

Effect of Apolipoprotein E4 Allele on Plasma LDL Cholesterol Response to Diet Therapy in Type 2 Diabetic Patients

MIEKO SAITO, MD, PHD¹
 MASAOKI ETO, MD, PHD¹
 HAYAMI NITTA²
 YUKIKO KANDA, MD¹
 MAKOTO SHIGETO, MD¹
 KATSURA NAKAYAMA, MD¹
 KAZUHIITO TAWARAMOTO, MD¹

FUMIKO KAWASAKI, MD¹
 SHINJI KAMEI, MD¹
 KENJI KOHARA, MD¹
 MASAFUMI MATSUDA, MD, PHD¹
 MICHIIHIRO MATSUKI, MD, PHD¹
 KOHEI KAKU, MD, PHD¹

OBJECTIVE — The aim of this study was to investigate the effect of apolipoprotein (apo)E4 allele on plasma LDL cholesterol response to calorie-restricted diet therapy in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — Twenty-four diabetic patients with the apoE3/3 genotype and 11 diabetic patients with the apoE4/3 genotype were recruited. Participants were hospitalized for calorie-restricted diet therapy (25.0 kcal · kg body wt⁻¹ · day⁻¹) for 14 days. Body weight, fasting plasma glucose (FPG) levels, and plasma lipid levels on hospital days 1 and 14 were compared between the two apoE genotype groups.

RESULTS — There were no significant differences in baseline FPG levels, HbA_{1c} levels, BMI, and plasma levels of total cholesterol, triglyceride, and HDL cholesterol between the two apoE genotype groups, but baseline plasma levels of LDL cholesterol were significantly higher in the apoE4/3 group than in the apoE3/3 group. Body weight decreased slightly and FPG levels decreased significantly after diet therapy in both apoE genotype groups. In the apoE3/3 group, only plasma levels of triglyceride decreased significantly after diet therapy, whereas in the apoE4/3 group, plasma levels of triglyceride, total cholesterol, and LDL cholesterol decreased significantly after diet therapy. The decrease (percentage of change) in total cholesterol (−16.3 vs. −6.6%) and LDL cholesterol (−15.6 vs. −0.7%) after diet therapy was significantly greater in the apoE4/3 group than in the apoE3/3 group.

CONCLUSIONS — Calorie-restricted diet therapy is more effective in reducing plasma LDL cholesterol in type 2 diabetic patients with the apoE4 allele.

Diabetes Care 27:1276–1280, 2004

Type 2 diabetes is associated with a twofold increased risk of coronary heart disease (CHD) in Japan (1). A high plasma level of LDL cholesterol is one of the risk factors for CHD. Genetic factors have been thought to be associated with high plasma levels of LDL cholesterol.

We previously reported that type 2 diabetic patients had significantly higher plasma levels of LDL cholesterol than nondiabetic subjects (2), and that apolipoprotein (apo)E4 is one of the genetic factors for high levels of plasma LDL cholesterol in type 2 diabetic patients (3,4).

From the ¹Department of Internal Medicine, Division of Diabetes & Endocrine, Kawasaki Medical School, Kurashiki, Japan; and the ²Department of Clinical Nutrition, Kawasaki University of Medical Welfare, Kurashiki, Japan.

Address correspondence and reprint requests to M. Eto, MD, PhD, Diabetes & Endocrine Division, Department of Internal Medicine, Kawasaki Medical School, Matsushima 577, Kurashiki 701-0192, Japan. E-mail: eto@med.kawasaki-m.ac.jp.

Received for publication 20 November 2003 and accepted in revised form 26 February 2004.

Abbreviations: apo, apolipoprotein; CHD, coronary heart disease; FPG, fasting plasma glucose; TG, triglyceride.

© 2004 by the American Diabetes Association.

ApoE is one of the major protein constituents in triglyceride (TG)-rich lipoproteins and has an important role in cholesterol metabolism through its ability to bind to receptors (5). The apoE genetic polymorphism is well known. Three different apoE alleles (ε2, ε3, and ε4) at a single genetic locus produce the apoE isoforms apoE2, apoE3, and apoE4, respectively. According to genetic models of these three alleles, six apoE phenotypes (genotypes) are recognized (5). ApoE3 is the native form. ApoE4 is caused by a change of residue 112 from Cys to Arg and has increased catabolism of TG-rich lipoproteins, leading to increased LDL levels in plasma (5). Epidemiological studies (6) including ours (7) have shown a higher incidence of CHD in subjects with the apoE4 genotypes (apoE4/3 or apoE4/4 genotype) than in those with the apoE3/3 genotype.

Reduction of elevated levels of plasma cholesterol by dietary intervention can markedly reduce the risk for CHD (8). Lifestyle modification, particularly diet therapy is very essential to reduce plasma cholesterol and TG and glucose levels and to prevent CHD in diabetic patients. It is well known that there is a difference in plasma cholesterol response to diet therapy among individual subjects, that is, there exist hypo- and hyperresponders to diet (9). The difference is in part explained by genetic factors, which is related to its response to diet. ApoE4 is one of the candidate genes that may contribute to responsiveness to diet therapy, but it remains controversial (10). In diabetic patients there is little information concerning the relationship between the apoE4 allele and plasma LDL cholesterol response to diet therapy. Our previous cross-sectional study showed that hypercholesterolemia in type 2 diabetic patients with the apoE4 allele is more closely related to poor glycemic control (11). There is, therefore, a possibility that diabetic patients with the apoE4 allele are more responsive to diet therapy and correction of glycemic control.

Table 1—Baseline characteristics of type 2 diabetic patients with the apoE3/3 or the apoE4/3 genotype

Genotype	ApoE3/3	ApoE4/3	P*
n (male/female)	24 (10/14)	11 (4/7)	
Age (years)	61 ± 2	57 ± 3	NS
Duration of diabetes (years)	9.0 ± 1.3	9.5 ± 2.3	NS
BMI (kg/m ²)	25.2 ± 1.2	26.3 ± 0.9	NS
FPG (mg/dl)	185 ± 33	182 ± 17	NS
HbA _{1c} (%)	9.1 ± 0.4	8.7 ± 0.8	NS

Data are means ± SE. *P value for the apoE3/3 vs. the apoE4/3 genotype.

This study was undertaken to elucidate the effect of the apoE4 allele on plasma LDL cholesterol response to a 14-day in-hospital diet therapy in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

Twenty-four diabetic patients with the apoE3/3 genotype (10 males and 14 females) and 11 diabetic patients with the apoE4/3 genotype (4 males and 7 females) were recruited from our school hospital. All patients are Japanese. Excluded were patients with overt nephropathy, liver disease, or endocrine disease or patients who consumed alcohol. No medication known to influence the lipid state, except for oral hypoglycemic agents or insulin, was administered. The present study was undertaken according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before the study. All of the patients were hospitalized in our school hospital for the metabolic and dietary control. On admission, 12 patients were treated with diet alone, 6 patients with oral hypoglycemic agents, and 19 patients with insulin. During hospital days 1–14, all patients were treated with a diet of 25.0 kcal · kg body wt⁻¹ · day⁻¹ without any changes of medication. The in-hospital diet included 19% protein, 60% carbohydrate, and 21% fat of the total calories and 255 mg/day of cholesterol. The ratio of polyunsaturated, monounsaturated, and saturated fatty acids (P:M:S ratio) of the in-hospital diet was ~1:1:1. All patients recorded their own dietary intake 3 days before hospitalization. The records were completed by the in-depth interview by a dietitian at the hospital. Based on the dietary records, total energy intake and intake of fat, cholesterol, and fatty acids were calculated. The energy derived from

protein, fat, and carbohydrates relative to the total energy intake was also calculated. The food composition database (12) was used in these calculations. There was no significant difference in the daily calorie intake before hospitalization (average 32.3, apoE3/3 genotype 33.4 ± 1.5, and apoE4/3 genotype 32.8 ± 1.7 kcal · kg body wt⁻¹ · day⁻¹), cholesterol intake before hospitalization (average 261, apoE3/3 genotype 260 ± 34, and apoE4/3 genotype 263 ± 26 mg/day), and fat intake before hospitalization (average 20.7%, apoE3/3 genotype 21.0 ± 1.5%, and apoE4/3 genotype 19.6 ± 3.3% of total calorie intake) between the two apoE genotype groups. P:M:S ratio in the diet before hospitalization was ~1:1:1.

Body weight, fasting plasma glucose (FPG) levels, and plasma levels of total cholesterol, TG, HDL cholesterol, and LDL cholesterol were measured in the morning after an overnight fast on hospital days 1 and 14. The plasma total cholesterol, TG and HDL cholesterol, and FPG were measured by enzymatic methods. LDL cholesterol was calculated by the Friedewald formula (13). This formula was available because plasma levels of TG in all patients were <400 mg/dl. Baseline HbA_{1c} was measured by high-performance liquid chromatography.

ApoE phenotypes and genotypes were determined by the following methods. A method for apoE phenotyping directly from plasma by isoelectric focusing and immunoblotting (Phenotyping ApoE IEF System; Joko Company, Tokyo, Japan) was used. In addition, apoE genotypes were determined by the PCR restriction fragment–length polymorphism method reported by Hixon et al. (14). If apoE phenotypes and genotypes are not matched, this suggests that there is another mutation in apoE. However, both

were matched in all cases of the present study.

All values were expressed as the mean ± SE, and the significance of differences between the means was determined by Student's *t* test. The statistical analyses were conducted using the SAS system (StatView) (15). *P* < 0.05 was considered significant.

RESULTS— Baseline characteristics of type 2 diabetic patients with the apoE3/3 or apoE4/3 genotype are shown in Table 1. There were no significant differences in the age and duration of diabetes between the two apoE genotype groups. There were no significant differences in baseline FPG levels, baseline HbA_{1c} levels, or baseline BMI between the two apoE genotype groups. As shown in Table 2, there were no significant differences in baseline (before diet therapy) plasma levels of total cholesterol, TG, and HDL cholesterol between the two apoE genotype groups, but baseline plasma levels of LDL cholesterol were significantly (*P* < 0.01) higher in the apoE4/3 genotype group (147 ± 3 mg/dl) than in the apoE3/3 group (134 ± 2 mg/dl).

The changes of body weight, FPG levels, and plasma levels of lipids before and after diet therapy in the apoE3/3 and apoE4/3 genotype groups are shown in Table 2. Body weight decreased slightly but not significantly after diet therapy in both apoE genotype groups. FPG levels decreased significantly (*P* < 0.001) after diet therapy in both apoE genotype groups. In the apoE3/3 group, plasma levels of TG decreased significantly (*P* < 0.05) after diet therapy, but plasma levels of total, LDL, and HDL cholesterol did not change after diet therapy. However, in the apoE4/3 group, plasma levels of total and LDL cholesterol and TG decreased significantly (*P* < 0.05, *P* < 0.001, and *P* < 0.05, respectively) after diet therapy. Plasma levels of HDL cholesterol did not change after diet therapy in the apoE3/3 or apoE4/3 genotype group. Plasma levels of LDL cholesterol after diet therapy were significantly (*P* < 0.05) lower in the apoE4/3 group (125 ± 2 mg/dl) than in the apoE3/3 group (133 ± 3 mg/dl).

The decrease (percentage of change) before and after diet therapy is shown in Fig. 1. The decrease (percentage of change) in body weight, FPG levels, and plasma levels of HDL cholesterol and TG after diet therapy was not significantly dif-

Table 2—Body weight and FPG and plasma lipid levels before and after diet therapy in type 2 diabetic patients with the apoE3/3 or the apoE4/3 genotype

	ApoE3/3 genotype			ApoE4/3 genotype		
	Before	After	P*	Before	After	P*
Body weight (kg)	64.3 ± 3.0	61.9 ± 2.6	NS	65.1 ± 1.9	63.1 ± 5.2	NS
FPG (mg/dl)	185 ± 33	122 ± 20	<0.001	182 ± 17	135 ± 17	<0.001
Total cholesterol (mg/dl)	224 ± 8	207 ± 7	NS	235 ± 10	195 ± 8	<0.05
LDL cholesterol (mg/dl)	134 ± 2	133 ± 3	NS	147 ± 3†	125 ± 2‡	<0.001
HDL cholesterol (mg/dl)	50 ± 3	47 ± 2	NS	43 ± 3	40 ± 2	NS
Triglyceride (mg/dl)	199 ± 20	136 ± 12	<0.05	224 ± 25	153 ± 15	<0.05

Data are means ± SE. *P values before vs. after diet therapy; †P < 0.01 vs. before diet therapy in patients with the apoE3/3 genotype; ‡P < 0.05 vs. after diet therapy in patients with the apoE3/3 genotype.

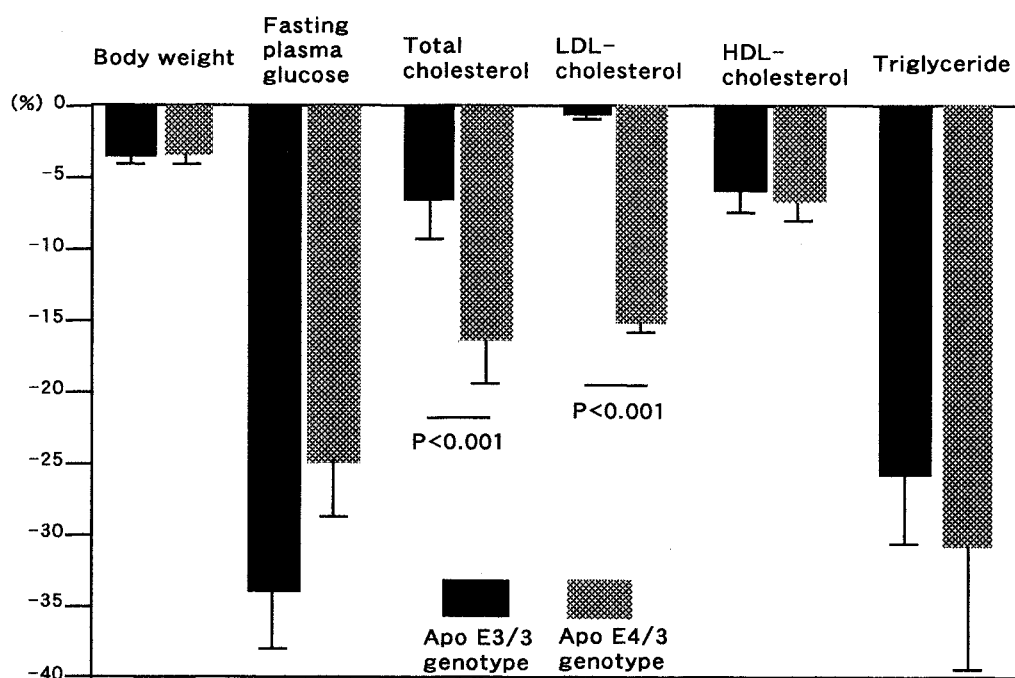
ferent between the apoE genotype groups, whereas the decrease (percentage of change) in total (−16.3 vs. −6.6%) and LDL (−15.6 vs. −0.7%) cholesterol after diet therapy was significantly ($P < 0.001$) greater in the apoE4/3 group than in the apoE3/3 group.

CONCLUSIONS— In the present study, we examined the effect of the apoE4 allele on plasma LDL cholesterol response to 14-day in-hospital diet therapy in type 2 diabetic patients. Diabetic patients with the apoE3/3 or apoE4/3 genotype showed a similar magnitude of improvement in plasma FPG and TG levels after diet therapy. However, diabetic pa-

tients with the apoE3/3 genotype showed no improvement of plasma LDL cholesterol, whereas diabetic patients with the apoE4/3 genotype showed a significantly greater improvement of plasma total and LDL cholesterol after diet therapy. The improvements in plasma glucose, cholesterol, and TG after diet therapy observed in this study may be mainly attributed to strict calorie restriction by hospitalization because only the daily calorie intake was significantly changed from 33.2 before hospitalization to 25.0 kcal · kg body wt^{−1} · day^{−1} after hospitalization, whereas cholesterol intake (261 vs. 255 mg/day) and fat intake (20.7 vs. 21.0% of total calorie intake) were not different be-

fore and after hospitalization. The present study, therefore, indicates that calorie-restricted diet was associated with significantly greater improvement of plasma LDL cholesterol in diabetic patients with the apoE4 allele. Calorie-restricted diet is, of course, the most fundamental diet therapy for diabetic patients. As far as we know, this is the first study to describe that the apoE4 allele links calorie restriction to greater improvement of plasma LDL cholesterol in type 2 diabetic patients.

Mortality from CHD is lower in Japan than in western countries, which is in part due to the Japanese low-fat diet. However, national surveys (16) conducted in

**Figure 1**—The decrease (percentage of change) in body weight, FPG levels, and plasma levels of total, LDL, and HDL cholesterol and TG before and after calorie-restricted diet therapy in type 2 diabetic patients with the apoE4/3 or apoE3/3 genotype. Data are expressed as means ± SE.

Japan indicate that although the mean total energy intake has remained steady, fat intake increased to 26.5% of total energy intake in the year 2000. Japanese diabetic patients are recommended to have 20–25% energy intake from fat, 15–20% from protein, and 60% from carbohydrate and to have a daily calorie intake of 25–30 kcal · kg body wt⁻¹ · day⁻¹ and a cholesterol level <300 mg/day (17,18). Therefore, the in-hospital diet selected in the present study is the diet recommended for Japanese diabetic patients. It is of great interest that fat intake remained 20.7% in patients ~60 years of age, even before hospitalization. As a result, there was only a difference in the daily calorie intake and no difference in fat or cholesterol intake before and after hospitalization; thus, the effect of fat or cholesterol intake on the results may be negligible in the present study.

There have been many reports concerning the effect of the apoE4 allele on plasma cholesterol response to low-fat and/or low-cholesterol diet therapy in nondiabetic subjects (10). The presence of the apoE4 allele was suggested to enhance intestinal cholesterol absorption (19) and then to increase plasma cholesterol response to dietary cholesterol. In fact, it was reported that low-fat and low-cholesterol diets contribute to greater improvement of plasma total and LDL cholesterol in normal subjects with the apoE4/4 or apoE4/3 genotype (20), which is supported by a meta-analysis (21). In addition, it was reported that the apoE genotype does not predict lipid response to changes in dietary saturated fatty acids (22). In the present study, there were no significant differences in dietary cholesterol and fat intake or in the ratio of dietary fatty acids before and after hospitalization; thus, these factors may not explain the present finding of greater cholesterol response in diabetic patients with the apoE4 allele.

Diabetic patients with the apoE4/3 genotype had significantly higher baseline plasma levels of LDL cholesterol than those with the apoE3/3 genotype, which is consistent with our previous findings (3,4). We reported that obesity and/or poor glycemic control contribute(s) to high plasma levels of LDL cholesterol in diabetic subjects with the apoE4 allele (11) or in obese subjects with the apoE4 allele (23). Since there were no significant differences in baseline levels of FPG, BMI,

and dietary fat and cholesterol intake between the diabetic patients with apoE4/3 and apoE3/3 genotypes, these may not account for higher baseline plasma levels of LDL cholesterol in diabetic patients with the apoE4/3 genotype. ApoE4 was reported to be more effective in converting TG-rich lipoproteins to LDL, leading to increased LDL levels in plasma (5,24). In addition, there is a report that intestinal cholesterol absorption efficiency is greater in subjects with the apoE4 allele, although this is not confirmed in diabetic patients (19). Thus, these effects of apoE4 may account for higher baseline plasma levels of LDL cholesterol in diabetic patients with the apoE4/3 genotype.

Plasma levels of LDL cholesterol were significantly decreased after diet therapy in diabetic patients with the apoE4/3 genotype than in those with the apoE3/3 genotype. The mechanism of greater LDL cholesterol response to calorie restriction in diabetic patients with the apoE4 allele remains at present unknown. Calorie restriction may decrease plasma glucose and decrease visceral fat mass and circulating fatty acid concentration, resulting in the decrease of VLDL production in the liver and the decrease of plasma TG, which reflects VLDL. Calorie restriction may also improve insulin sensitivity, increase plasma glucose disappearance, and possibly stimulate lipoprotein lipase activity, resulting in enhanced conversion of VLDL to LDL and the decrease of plasma TG. In fact, body weight fell slightly, and FPG levels and plasma levels of TG fell significantly at the same extent after calorie-restricted diet in diabetic patients with the apoE4/3 or apoE3/3 genotype. In addition, calorie restriction improves hyperglycemia and may reduce glycated LDL, which is less effectively catabolized by LDL receptor and which accumulates in plasma (25), resulting in the decrease of plasma LDL. Murakami et al. (26) reported that 7-day calorie-restricted diet therapy was effective to reduce plasma TG and glucose levels but not effective to reduce plasma LDL cholesterol levels in type 2 diabetic patients with the apoE3/3 genotype or even in those with the apoE4 genotypes; this suggests that plasma LDL cholesterol response to calorie restriction is slower than plasma glucose and TG response to calorie restriction in diabetic patients. The present study indicates that long-term (at least 14 days) calorie restriction reduces plasma LDL cholesterol lev-

els in type 2 diabetic patients with the apoE4/3 genotype but not in those with the apoE3/3 genotype. The presence of apoE4 is possibly associated with faster catabolism of lipoproteins including LDL (24). It is unknown whether diabetic patients with the apoE3/3 genotype are nonresponders of plasma LDL cholesterol to calorie restriction or they are responders when they follow the calorie-restricted diet for the longer term.

ApoE4 is a genetic factor that leads to high plasma levels of LDL cholesterol and CHD in nondiabetic subjects (6,7) and in diabetic patients (3,27). Reduction of elevated levels of plasma LDL cholesterol is very important to prevent CHD in diabetic patients with the apoE4 allele. The 14-day calorie-restricted diet therapy is a beneficial measure to treat hypercholesterolemia in type 2 diabetic patients with the apoE4/3 genotype, since the apoE4 allele appears to link calorie restriction to greater improvement of plasma LDL cholesterol. Further studies are needed to elucidate the detailed mechanisms and the effects of other genes on cholesterol response to diet.

Acknowledgments— This study was supported by a grant-in-aid (no. 14571112) from the Ministry of Education, Science and Culture of Japan and by project grants (no. 14-507 and no. 15-504) from Kawasaki Medical School.

References

1. Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Yoshitake T: Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes* 45 (Suppl. 3):S14–S16, 1996
2. Eto M, Watanabe K, Iwashima Y, Morikawa A, Oshima E, Sekiguchi M, Ishii K: Apolipoprotein E polymorphism and hyperlipemia in type II diabetes. *Diabetes* 35: 1374–1382, 1986
3. Eto M, Watanabe K, Iwashima Y, Morikawa A, Chonan N, Oshima E, Sekiguchi M, Ishii K: Increased frequency of apolipoprotein ε4 allele in type II diabetes with hypercholesterolemia. *Diabetes* 36:1301–1306, 1987
4. Eto M, Watanabe K, Makino I, Ishii K: Apolipoprotein E allele frequency in non-insulin-dependent diabetes mellitus with hypertriglyceridemia (type IIb, III, IV, and V hyperlipoproteinemia). *Metabolism* 40:776–780, 1991
5. Mahley RW: Apolipoprotein E: chole-

- terol transport protein with expanding role in cell biology. *Science* 240:622–630, 1988
6. Wilson PWF, Schaefer EJ, Larson MG, Ordovas JM: Apolipoprotein E alleles and risk of coronary heart disease: a meta-analysis. *Arterioscler Thromb Vasc Biol* 16: 1250–1255, 1996
 7. Eto M, Watanabe K, Ishii K: Increased frequencies of apolipoprotein ϵ 2 and ϵ 4 alleles in patients with ischemic heart disease. *Clin Genet* 36:183–188, 1989
 8. Ringer SH: Primary prevention of coronary heart disease by diet. *Bull NY Acad Med* 44:936–949, 1968
 9. Katan MB, Beynen AC: Characteristics of human hypo- and hyperresponders to dietary cholesterol. *Am J Epidemiology* 125: 387–399, 1987
 10. Masson LF, McNell G, Avenell A: Genetic variation and the lipid response to dietary intervention: a systematic review. *Am J Clin Nutr* 77:1098–1111, 2003
 11. Eto M, Watanabe K, Makino I: Relationship of metabolic control and body weight to hypercholesterolemia in NIDDM patients with apolipoprotein E4. *Diabetes Care* 14:127–129, 1991
 12. Kagawa Y: *Food Composition Database*. Tokyo, Kagawa Nutrition University Press, 2003
 13. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
 14. Hixon JE, Vernier DT: Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 31:545–548, 1990
 15. Statistical Analysis System Institute: *StatView Reference Manual*. Cary, NC, SAS Institute, 1998
 16. Nutrition Division, Public Health Service, Ministry of Health, Labour and Welfare, Japan: *Nutritional Status of Japanese, Results From the National Nutrition Survey*. Japan Food Association, Tokyo, Dai-Ichi Publishing Co., 2003
 17. Iwamoto Y, Kasuga M, Kanazawa Y, Sakurai H, Shima K, Totota R, Nanjou K, Kadowaki T: *Therapy Guide for Diabetic Patients, 2000 Edition*. Tokyo, Japan Diabetes Society, 2000
 18. Kita T, Mabuchi H, Itakura H, Ueshima K, Egusa G, Eto M, Kashiwagi A, Sasaki A, Shimamoto K, Suehiro T, Teramoto T, Biro S, Hirobe K, Funahashi T: *Guideline for Atherosclerosis Treatment, 2002 Edition*. Tokyo, Japan Atherosclerosis Society, 2002
 19. Kesaniemi YA, Ehnholm C, Miettinen TA: Intestinal cholesterol absorption efficiency in man is related to apoprotein E phenotype. *J Clin Invest* 80:578–581, 1987
 20. Miettinen HE, Gylling H, Vanhanen H: Serum cholesterol response to dietary cholesterol and apoprotein phenotype (Letter). *Lancet* 2:1261, 1988
 21. Lopez-Miranda J, Ordovas JM, Mata P, Lichtenstein AH, Clevidence B, Judd JT, Schsefer EJ: Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. *J Lipid Res* 35:1965–1975, 1994
 22. Lefevre M, Ginsberg HN, Kris-Etherton PM, Elmer PJ, Stewart PW, Ershow A, Pearson TA, Roheim PS, Ramakrishnan R, Derr J, Gordon DJ, Reed R, the DELTA Research Group (Dietary Effects on Lipoproteins and Thrombogenic Activity): ApoE genotype does not predict lipid response to changes in dietary saturated fatty acids in a heterogenous normolipidemic population. *Arterioscler Thromb Vasc Biol* 17:2914–2923, 1997
 23. Eto M, Watanabe K, Ishii K: Apolipoprotein E polymorphism and hyperlipoproteinemia in obesity. *Int J Obes* 13:433–440, 1989
 24. Gregg RE, Zecvh LA, Shaefer EJ, Stark D, Wilson D, Brewer HB Jr: Abnormal in vivo metabolism of apolipoprotein E4 in humans. *J Clin Invest* 78:815–821, 1986
 25. Lyons TJ: Glycation and oxidation: a role in the pathogenesis of atherosclerosis. *Am J Cardiology* 71:26B–31B, 1993
 26. Murakami K, Shimizu M, Yamada N, Ishibashi S, Shimano H, Yazaki Y, Akanuma Y: Apolipoprotein E polymorphism is associated with plasma cholesterol response in a 7-day hospitalization study for metabolic and dietary control in NIDDM. *Diabetes Care* 16:564–569, 1993
 27. Laakso M, Kesaniemi A, Kervinen K, Jauhiainen M, Pyorala K: Relation of coronary heart disease and apolipoprotein E phenotype in patients with non-insulin dependent diabetes. *Br Med J* 303:1159–1192, 1991