Influences of Apolipoprotein E Polymorphism on the Response of Plasma Lipids to the Ad Libitum Consumption of a High-Carbohydrate Diet Compared With a High–Monounsaturated Fatty Acid Diet

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The purpose of this study was to assess the contribution of the apolipoprotein E (apoE) polymorphism and factors, such as age and waist circumference, to variations in plasma low-density lipoprotein-cholesterol (LDL-C) response following ad libitum consumption of a diet rich in complex carbohydrates (high-CHO: 58% of energy as CHO) versus a diet rich in fat and monounsaturated fatty acids (high-MUFA: fat, 40% of energy and 22% as MUFA). Sixty-five men participated in this parallel 6- to 7-week study involving either a high-CHO or a high-MUFA diet. Fasting plasma lipid profile and anthropometry were determined at the beginning and at the end of the dietary period. The high-CHO and high-MUFA diets both induced significant ($P < .01$) and comparable reductions in body weight and waist circumference. These changes were associated with a significant ($P < .01$) and comparable decrease in LDL-C (−19% and −16%, respectively). Stepwise multiple regression analyses showed that 32% of the variation in the LDL-C response to the high-CHO diet was attributable to the apoE polymorphism (18.5%, $P = .04$) and waist circumference (13.5%, $P = .03$) indicating that men with a waist circumference greater than100 cm and the E2 allele had the greatest reduction in plasma LDL-C after the high-CHO diet. On the other hand, in the high-MUFA group, waist circumference was the only significant contributing factor to the LDL-C response and accounted for 44.5% of its variance. In conclusion, the plasma LDL-C response to ad libitum comsumption of a high-CHO and a high-MUFA diets are not modulated to the same extent by the apoE polymorphism and waist circumference.

THE RESPONSE OF plasma lipoproteins to dietary interventions shows considerable interindividual variations,[1] and many studies have addressed the role of gene-nutrient interactions in the response of plasma lipoprotein concentrations to variations in intakes of fat, cholesterol, alcohol, and carbohydrate.[1-3] Within subjects, this response to dietary changes has been shown to be reproducible and seems to be related, in part, to the genetic characteristics of individuals.[4] Several candidate gene loci have been shown to explain a significant, but still rather small, proportion of interindividual variability in dietary response. Genetic variation at the apolipoprotein E (apoE) locus, as well as apoA4, apoB, and LPL polymorphism are among the best studied genetic determinants of plasma lipoprotein response to dietary interventions.[5]

Despite the large number of studies examining the relationship between apoE polymorphism and low-density lipoprotein-cholesterol (LDL-C) response to dietary changes, the significance of the reported associations remains controversial, and genetic variability at the apoE locus continues to be the focus of much attention.[1] In fact, there is an obvious need to investigate which specific dietary modifications would be responsible for the reported associations between apoE polymorphism and the magnitude of lipoprotein responses to dietary interventions. Most of the previous observational and interventional studies focused on the effect of the apoE polymorphism on lipoprotein responses to dietary saturated fat and cholesterol, whereas less is known about the effect of other macronutrients. Furthermore, most of these nutritional studies have been conducted under isocaloric conditions in which body weight was held constant, and little is known about the effect of the apoE polymorphism on lipoprotein responses under ad libitum conditions that more closely resemble real life feeding patterns. Therefore, the aim of the present study was to investigate the effect of the apoE polymorphism and other constitutional determinants, such as age and waist circumference, on plasma lipoprotein responses to an ad libitum diet either rich in complex carbohydrates (high-CHO diet) or in fat and monounsaturated fatty acids (high-MUFA diet).

MATERIALS AND METHODS

Subjects

Sixty-five men (mean age, 37.5 ± 11.2 [SD] years; body mass index [BMI], 29.2 ± 4.9 kg/m^2; Table 1) were recruited in the Québec City metropolitan area. Exclusion criteria included endocrine, cardiovascular, hepatic and renal disorders, use of medication known to affect lipid metabolism, smoking, and significant change in body weight within the year that preceded study onset. Individuals with excessive alcohol intake, unusual dietary habits, and food aversions or allergies were also excluded. Each participant signed a consent form approved by the Clinical Research Ethical Committee of Laval University.

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Table 1. Baseline Characteristics of Subjects According to Diets

	High-CHO Diet (n = 33)	High-MUFA Diet (n = 32)	*P*
ApoE genotypes			.67
E3/E2 (%)	3 (9)	5 (16)	
E3/E3 (%)	22 (67)	21 (65)	
E4/E3 (%)	8 (24)	6 (19)	
Age (yr)	35.9 ± 9.6	39.1 ± 12.5	.24
Weight (kg)	87.7 ± 14.3	89.3 ± 15.7	.68
Body mass index (kg/m^2)	28.8 ± 4.5	29.6 ± 5.3	.53
Waist circumference (cm)	95.3 ± 13.3	98.3 ± 15.6	.41
Plasma total cholesterol (mmol/L)	4.43 ± 1.05	4.66 ± 0.97	.36
LDL-C (mmol/L)	2.91 ± 0.88	3.13 ± 0.83	.31
HDL-C (mmol/L)	1.08 ± 0.19	1.00 ± 0.17	.09
Plasma TG (mmol/L)	1.30 ± 0.73	1.49 ± 0.65	.07
LDL-apoB (g/L)	0.84 ± 0.25	0.91 ± 0.22	.26
LDL-PPD (Å)	258.5 ± 5.7	257.4 ± 5.7	.44

Experimental Design

Subjects were randomized to either a low-fat, high-carbohydrate diet (high-CHO) or a high-fat diet rich in monounsaturated fatty acids (high-MUFA), which they consumed for 6 to 7 weeks (Table 2). The baseline characteristics of subjects according to diets are summarized in Table 1. The 2 dietary groups were comparable for age, physical characteristics, lipid, and apo levels. Participants and staff performing laboratory measures were blinded to dietary treatments. On weekdays, just before lunch, body weight was recorded while subjects were standing with their back to the scale to avoid fixation on body weight fluctuations. Compliance to the experimental diets was assessed using riboflavin incorporated in the foods, and only 2 subjects were excluded from the analysis due to a low compliance.

Experimental Diets

The nutritional composition of the experimental diets was calculated with the Canadian Nutrient File database (Health Canada, Ottawa, 1997) and the Nutrition Data System for Research (NDS-R) software (Nutrition Coordinating Center, Minneapolis, MN, Database version 4.03-30, 1999). The experimental diets consisted of usual solid foods that were prepared daily in our metabolic kitchen and weighed in individual portions. Inasmuch as this was possible, both experimental diets were formulated to have a very similar food composition, and differed mainly with respect to the proportion of the food items/ingredients and, thereby macronutrients (Table 2).

Dietary Intervention

Each participant received food in quantities that met 150% of their habitual daily energy intake as assessed by a 3-day food record completed before the dietary intervention and 200-kcal snacks provided on demand. To ensure that the macronutrient content of each diet was conserved, food in each meal was disposed in the participant's plate so that they could consume the same proportion of each component. For example, if a participant consumed 60% of the main dish, he had to

Table 2. Composition of the Usual and Experimental Diets

Nutrients	Pre-high-CHO	Pre-high-MUFA	*P*
Usual diets consumed before the experimentation (baseline diets)			
Proteins (% kcal)	14.4 ± 2.8	15.6 ± 2.6	.07
Carbohydrates (% kcal)	51.2 ± 7.0	46.8 ± 6.8	.01
Total fibers (g/1,000 kcal)	10.3 ± 38	9.1 ± 4.9	.28
Fats (% kcal)	35.0 ± 5.4	37.2 ± 6.0	.13
Saturated (% kcal)	11.9 ± 2.3	13.6 ± 3.4	.02
Monounsaturated (% kcal)	13.3 ± 2.6	14.1 ± 2.7	.25
Polyunsaturated (% kcal)	7.0 ± 2.3	6.5 ± 1.9	.41
Cholesterol (mg/1,000 kcal)	111.0 ± 41.0	155.5 ± 53.9	.01
P/S ratio	0.62 ± 0.3	0.51 ± 0.2	.08
Nutrients	**High-CHO**	**High-MUFA**	
Experimental diets consumed ad libitum during 6 to 7 weeks			
Proteins (% kcal)	15.9	15.2	
Carbohydrates (% kcal)	58.3	44.7	
Total fibers (g/1,000 kcal)	14.2	10.1	
Fats (% kcal)	25.8	40.1	
Saturated (% kcal)	6.0	8.2	
Monounsaturated (% kcal)	13.3	22.5	
Polyunsaturated (% kcal)	5.1	7.6	
Cholesterol (mg/1,000 kcal)	105.8	110.1	
P/S ratio	0.87	0.93	

Abbreviation: P/S, polyunsaturated/saturated fat ratio.

Table 3. Baseline Anthropometric Variables and Lipid Profiles of Subjects According to apoE Genotype

	E3/E2 (n = 8)	E3/E3 (n = 43)	E4/E3 (n = 14)	*P*
Age (yr)	37.3 ± 13.8	36.9 ± 10.5	39.3 ± 12.4	.79
Weight (kg)	87.5 ± 18.2	88.3 ± 14.7	89.6 ± 14.8	.95
Body mass index (kg/m^2)	27.9 ± 5.4	29.4 ± 4.9	29.1 ± 4.7	.72
Waist circumference (cm)	93.3 ± 20.2	97.3 ± 13.2	97.6 ± 15.0	.76
Plasma total cholesterol (mmol/L)	3.90 ± 0.55	4.53 ± 1.01	4.96 ± 1.07	.06
LDL-C (mmol/L)	2.40 ± 0.50*	3.04 ± 0.85	3.33 ± 0.88	.04
HDL-C (mmol/L)	1.09 ± 0.17	1.01 ± 0.17	1.10 ± 0.23	.21
Plasma TG (mmol/L)	1.15 ± 0.31	1.43 ± 0.72	1.41 ± 0.77	.74
LDL-apoB (g/L)	0.67 ± 0.14†	0.89 ± 0.23	0.95 ± 0.26	.02
LDL-PPD (Å)	258.0 ± 4.5	258.2 ± 5.7	257.2 ± 6.6	.85

*Significantly different from E4/E3.

†Significantly different from E3/E3 and E4/E3.

consume 60% of the bread and 60% of the desert. All leftovers were returned to the laboratory and weighed to calculate actual caloric and nutrient intakes.

Laboratory Methods

Blood samples were collected after a 12-hour fasting period at the beginning and at the end of the study. Samples were then immediately centrifuged at 4°C for 10 minutes at 3,000 rpm, and plasma was stored in tubes containing benzamidine (0.03%) at 4°C until processed.[6] Triglyceride (TG)-rich lipoproteins (d < 1.006 g/mL) were separated by ultracentrifugation of plasma in a 50.3 Beckman rotor (Fullerton, CA) at 4°C for 18 hours. High-density lipoprotein-cholesterol (HDL-C) was measured in the supernatant collected after heparin-chloride and $MnCl_2$ precipitation of apoB-containing lipoproteins in plasma.[7] LDL-C was calculated using the Friedwald formula unless plasma TG levels were greater than 4.5 mmol/L. Plasma and lipoprotein cholesterol and TG levels were determined enzymatically on a Technicon RA 500 (Bayer, Tarrytown, NY).

Distinct subpopulations of LDL particles in whole plasma were separated by size using nondenaturing 2% to 16% gradient gel electrophoresis.[8] Particle size was quantified by densitometric scanning of Sudan Black-stained gels using Image master 1 D Prime software (Amersham, NJ), v3.01. LDL peak particle diameter (LDL-PPD) was identified as the most important subclass of LDL in each individual and was calculated from calibration curves using plasma standards of known diameter. The coefficient of variation of the calculated particle diameters was estimated to be 2%.

DNA Analysis

The apoE genotype was determined by polymerase chain reaction (PCR)-amplification of a 244-bp fragment of the exon 4 of the apoE gene with oligonucleotides F4 and F6 and digestion of PCR fragments with the restriction enzyme HhaI.[9] Table 3 shows the baseline anthropometric variables and lipoprotein profiles of subjects according to apoE genotype. No significant difference across apoE genotype was observed for age, body mass index (BMI), total cholesterol, HDL-C, TG levels, and LDL-PPD. However, as compared with carriers of the apoE3/E3 and apoE4/E3 genotypes, subjects with the apoE2/E3 genotype had lower plasma levels of LDL-C and LDL-apoB.

Statistical Analysis

The chi-square test was used to compare the distribution of apoE alleles in the 2 diet groups. Differences in age, BMI, mean baseline levels and percentage changes of plasma lipids, lipoproteins, and apoprotein concentrations among groups were assessed by 1-way analysis of variance (ANOVA) using the Tukey-Kramer HSD post hoc test when a significant group effect was observed. In the different analyses, plasma TG data were log-transformed to normalize their distribution. Stepwise multiple regression analyses were subsequently used to estimate the independent contributions of the apoE genotype, age, waist circumference, plasma TG levels, and BMI to the variance in the percentage of response of plasma LDL-C levels. These analyses were performed using the JMP statistical software (release 5.01a, SAS, Cary, NC).

RESULTS

Variability in the Response to Dietary Intervention

As shown in Fig 1, the ad libitum consumption of the high-CHO and high-MUFA diets induced a significant ($P <$ .01) yet comparable decrease in body weight (−2.8% ± 2.8% and −2.3% ± 3.2%, respectively, $P = .97$) and waist circum-

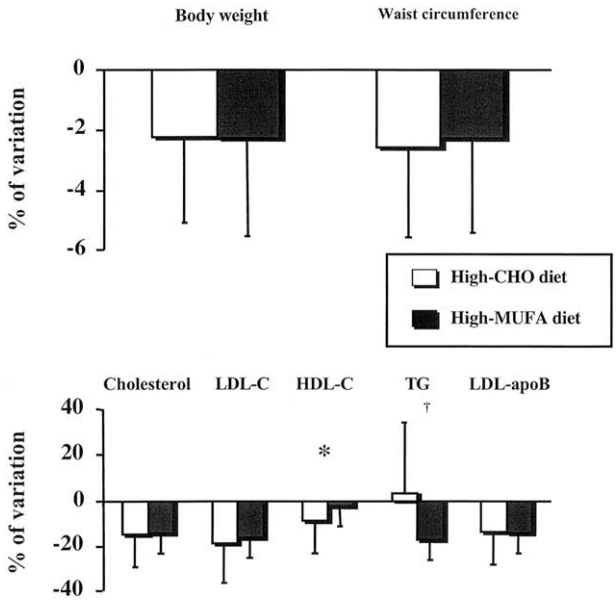

Fig 1. (A) Percentage of variation in weight and waist circumference after a 6- to 7-week high-CHO diet or a high-MUFA diet. Results are means ± SD. (B) Percentage of variation in plasma lipids after ad libitum consumption of a high-CHO diet and a high-MUFA diet. Results are means ± SD. *$P = .05$; †$P < .01$.

Table 4. Anthropometric Variables and Lipid Profiles of Subjects According to apoE Genotype After High-CHO and High-MUFA Diets

	E3/E2 (n = 3)			E3/E3 (n = 22)			E4/E3 (n = 8)			
	Pre†	Post‡	P§	Pre	Post	P	Pre	Post	P	P*
High-CHO diet										
Weight (kg)	88.6 ± 23.3	85.6 ± 22	.20	85.6 ± 12.5	84.0 ± 11.7	<.01	93.1 ± 16.2	90.2 ± 15.6	.05	.47
BMI (kg/m^2)	27.6 ± 6.2	26.6 ± 5.9	.20	28.4 ± 4.3	27.9 ± 4.1	<.01	30.2 ± 5.0	29.3 ± 4.8	.04	.47
Waist circ (cm)	88.7 ± 22.1	87.2 ± 21.0	.23	94.8 ± 10.0	92.7 ± 9.5	<.01	99.3 ± 17.4	94.9 ± 15.3	.05	.27
Total C (mmol/L)	4.09 ± 0.80	2.93 ± 0.18	.09	4.27 ± 1.06	3.72 ± 0.85	<.01	4.99 ± 1.02	3.98 ± 0.88	<.01	.09
LDL-C (mmol/L)	2.51 ± 0.69	1.58 ± 0.15	.10	2.81 ± 0.88	2.34 ± 0.71	<.01	3.36 ± 0.86	2.50 ± 0.66	<.01	.07
HDL-C (mmol/L)	1.13 ± 0.20	1.00 ± 0.13	.16	1.07 ± 0.18	0.98 ± 0.16	.01	1.09 ± 0.24	0.96 ± 0.28	.14	.84
TG (mmol/L)	1.19 ± 0.44	0.96 ± 0.10	.43	1.27 ± 0.68	1.29 ± 0.67	.74	1.41 ± 0.98	1.44 ± 1.26	.75	.63
LDL-apoB (g/L)	0.69 ± 0.20	0.52 ± 0.03	.30	0.82 ± 0.25	0.72 ± 0.22	<.01	0.96 ± 0.26	0.75 ± 0.17	<.01	.24
LDL-PPD (Å)	258.1 ± 6.5	259.0 ± 2.6	.75	258.8 ± 5.5	256.8 ± 5.1	<.01	257.9 ± 6.5	257.9 ± 8.3	.98	.27
	E3/E2 (n = 5)			E3/E3 (n = 21)			E4/E3 (n = 6)			P*
High-MUFA diet										
Weight (kg)	86.8 ± 17.6	84.2 ± 16.1	.05	91.1 ± 16.6	88.9 ± 16.2	<.01	84.9 ± 12.5	83.6 ± 14.1	.40	.86
BMI (kg/m^2)	28.1 ± 5.7	27.3 ± 5.2	.05	30.4 ± 5.4	29.4 ± 5.4	<.01	27.7 ± 4.3	27.3 ± 4.7	.38	.85
Waist circ (cm)	96.1 ± 21.1	93.3 ± 18.8	.11	99.7 ± 15.6	97.5 ± 15.4	<.01	95.4 ± 12.4	93.2 ± 14.0	.35	.95
Total C (mmol/L)	3.78 ± 0.41	3.25 ± 0.47	.11	4.80 ± 0.90	4.03 ± 0.65	<.01	4.91 ± 1.23	4.24 ± 1.20	.01	.94
LDL-C (mmol/L)	2.33 ± 0.44	1.93 ± 0.40	.17	3.28 ± 0.77	2.66 ± 0.50	<.01	3.29 ± 0.99	2.75 ± 0.94	.03	.95
HDL-C (mmol/L)	1.07 ± 0.16	1.08 ± 0.21	.89	0.95 ± 0.14	0.91 ± 0.16	.11	1.12 ± 0.23	1.13 ± 0.29	.98	.60
TG (mmol/L)	1.12 ± 0.27	0.84 ± 0.12	.07	1.61 ± 0.74	1.35 ± 0.68	.02	1.42 ± 0.44	1.05 ± 0.42	<.01	.42
LDL-apoB (g/L)	0.65 ± 0.12	0.56 ± 0.10	.07	0.96 ± 0.19	0.82 ± 0.16	<.01	0.94 ± 0.27	0.79 ± 0.23	<.01	.88
LDL-PPD (Å)	257.9 ± 3.8	259.1 ± 4.5	.24	257.6 ± 5.9	257.4 ± 6.0	.64	256.3 ± 7.2	257.2 ± 6.5	.34	.27

Abbreviations: BMI, body mass index; waist circ, waist circumference; C, cholesterol.

*P represents the P value for the difference between the % of variation among the 3 genotypes.

†Pre, before the intervention.

‡Post, after the 6 to 7-week intervention.

§P represents the P value for the difference within each genotype group (post − pre value).

ference (−2.6% ± 3.0% and −2.3% ± 3.1%, respectively, $P = .71$). Similarly, plasma total cholesterol, LDL-C, and LDL-apoB levels were significantly reduced in both groups, and the difference between the 2 experimental diets was not significant. There was a significant ($P = .05$) difference in the percent changes of plasma HDL-C concentrations between the 2 experimental diets (CHO: −9.0% ± 14.4%; MUFA: −2.5% ± 12.2%). There was also a significant ($P < .01$) difference in the percent changes of plasma TG levels between the 2 experimental diets (CHO: +3.3% ± 31.3%, MUFA: −17.1% ± 25.4%). Despite the variation in plasma TG levels after either the high-CHO or the high-MUFA diet, no significant effect was noted on LDL-PPD (data not shown).

Table 4 shows the anthropometric variables and lipid profiles of subjects according to apoE genotype after both diets. In the high-CHO group, apoE2/E3 carriers tend to experience a greater reduction in total cholesterol (−1.17 ± 0.65 mmol/L) and LDL-C (−0.93 ± 0.55 mmol/L) compared with apoE3/E3 and E4/E3 carriers, but the CHO-related differences among the 3 genotypes did not reach statistical significance. To further characterize the influences of apoE polymorphism on the response of plasma lipids to the 2 experimental diets, we have compared the percentage of variation in plasma lipoprotein levels attributable to the apoE genotype after diet intervention (Fig 2). Carriers of an E2 allele consuming a high-CHO diet had a greater reduction in their LDL-C (−34.8% ± 13.3%) than E3 (−14.1% ± 18.7%) and E4 (−25.4% ± 8.2%) carriers. There was no significant association between the magnitude of LDL-C response and apoE genotype in the subjects consuming the high-MUFA diet (Table 4 and Fig 2). Similarly, no significant association was observed between the apoE polymorphism and variations in LDL-PPD (data not shown).

Despite randomization, usual baseline diets (preintervention diets) consumed by the subjects before the experiment contained some significant differences. Men assigned to the experimental high-CHO diet had a usual baseline diet higher in carbohydrates, but lower in saturated fatty acids and cholesterol compared with men who were assigned to the experimental high-MUFA group (Table 1). Thus, all models used for our

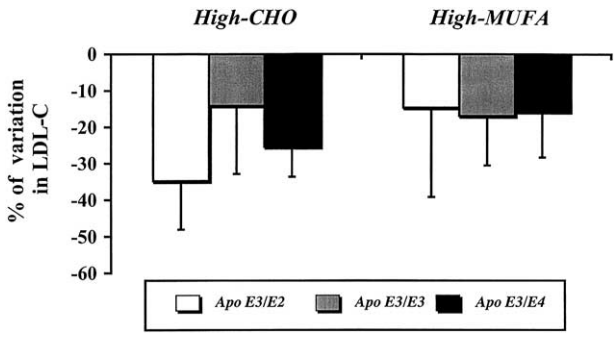

Fig 2. Percentage of variation in plasma LDL-C after a 6- to 7-week ad libitum consumption of a high-CHO diet and a high-MUFA diet. Results are means ± SD.

Table 5. Contribution of the apoE Genotype to Percent of Plasma LDL-C Response to High-CHO and High-MUFA Diets

Diets	Independent Variables	Total ($R^2 \times 100$)	Partial ($R^2 \times 100$)	*P*
CHO	ApoE genotype	33.3	18.5	.04
	Age (yr)		1.3	.48
	Waist circumference (cm)		13.5	.03
MUFA	ApoE genotype	45.2	0.2	.97
	Age (yr)		0.4	.68
	Waist circumference (cm)		44.5	<.01

NOTE. R squared, coefficient of multiple determination indicating the proportion of the variance in the percentage of lipoprotein changes explained by the independent variables; *P,* probability value. Baseline plasma LDL-C and TG levels as well as %kcal provided by carbohydrates, saturated fatty acids and quantity of cholesterol in usual diet were also included in the model.

multiple regression analyses were adjusted for baseline carbohydrate, saturated fatty acid, and cholesterol intakes. Stepwise multiple regression analyses (Table 5) showed that 32% of the variation in the LDL-C response to the high-CHO diet was attributable to apoE polymorphism (18.5%, $P = .04$) and baseline waist circumference (13.5%, $P = .03$). These results indicated that men with a baseline waist circumference greater than 100 cm and the apoE3/2 genotype had the greatest percent reduction in plasma LDL-C levels. On the other hand, in the high-MUFA group, baseline waist circumference was the only contributing factor to the LDL-C response and accounted for 44.5% of its variance.

DISCUSSION

The purpose of this study was to investigate the effect of the apoE polymorphism and other constitutional determinants such as age and waist circumference on plasma lipoprotein responses to an ad libitum consumption of either a high-CHO or a high-MUFA diet. Our results showed that carriers of an E2 allele consuming a high-CHO diet experienced a greater reduction in their plasma LDL-C levels compared with E3 and E4 carriers. Our result is consistent with those of Jenkins et al[2] who reported that carriers of the E2 allele experienced the greatest reduction of total plasma cholesterol and LDL-C levels after the isocaloric intake of diets enriched with fibers compared with carriers of the E3 and E4 alleles. In addition, in our study, 32% of the percent variation in the LDL-C response to the ad libitum high-CHO diet was attributable to apoE polymorphism and baseline waist circumference, which represented 18.5%, and 13.5% of the total variance, respectively. Thus, these results suggest that apoE polymorphism is an independent predictor of LDL-C response to the high-CHO diet after adjustment for baseline waist circumference. On the other hand, in the high-MUFA diet group, baseline waist circumference was the only contributing factor to LDL-C response and accounted for as much as 44.5% of its variance. The apoE phenotype had no effect on LDL-C response to an ad libitum high-MUFA diet. Sarkkinen et al[10] reported similar results when they investigated the interaction of apoE polymophism in hypercholesterolemic men and women after the isocaloric intake of saturated fatty acids or MUFA. However, our observations contrast with results from the Delta study,[11] which reported that apoE genotype did not predict the lipid response to a low saturated fatty acid diet in 103 normolipidemic subjects. The partially contradictory results obtained from previous studies addressing the role of the apoE polymorphism in the response of plasma lipid levels to variations in fat and cholesterol intakes were reviewed extensively.[1,5] Large number of reports showed significant associations between the E4 allele and an increased LDL-C response to dietary intervention,[12-14] however, the same number of reports failed to replicate such associations.[11,15,16] Several hypotheses can explain these discrepancies. One is that the apoE polymorphism affects the response of cholesterol only in men, not in women, or only in populations in which baseline plasma total cholesterol levels differ significantly between the various apoE genotypes. Another possible explanation is that the apoE polymorphism may only affect the response of plasma cholesterol to specific dietary changes. The present study supports this concept, because we have observed that the plasma LDL-C responses to high-CHO and high-MUFA diets are not modulated to the same extent by the apoE polymorphism.

This study also showed a significant association between plasma LDL-C response to high-CHO and high-MUFA diets and baseline waist circumference. Interestingly, this association remained significant even after adjustment for the apoE polymorphism and other confounding variables, such as baseline LDL-C and TG levels, as well as baseline carbohydrate, saturated fatty acid, and cholesterol intakes. We have observed that subjects with a larger waist circumference before dietary interventions had a greater reduction in plasma LDL-C levels after the ad libitum consumption of either the high-CHO diet or the high-MUFA diet. This observation contrasts with the previous findings of Jansen et al,[17] who demonstrated that baseline BMI was inversely correlated with the magnitude of LDL-C response to an hypolipidemic diet, because subjects with a greater BMI have a lower decrease in plasma LDL-C than normal weight individuals. Denke et al[18] also reported that BMI predicted lipid response. In their study, heavier individuals had less LDL-C response to dietary change. One possible explanation for these discrepancies could depend on the experimental design. Both studies were performed in crossover, isocaloric design, while ours was performed in a parallel, ad libitum set-up allowing weight fluctuation.

The mechanism underlying the differential impact of the apoE polymorphism on lipoprotein response to specific dietary interventions is not known. It is reasonable to assume that the mechanism by which plasma LDL-C responses to dietary changes are increased in E3/E2 carriers may be related to the slower catabolic rate of E2 as compared with E3 or E4[19] and by the difference in the regulation of apoE expression between the high-CHO and the high-MUFA diets. As compared with the

high-MUFA diet, the high-CHO diet could reduce intracellular hepatic cholesterol concentrations to a greater extent in carriers of an E2 allele, thus increasing the upregulation of LDL receptor expression and LDL particle uptake. In fact, it has been shown that the various apoE isoforms differ in binding affinity for the LDL receptor and the LDL receptor-related protein, TG-rich lipoprotein particles, and HDL.[20-22] As expected from previous population studies, our results showed that carriers of the E2 allele had lower plasma LDL-C levels, while carriers of E4 allele had higher LDL-C concentrations than E3 homozygotes.[23-25]

In conclusion, the results of the present study have shown that the LDL-C responsiveness to an ad libitum consumption of a high-CHO diet, but not to a high-MUFA diet, is modulated by the apoE polymorphism. Additional studies need to be carefully designed in term of sample size, subject characteristics (men, women, obese, hyperlipidemic subjects), and dietary interventions (carbohydrates, amount of fat, type of fat) to further examine this issue. Moreover, the genetic heritabilities of diet responsiveness need to be explored within large families to identify new responsiveness loci. In the meantime, we believe that the factors presented in this study may provide useful markers to predict the efficacy of dietary intervention.

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