, and apo E genotype ($P < .001$). Relations between fasting TG and postprandial TG and RP were therefore analyzed in separate apo E groups: no correlation was observed between fasting TG and plasma TG AUIC in the apo E3 group, while a strong positive correlation was observed in the E2 and E4 groups (Fig 1A). A positive correlation was also observed between fasting TG and RP AUIC in the E4 but not in the E2 and in E3 groups (Fig 1B).

BMI correlated negatively with postprandial TG AUIC ($r = -0.332$, $P < .05$), but not with RP AUIC. This correlation observed in univariate analysis between BMI and TG AUIC remained significant in multivariate analysis ($P = .01$). When analyzing this relationship in separate apo E groups, no correlation was observed in the E3 and E2 groups, in contrast with the E4 group, which exhibited a negative correlation between BMI and TG AUIC ($r = -0.77$, $P < .001$).

When studying the other continuous variables, no influence on TG AUIC or RP AUIC was observed for gender, glucose, and insulin levels in univariate analysis. Age did not correlate with either TG AUIC or RP AUIC when studied as a continuous variable.

Age-by-Apo E Interaction

A significant age × apo E interaction was observed on TG clearance after the oral fat load in multivariate analysis ($P < .01$). A comparison of postprandial TG was made between older (>55 years) and younger (≤55 years) subjects; in contrast with E3/E3 carriers, older E2 and E4 carriers exhibited a 1.5- to 2-fold higher plasma TG AUIC than their younger counterparts (Fig 2). The same age × apo E genotype interaction was observed for nonchylomicron TG AUIC ($P < .001$), but not for chylomicron TG AUIC (data not shown). This

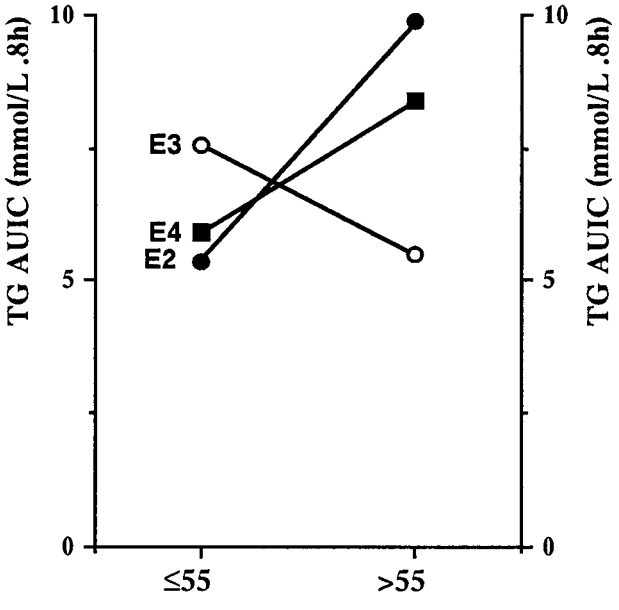

Fig 2. Age × apoE interaction on plasma TG AUIC after an oral fat load, ≤55 *v* 55 years, $P < .001$.

age × apo E genotype interaction was independent of fasting TG, BMI, and gender. Although the age × apo E interaction was not significant for RP AUIC, the same effect of age on RP clearance was suggested since older E4 and E2 carriers exhibited a 2.5- to 3-fold higher RP AUIC compared to their younger counterparts, in contrast with E3 carriers (data not shown).

Gender Interaction With Other Variables

No interaction was observed between gender on one hand and apo E and age on the other hand.

DISCUSSION

The genetic influence of apo E polymorphism on postprandial lipemia has been extensively studied in nondiabetic patients, but few studies have been performed in NIDDM.[15] In diabetes, apo E glycosylation should modify the interaction of apo E isoforms with their hepatic receptors and hence apo E–mediated TRL clearance.[21]

In the current study, the analysis of TRL postprandial profile was performed during the 8 hours following the ingestion of a vitamin A–fatty meal in order to obviate the incorporation of retinyl esters into LDL or HDL particles, which occurs after the ninth hour.[22] The present study performed on a larger group of NIDDM patients reinforces our previous finding that E2 and E4 carriers exhibit an enhanced postprandial RP peak compared to E3/E3 carriers.[15] Most studies on the influence of apo E genotype on postprandial lipemia were performed in nondiabetic subjects and showed a delayed clearance of TRL after a fatty meal in E2 carriers,[23,24] restricted to homozygous E2 in some investigations.[25,26] Data concerning the effect of an E4 allele on postprandial lipemia remain controversial,[23,27,28] but in an analysis on the effect of a fatty acid–enriched mixed meal in 16 healthy young subjects, Bergeron and Havel found that both TRL apo B48 and apo B100 clearance were delayed in E4 compared to E3 carriers,[14] in the same way as in the current study. Dallongeville et al reported from a large European sample of 882 young adults an enhanced TG response after an oral fat load in E2 and E4 carriers compared to homozygous E3.[29]

The main finding from the present study resides in the identification of interactions between apo E polymorphism and other determinants of postprandial TG clearance, such as age, body weight, and fasting TG pool, which were not yet reported in previous investigations. Regarding the influence of age on postprandial lipemia, previous studies were performed in nondiabetic subjects and showed a correlation between age and the postprandial TG response to a fatty meal,[30] resulting from a delayed clearance of intestinally derived TRLs in older subjects.[31] In the current study, no linear relationship was found between age and the postprandial rise of TG when analyzing the whole NIDDM group, possibly due to the relatively narrow age range in our experimental group compared to previous study groups,[30,31] or attributable to diabetes per se. Nevertheless, when such relationship between age and postprandial TG was studied in multivariate analysis, an age × apo E interaction was clearly demonstrated, since the enhancement of postprandial lipemia by aging was observed in the E2 and E4 groups, but not in the E3 group. To our knowledge, this is the first study to suggest that aging unmasks the deleterious effect of non-E3 alleles on postprandial TG clearance. The obvious age × apo E interaction in the E2 and E4 groups when separating the whole sample into 2 age classes with a cut-off at 55 years contrasted with the lack of significant linear correlation between age and postprandial TG. Such data suggest a threshold effect of age on postprandial lipemia in E2 and E4 carriers. In a recent longitudinal study in nondiabetic male subjects, Jarvik et al observed an age × apo E interaction on fasting lipid levels.[32] Their findings contrast with the present data, since the higher fasting TG level they observed in E4/3 compared to E3/3 carriers at the first determination (mean age, 48 years) was no longer observed at the second and third determinations (mean age, 58 and 63 years, respectively). Zerba et al also observed a decrease in plasma apo E variance with aging.[33] In contrast, the multigeneration pedigree study of 42 subjects with familial dysbetalipoproteinemia performed by de Knijff et al showed that aging worsened the lipid abnormalities driven by the apo E3-Leiden mutation.[34]

In opposition to previous data,[18] a negative correlation between BMI and postprandial TG was observed in the present study. The BMI × apo E interaction on postprandial lipemia modulates such a correlation, since it was actually restricted to E4 carriers. This negative correlation remains unexplained, but one could hypothesize defective insulin-mediated lipoprotein lipase activity in lean NIDDM subjects carrying the E4 allele.

In the current study, the fasting TG × apo E interaction on postprandial lipemia was also of paramount importance for interpreting the correlation found between fasting TG and postprandial TRL that was previously emphasized by most investigators in diabetics[15,35,36] and nondiabetic subjects.[37] The correlation found here was actually restricted to E4 and E2 carriers, and the correlation between fasting TG and RP AUIC was restricted to the sole E4 carriers.

Interactions between apo E polymorphism, BMI, age, and the fasting TG pool might thus need to be considered in order to accurately analyze the TG postprandial profile after an oral fat load. Our data emphasize the adverse and probably cumulative interaction of aging and mild fasting hypertriglyceridemia on postprandial lipemia in non-E3 carriers, and therefore might help to select NIDDM patients with a high-risk postprandial lipid profile. These findings might aid in defining the link between apo E polymorphism and the atherosclerotic vascular risk.[10-12]

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