Triglyceride levels are ethnic-specifically associated with an index of stearoyl-CoA desaturase activity and n-3 PUFA levels in Asians

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Abstract **Accumulated evidence suggests that hypertriglyceridemia (HTG) is independently associated with an increased incidence of cardiovascular disease. The hypotriglyceridemic effects of n-3 PUFAs have been confirmed in Caucasians, but the effect in Asians is less clear. Recent evidence indicates that stearoyl-CoA desaturase (SCD) activity induced with high-carbohydrate diets increases plasma triglyceride levels. We investigated the relationship between triglyceride levels and the ratio of plasma oleic acid to stearic acid (the 18:1/18:0 ratio), a plasma marker of SCD activity, and n-3 PUFAs in 411 Japanese, 418 Korean, and 251 Mongolian adults. The Japanese and Koreans had higher values for triglyceride than their Mongolian counterparts, despite lower body mass index values for the Japanese and Koreans. The Japanese and Koreans ate fish more frequently and had remarkably higher values for n-3 PUFAs than did the Mongolians. Multiple regression analysis showed that triglyceride levels had a great magnitude of correlation with the increases in 18:1/18:0 ratio for the Japanese and Mongolians, and n-3 PUFAs remained significant for the Mongolians. HTG is ethnicity-specifically associated with an increase in the 18:1/18:0 ratio and a decrease in n-3 PUFA in plasma for Japanese, Koreans, and Mongolians.**—Shiwaku, K., M. Hashimoto, K. Kitajima, A. Nogi, E. Anuurad, B. Enkhmaa, J-M. Kim, I-S. Kim, S-K. Lee, T. Oyunsuren, O. Shido, and Y. Yamane. **Triglyceride levels are ethnic-specifically associated with an index of stearoyl-CoA desaturase activity and n-3 PUFA levels in Asians. *J. Lipid Res.* 2004.** 45: **914–922.**

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The prevalence of hypertriglyceridemia (HTG) has increased concomitantly with the global obesity epidemic. Accumulated evidence suggests that HTG is independently associated with an increased incidence of cardiovascular disease (1–3). The cause of HTG is not completely understood, although the most common metabolic basis for HTG seems to be insulin resistance in association with higher levels of plasma VLDL, which are determined by increased rates of secretion from the liver as well as by reduced rates of catabolism (2). Apparently, apolipoprotein B-100 in the liver is constitutively synthesized, and VLDL secretion is regulated mainly by the availability of the core lipids (triglyceride and cholesteryl esters) (4, 5). Both lipogenesis and the delivery of fatty acids stimulate the availability of triglyceride and cholesteryl esters and subsequently the assembly of VLDL in the liver (5).

In lipogenesis, a high-carbohydrate diet induces an increase in the plasma level of triglyceride by the induction of stearoyl-CoA desaturase (SCD) activity in the liver of mice (6). A critical step in the biosynthesis of monounsaturated fatty acid is the introduction of the first *cis* double bond in the Δ9 position in several fatty acyl-CoA substrates (7). The preferred substrates are palmitoyl- and stearoyl-CoA, which are converted to palmitoleoyl- and oleoyl-CoA, respectively.

Liver and adipose tissue are considered the principal sites of de novo lipogenesis in mice and humans (5). Both

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Abbreviations: ASP, acylation-stimulating protein; BMI, body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, HDL-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; HTG, hypertriglyceridemia; LDL-C, LDL-cholesterol; LNA, α-linolenic acid; SCD, stearoyl-CoA desaturase; SREBP, sterol-regulatory element binding protein.

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tissues have a high capacity to convert carbohydrate to fatty acids when glycolytic and lipogenic enzymes are induced and activated. Although the supply of fatty acids to the liver cell is rate limiting for the secretion of VLDL triglyceride in both mice and humans, adipose tissue may be the major source of carbohydrate-derived fatty acids that end up as VLDL triglyceride in humans (8). Therefore, it is possible that plasma triglyceride correlates with liver SCD in mice but with liver and adipose SCD activities in humans (9). Mice have three isoforms of the SCD gene (SCD1, SCD2, and SCD3), and a high-carbohydrate diet has induced hepatic SCD1 mRNA expression and SCD1 activities (7). As humans have only a single functional SCD gene on chromosome 10 (10), the relationship between SCD activity and plasma triglyceride might be different in mice and humans. Because SCD activity is not measured directly clinically in human tissue, a simple plasma marker of SCD activity, the ratio of plasma oleic acid to stearic acid (the 18:1/18:0 ratio), has been developed in mice and humans (11). The SCD mechanism for HTG has been demonstrated in several types of rodents, but very little is known about the role of SCD in humans.

Observational and interventional studies have confirmed that n-3 PUFAs have significant hypotriglyceridemic effects in Caucasians (12) by decreasing the hepatic production of VLDL triglyceride via sterol-regulatory element binding protein (SREBP)-dependent and SREBP-independent mechanisms (13, 14). However, the hypotriglyceridemic effects of n-3 PUFAs in Asian populations with different frequencies of fish intake is less clear. Therefore, it is of interest whether SCD activity is related to HTG in various Asian ethnic populations having different lifestyles and whether SCD activity contributes to HTG independent of n-3 PUFA intake, insulin resistance, and obesity. We investigated the relationships between HTG and the 18:1/18:0 ratio, as a plasma marker of SCD activity, n-3 PUFAs, insulin resistance, and obesity in Japanese, Korean, and Mongolian subjects, who, of the northeast Asian populations, are relatively close genetically (15) but have relatively large differences in body composition (16–18) and diet, especially fish and carbohydrate intake (19).

SUBJECTS AND METHODS

Subjects

A total of 749 Japanese, aged 30–60 years (386 men and 363 women), participated in regular health checkups at manufacturing factories and offices in Shimane Prefecture, Japan, from 1999 to 2002 (17). From this group, 411 individuals (193 men and 218 women) were randomly chosen and examined for data on fatty acid composition and metabolic measurements in their plasma. A total of 418 Koreans, aged 30–60 years (240 men and 178 women), were recruited during regular health checkups at various workplaces by the Health Promotion Center of Dong-A University in Busan, Korea, in 2003. Additionally, a total of 251 Mongolians, aged 30–60 years (99 men and 152 women), were chosen by random sampling from lists of workers from two large companies (a cashmere factory and a power plant) in Ulaanbaatar, Mongolia (17). The overall recovery rate was 99% for participants of the regular health checkups for the Koreans and Mongolians. No participants were using prescription medications for diabetes, hyperlipidemia, or hypertension. Information on each participant's lifestyle was obtained using a self-reported questionnaire, including information on smoking, alcohol consumption, exercising for more than 20 min twice per week, meat intake more than twice per day, and fish intake more than once per week.

The ethics committee of Shimane University School of Medicine approved all study protocols, and all subjects gave written informed consent.

Measurements

After an overnight fast, the body weight of each subject was measured with a standard scale to an accuracy of ±0.2 kg while dressed in very light clothing, and height was measured to an accuracy of ±0.5 cm using a height bar fixed on a wall with subjects standing straight with back, buttocks, and heels against the wall. Body mass index (BMI) was calculated as weight (kilograms) divided by height squared (meters squared). Blood pressure was measured at the right arm using a standard sphygmomanometer (Nippon Rinsho Kikaikogyo, Tokyo, Japan) with the participants seated.

During the weekdays of Monday through Friday, venous blood was collected from the antecubital vein after a 12 h overnight fast. This procedure was followed for each ethnic group. The blood samples were separated at laboratories in Busan and Ulaanbaatar and stored temporarily at −80°C in deep freezers. We transferred these samples from Busan and Ulaanbaatar to Shimane using freezing coolant and dry ice during a 12 h period. All samples were frozen at −80°C in our laboratory and used in this study, all within a 3 month period. The concentrations of total cholesterol, HDL-cholesterol (HDL-C), triglyceride, FFAs, and glucose were measured using an enzymatic assay kit (Wako Pure Chemical, Osaka, Japan). The levels of LDL-cholesterol (LDL-C) were calculated by the following formula: total cholesterol (mg/dl) − HDL-C (mg/dl) − 0.20× triglyceride (in cases of <400 mg/dl triglyceride) or total cholesterol (mg/dl) − HDL-C (mg/dl) − 0.16× triglyceride (in cases of ≥400 mg/dl triglyceride) (20). Concentrations of insulin were measured by Insulin-EIA test (Wako Pure Chemical). Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated by the following formula: fasting plasma insulin (μU/ml) × fasting plasma glucose (mg/dl) ÷ 405 (21).

Fatty acid composition was determined using a modification of the one-step analysis (22) as previously described (23) for a good recovery of total plasma fatty acid, rather than by the conventional Folch procedure (22). To 100 μl of plasma, 2.0 ml of methanol-*n*-octane (4:1, v/v) containing 10 mg of tricosanoic acid as an internal standard and 200 μl of acetyl chloride were added. The mixture was incubated at 100°C for 60 min and cooled, then neutralized with 0.5 N aqueous NaOH containing 10% sodium chloride. The neutralized mixture was shaken for 10 min at room temperature and centrifuged at 1,800 *g* for 5 min. The octane phase with the fatty acid methyl esters was directly subjected to gas chromatography. The gas chromatography separation was done on a model 5890II chromatograph (Hewlett-Packard, Avondale, PA) equipped with a flame ionization detector and an automatic sampler (model 7673). A 30 m × 0.25 mm capillary column (DB-WAX P/N 122-7032; J&W Scientific) was initially maintained at 100°C for 1 min, increased to 180°C at 20°C/min, increased to 240°C at 2°C/min, further increased to 260°C at 4°C/min, and maintained for 5 min. We verified no change of the fatty acid composition of the fresh and frozen plasma, which was obtained from a healthy subject and

stored at −80°C in deep freezers. In addition, we used an automatic sampler to avoid artifactual errors and measured a standard solution of fatty acids containing an internal standard (10 μg of tricosanoic acid) as a reference every 20 samples. The coefficient of variation of the reference plasma was less than 5% of the molecular percentage of each fatty acid. Fatty acid composition was expressed as molecular percentage per milliliter of total plasma. Several fatty acid indexes were derived from the primary data: the total percentage of saturated fatty acids, which was calculated as the sum of the percentages of palmitic acid (16:0) and stearic acid (18:0); the total percentage of monounsaturated fatty acids, which was represented as the percentage of oleic acid (18:1); the total percentage of n-3 PUFAs, which was calculated as the sum of the percentages of α-linolenic acid (LNA; 18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3), docosapentaenoic acid (22:5n-3), and docosahexaenoic acid (DHA; 22:6n-3); and the total percentage of n-6 PUFAs, calculated as the sum of the percentages of linoleic acid (18:2n-6) and arachidonic acid (20:4n-6). The total plasma 18:1/18:0 ratio for each group was calculated by dividing the molecular percentage of oleic acid by the molecular percentage of stearic acid (11).

Statistical analyses

Analysis of data was carried out using SPSS statistical analysis software (version 10.0J; SPSS, Inc., Tokyo, Japan). Results are expressed as means ± SD. Because the data for triglyceride, insulin, and HOMA-IR were significantly skewed, they were transformed logarithmically before performing a statistical analysis. Subjects were deemed to have HTG if they had more than 150 mg/dl plasma triglyceride levels, in accordance with the Third Report of the National Cholesterol Educational Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (24). A general Kendal test was used for the frequency of the ethnicities, and post hoc analyses by means of the Kendal test for two independent samples were used for the frequency of each ethnicity, using the Japanese group as a reference category. One-way ANOVA for three ethnic groups was used to assess the differences in metabolic parameters by ethnicity, and post hoc analyses were performed by Bonferroni test for two independent samples, again using the Japanese group as a reference category. To assess the relationships among the 18:1/18:0 ratio, n-3 PUFAs, and metabolic parameters, correlation coefficients with and without adjustment for age, BMI, and HOMA-IR

TABLE 1. Lifestyle, metabolic characteristics, and total plasma fatty acid composition of subjects by gender and ethnicity

	Male				Female			
Variable	Japanese	Koreans	Mongolians	*P*	Japanese	Koreans	Mongolians	*P*
Number	193	240	99		218	178	152	
Age (years)	46.6 ± 6.9	42.9 ± 8.3[a]	44.7 ± 6.4	<0.001	47.5 ± 7.2	44.8 ± 7.4[a]	42.1 ± 6.1[a]	<0.001
Lifestyles								
Current smoking (%)	107 (55.2)	216 (90.0)[a]	59 (59.0)	<0.001	18 (8.3)	9 (5.1)	14 (9.2)	0.006
Current drinking (%)	172 (89.1)	184 (76.7)[a]	70 (70.0)[a]	<0.001	93 (42.7)	59 (33.1)	46 (30.3)[a]	0.008
Exercise (⩾ twice per week, %)	26 (13.4)	113 (47.1)[a]	10 (10.0)	<0.001	54 (24.8)	55 (30.9)[a]	22 (14.5)[a]	0.010
Meat intake (⩾ twice per day, %)	82 (42.3)	13 (5.4)[a]	93 (93.0)[a]	<0.001	95 (43.6)	14 (7.9)[a]	125 (82.2)[a]	<0.001
Fish intake (⩾ once per week, %)	182 (93.8)	233 (97.1)	29 (29.0)[a]	<0.001	203 (93.1)	168 (94.4)	46 (30.3)[a]	0.002
Anthropometric parameters								
Height (cm)	167 ± 6	170 ± 6.2[a]	168 ± 6	<0.001	155 ± 5	157 ± 5[a]	156 ± 5	<0.001
Weight (kg)	65.6 ± 11.0	70.3 ± 9.4[a]	74.9 ± 13.1[a]	<0.001	54.2 ± 8.9	58.0 ± 7.7[a]	62.6 ± 11.6[a]	<0.001
BMI (kg/m^2)	23.3 ± 3.3	24.3 ± 3.0[a]	26.4 ± 4.2[a]	<0.001	22.5 ± 3.4	23.6 ± 3.1[a]	25.6 ± 4.6[a]	<0.001
Systolic BP (mmHg)	124 ± 16	120 ± 13[a]	125 ± 17	0.003	119 ± 16	114 ± 15[a]	119 ± 22	0.007
Diastolic BP (mmHg)	78 ± 10	80 ± 8[a]	88 ± 14[a]	<0.001	73 ± 12	75 ± 9	84 ± 14[a]	<0.001
Metabolic parameters (plasma)								
Total cholesterol (mg/dl)	205 ± 34	199 ± 32	187 ± 39[a]	<0.001	207 ± 34	193 ± 34[a]	176 ± 33[a]	<0.001
LDL-C (mg/dl)	127 ± 31	142 ± 33[a]	113 ± 35[a]	<0.001	132 ± 31	131 ± 34	103 ± 31[a]	<0.001
HDL-C (mg/dl)	54 ± 16	47 ± 10[a]	50 ± 12[a]	<0.001	57 ± 14	52 ± 10[a]	55 ± 12	<0.001
Triglyceride (mg/dl)	132 ± 98	142 ± 85	124 ± 105	0.008	92 ± 53	106 ± 56[a]	89 ± 55	0.001
FFAs (mEq/l)	0.37 ± 0.20	0.47 ± 0.21[a]	0.44 ± 0.19[a]	<0.001	0.42 ± 0.19	0.50 ± 0.2[a]	0.46 ± 0.26	0.001
Glucose (mg/dl)	100 ± 23	100 ± 22	101 ± 40	NS	96 ± 14	92 ± 16	91 ± 20[a]	0.010
Insulin (μU/ml)	5.8 ± 6.0	7.2 ± 7.1	7.7 ± 5.7[a]	<0.001	5.5 ± 4.5	5.3 ± 2.9	6.9 ± 4.3[a]	<0.001
HOMA-IR	1.47 ± 1.73	1.75 ± 2.08[a]	2.10 ± 2.21[a]	<0.001	1.33 ± 1.17	1.22 ± 0.77	1.62 ± 1.24[a]	0.001
Fatty acid composition (total plasma)								
Palmitic acid (mol%)	25.8 ± 2.7	24.2 ± 2.2[a]	24.7 ± 2.6[a]	0.001	24.2 ± 2.0	23.6 ± 2.4[a]	24.2 ± 2.6	<0.001
Stearic acid (mol%)	8.1 ± 1.2	6.6 ± 0.76[a]	8.2 ± 1.0	<0.001	7.6 ± 1.1	6.8 ± 0.8[a]	8.2 ± 1.0[a]	<0.001
Oleic acid (mol%)	20.0 ± 3.9	20.6 ± 3.1	23.2 ± 3.8[a]	<0.001	17.6 ± 2.5	17.9 ± 2.6	21.0 ± 2.8[a]	<0.001
Linoleic acid (mol%)	29.9 ± 5.0	35.0 ± 4.5[a]	31.9 ± 4.9[a]	<0.001	34.0 ± 3.8	37.5 ± 5.1[a]	34.4 ± 4.5	<0.001
LNA (mol%)	0.5 ± 0.3	0.6 ± 0.5	0.7 ± 0.3[a]	<0.001	0.6 ± 0.3	0.6 ± 0.3	0.7 ± 0.3[a]	0.002
Arachidonic acid (mol%)	5.8 ± 1.5	6.0 ± 1.2[a]	5.9 ± 1.3	0.042	6.2 ± 1.2	6.5 ± 1.1[a]	6.0 ± 1.2	0.001
EPA (mol%)	3.3 ± 2.0	1.9 ± 0.12[a]	1.1 ± 0.3[a]	<0.001	2.9 ± 1.4	2.0 ± 1.1[a]	1.0 ± 0.3[a]	<0.001
DPA (mol%)	1.0 ± 0.3	0.6 ± 0.19[a]	1.1 ± 0.2[a]	<0.001	0.9 ± 0.2	0.6 ± 0.2[a]	1.1 ± 0.2	<0.001
DHA (mol%)	5.7 ± 1.8	4.4 ± 1.2[a]	3.1 ± 0.6[a]	<0.001	6.1 ± 0.1	4.9 ± 1.1[a]	3.4 ± 0.1[a]	<0.001
n-3 PUFAs (mol%)	9.4 ± 3.6	7.5 ± 0.3[a]	5.0 ± 0.7[a]	<0.001	9.6 ± 0.3	8.2 ± 2.3[a]	5.1 ± 0.1[a]	<0.001
18:1/18:0 ratio	2.53 ± 0.60	3.14 ± 0.54[a]	2.87 ± 0.51[a]	<0.001	2.34 ± 0.43	2.65 ± 0.45[a]	2.59 ± 0.47[a]	<0.001

BMI, body mass index; BP, blood pressure; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; HDL-C, HDL-cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, LDL-cholesterol; LNA, α-linolenic acid. The general Kendal test was used for the frequency of the ethnicities, and post hoc analyses by means of Kendal test for two dependent samples were used for the frequency of each ethnicity, using the Japanese as a reference category. One-way ANOVA for three ethnic groups was used to assess the differences in metabolic parameters by ethnicity, and post hoc analyses were performed by Bonferroni test for two independent samples, again using the Japanese as a reference category. One-way ANOVA was performed for logarithmically transformed values for triglyceride, insulin, and HOMA-IR. Data are means ± SD.

[a] $P < 0.025$ compared with Japanese counterparts.

were calculated. Multiple linear regression analysis was conducted to investigate whether triglyceride levels were independently related to gender, age, BMI, FFAs, HOMA-IR, the 18:1/18:0 ratio, and total n-3 PUFAs or major components of n-3 PUFAs for all subjects in the three ethnic groups and for those subjects in the three ethnic groups within the low range of n-3 PUFA levels (<8.0% n-3 PUFAs). Differences in the slopes of the regression lines for these relationships by gender were assessed using general linear mode multivariate analyses. A nominal two-sided *P* value of <0.05 was used to assess significance.

RESULTS

Lifestyle and metabolic parameters

Lifestyle and metabolic parameters for the Japanese, Korean, and Mongolian subjects are shown in **Table 1**. The Korean men had a significantly higher frequency of smoking, whereas the Japanese men had a significantly higher frequency of drinking alcoholic beverages, relative to the other ethnic groups. The Japanese and Koreans ate fish more frequently, whereas the Mongolians consumed meat more frequently. The Korean men and women had the highest rates for exercising more than twice per week.

Regarding anthropometric parameters, the men had significantly higher values for height, weight, and BMI than did the women. Mongolians of both genders had significantly higher values for BMI, followed by the Koreans and Japanese. Relative to the Japanese, the Korean men and women showed significantly lower values for HDL-C and significantly higher values for LDL-C. The Mongolian men and women had significantly higher values for diastolic blood pressure, insulin, and HOMA-IR and lower values for total cholesterol and LDL-C, again relative to the Japanese.

In fatty acid composition, Japanese of both genders showed remarkably higher values for EPA, DHA, and n-3 PUFAs, followed by the Koreans and Mongolians. Plasma EPA levels in the Japanese were three times those of the Mongolians, and DHA and n-3 PUFA levels were twice those of the Mongolians. Plasma EPA, DHA, and n-3 PUFA levels of the Koreans fell between those of the Japanese and Mongolians (Table 1). **Figure 1** illustrates the wide range of n-3 PUFAs in the Japanese (2.35–20.96%) and in the Koreans (3.10–16.80%), whereas the Mongolians had a very narrow range of n-3 PUFAs (2.89–7.90%). Japanese of both genders showed significantly lower values for LNA and arachidonic acid, relative to the Koreans, and significantly lower values for oleic acid and LNA, relative to the Mongolians.

Japanese of both genders showed significantly lower values for the 18:0/18:1 ratio, followed by the Mongolians

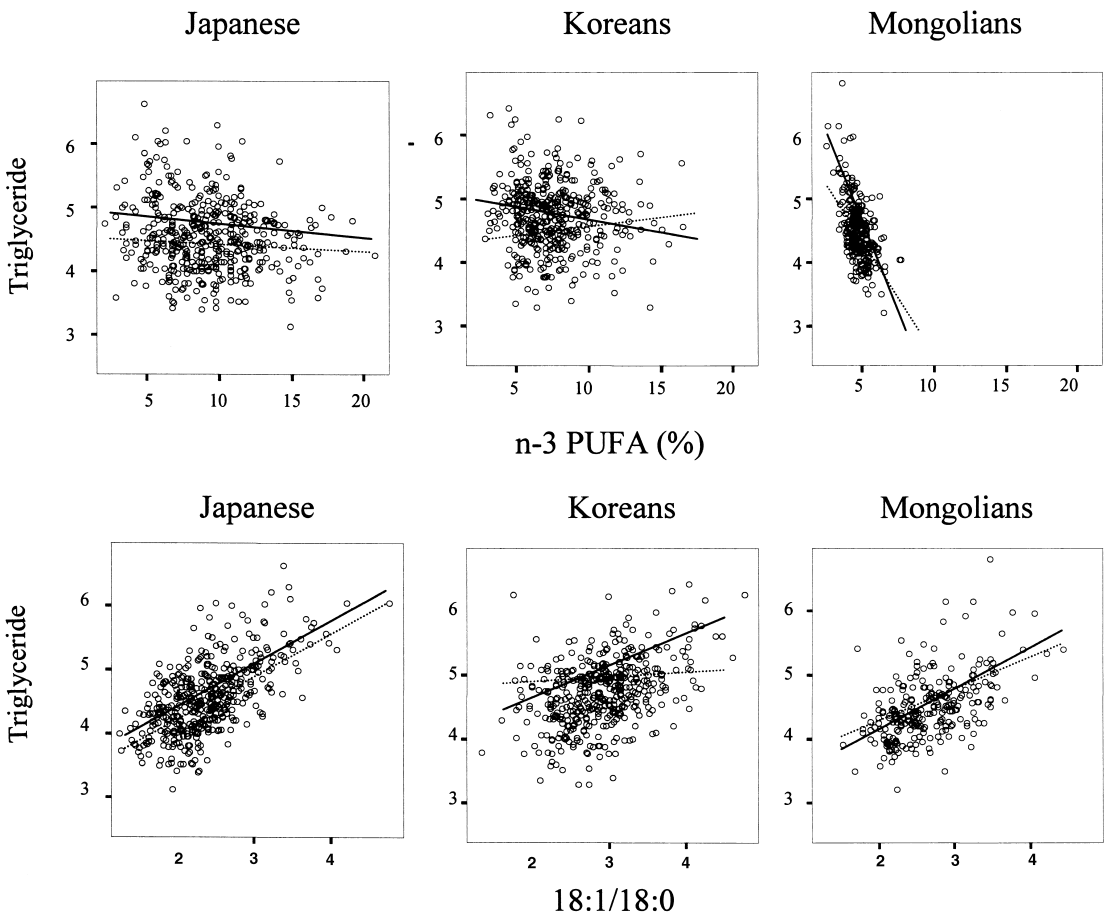

Fig. 1. Regression lines between triglyceride and the 18:1/18:0 ratio or n-3 PUFAs by ethnicity. Values of triglyceride were transformed logarithmically. The regression line is expressed as a solid line for males and as a broken line for females.

and the Koreans, and the men showed remarkably higher values than the women.

Triglyceride and metabolic parameters

Although the men of the three ethnic groups showed significantly higher triglyceride levels than the women, the Mongolians with higher BMI had slightly lower triglyceride levels than the Japanese and Koreans (Table 1). In the prevalence of HTG (≥150 mg/dl), men of the three ethnic groups had remarkably higher values than did the women (**Table 2**). The Korean men had the highest prevalence of HTG (33.3%), followed by the Japanese men (23.2%) and Mongolian men (23.0%), whereas the Korean women (15.7%) and Japanese women (13.3%) had a higher prevalence of HTG than the Mongolian women (6.6%), despite lower BMI values for the Japanese and Korean men and women. Graded increases in BMI were positively associated with the prevalence of HTG in both genders and all three ethnic groups. In obese men (BMI ≥ 25.0), slightly higher levels of HTG were observed in the Koreans (45.1%) compared with the Japanese (32.1%) and Mongolians (31.1%). In obese women (BMI ≥ 25.0), slightly higher levels of HTG were observed in the Japanese women (32.6%) and Koreans (26.8%) compared with the Mongolian women (13.5%). Koreans and Japanese of both genders had slightly higher prevalence of HTG at BMI < 25.0 compared with the Mongolians (Table 2).

The relationships between triglyceride and metabolic parameters in the three ethnic groups are summarized in **Table 3**. Pearson's correlation coefficients between triglyceride and metabolic parameters showed that the increase in triglyceride was significantly related to the increase in the 18:1/18:0 ratio (0.665 for Japanese men, 0.552 for Japanese women, and 0.494 for Korean men) and the decrease in HDL-C (−0.622 for Japanese men, −0.513 for Japanese women, −0.427 for Korean men, and −0.387 for Korean women), followed by BMI (0.360 for Japanese men, 0.437 for Japanese women, 0.350 for Korean men, and 0.291 for Korean women), HOMA-IR (0.282 for Japanese men, 0.299 for Japanese women, 0.263 for Korean men, and 0.259 for Korean women), age (0.177 for Japanese men, 0.313 for Japanese women, and 0.161 for Korean women), and n-3 PUFAs (−0.226 for Japanese men, −0.108 for Japanese women, and −0.178 for Korean men). In contrast, the highest correlation coefficient for the Mongolians was for n-3 PUFAs (−0.594 for men and −0.510 for women), followed by HOMA-IR (0.475 for men and 0.481 for women), 18:1/18:0 ratio (0.355 for men and 0.503 for women), HDL-C (−0.594 for men and −0.220 for women), and BMI (0.381 for men and 0.369 for women).

The relationships between triglyceride and the 18:1/18:0 ratio or n-3 PUFAs are shown in Fig. 1. A positive correlation between triglyceride and the 18:1/18:0 ratio was observed for the Japanese, Koreans, and Mongolians ($P < 0.001$), whereas a significant negative correlation between triglyceride and n-3 PUFAs was observed for the Mongolians ($P < 0.001$). Furthermore, an adjusted R^2 (0.027) between triglyceride and n-3 PUFAs for the Japanese was significant but remarkably less than that for the Mongolians (0.293). The slope of the regression line for the relationship between triglyceride and the 18:1/18:0 ratio or n-3 PUFAs by gender was significant for the Koreans but not for the Japanese or Mongolians.

Because of the differences among the three ethnic groups in age distribution, obesity, and insulin resistance, we adjusted for age, BMI, and HOMA-IR. Partial correlation coefficients after adjustment for age, BMI, and HOMA-IR revealed that increases in triglyceride were related to increases in the 18:1/18:0 ratio and decreases in HDL-C and n-3 PUFAs for Japanese of both genders. Increases in triglyceride were related to decreases in n-3 PUFAs and HDL-C and increases in the 18:1/18:0 ratio and LDL-C in the Korean men and to decreases in HDL-C and increases in LDL-C in Korean women. For the Mongolians, increases in triglyceride showed a great magnitude of corre-

TABLE 2. Prevalence of HTG by BMI classes

Ethnicity	BMI Class	HTG in Men	HTG in Women	*P* by Gender
Japanese	<23.0	15/93 (16.1%)	9/137 (6.6%)	
	23.0–24.9	12/44 (27.3%)	5/35 (14.3%)	
	≥25.0	18/56 (32.1%)	15/46 (32.6%)	
	Total	45/193 (23.2%)	29/218 (13.3%)	0.008
Koreans	<23.0	15/72 (20.8%)	6/81 (7.4%)	
	23.0–24.9	24/77 (31.2%)	7/41 (17.1%)	
	≥25.0	41/91 (45.1%)	15/56 (26.8%)	
	Total	80/240 (33.3%)[a]	28/178 (15.7%)	<0.001
Mongolians	<23.0	2/23 (8.7%)	0/49 (0.0%)	
	23.0–24.9	2/15 (13.3%)	0/29 (0.0%)	
	≥25.0	19/61 (31.1%)	10/74 (13.5%)[a]	
	Total	23/99 (23.0%)	10/152 (6.6%)[a]	<0.001
P by ethnicity	<23.0	NS	NS	
	23.0–24.9	NS	NS	
	≥25.0	NS	0.017	
	Total	0.032	0.032	

HTG, hypertriglyceridemia. HTG was defined as ≥150 mg/dl. The general Kendal test was used for the frequency of the BMI classes by gender or ethnicity. Post hoc analyses by means of Kendal test for two dependent samples were used for the frequency of each ethnicity, using the Japanese as a reference category.

[a] $P < 0.016$ compared with Japanese counterparts.

TABLE 3. Pearson's and partial correlation coefficients between triglyceride and metabolic parameters

Variable	Men				Women			
	Pearson	*P*	Partial	*P*	Pearson	*P*	Partial	*P*
Japanese								
Age (years)	0.177	0.014			0.313	<0.001		
BMI (kg/m^2)	0.360	<0.001			0.437	<0.001		
Systolic BP (mmHg)	0.163	0.024	0.008	NS	0.211	0.002	−0.001	NS
Diastolic BP (mmHg)	0.164	0.023	0.008	NS	0.200	0.003	0.008	NS
LDL-C (mg/dl)	0.114	NS	−0.026	NS	0.298	<0.001	0.136	0.047
HDL-C (mg/dl)	−0.622	<0.001	−0.524	<0.001	−0.513	<0.001	−0.387	<0.001
FFAs (mEq/l)	0.113	NS	0.015	NS	0.227	0.001	0.133	NS
HOMA-IR	0.282	<0.001			0.299	<0.001		
n-3 PUFAs (%)	−0.226	<0.001	−0.251	<0.001	−0.108	0.047	−0.204	0.003
18:1/18:0 ratio	0.665	<0.001	0.645	<0.001	0.552	<0.001	0.487	<0.001
Koreans								
Age (years)	−0.045	NS			0.161	0.032		
BMI (kg/m^2)	0.350	<0.001			0.291	<0.001		
Systolic BP (mmHg)	0.068	NS	−0.009	NS	0.171	0.023	0.071	NS
Diastolic BP (mmHg)	0.054	NS	−0.006	NS	0.069	NS	−0.038	NS
LDL-C (mg/dl)	0.497	<0.001	0.463	<0.001	0.293	<0.001	0.204	0.007
HDL-C (mg/dl)	−0.427	<0.001	−0.416	<0.001	−0.387	<0.001	−0.346	<0.001
FFAs (mEq/l)	0.110	NS	0.105	NS	−0.124	NS	−0.156	0.041
HOMA-IR	0.263	<0.001			0.259	<0.001		
n-3 PUFAs (%)	−0.178	0.006	−0.231	<0.001	0.142	NS	0.092	NS
18:1/18:0 ratio	0.494	<0.001	0.516	<0.001	0.114	NS	0.092	NS
Mongolians								
Age (years)	0.055	NS			0.133	NS		
BMI (kg/m^2)	0.381	<0.001			0.369	<0.001		
Systolic BP (mmHg)	0.150	NS	0.007	NS	0.197	0.015	0.059	NS
Diastolic BP (mmHg)	0.167	NS	−0.085	NS	0.268	0.001	0.097	NS
LDL-C (mg/dl)	0.367	<0.001	0.281	0.006	0.185	0.023	0.104	NS
HDL-C (mg/dl)	−0.594	<0.001	−0.479	<0.001	−0.220	0.007	−0.087	NS
FFAs (mEq/l)	0.078	NS	0.134	NS	0.050	NS	−0.011	NS
HOMA-IR	0.475	<0.001			0.481	<0.001		
n-3 PUFAs (%)	−0.594	<0.001	−0.545	<0.001	−0.510	<0.001	−0.509	<0.001
18:1/18:0 ratio	0.355	<0.001	0.362	<0.001	0.503	<0.001	0.457	<0.001

Correlation analyses were performed for logarithmically transformed values for triglyceride and HOMA-IR. Partial correlation analyses were performed in adjustment with age, BMI, and HOMA-IR.

lation with decreases in n-3 PUFAs and increases in the 18:1/18:0 ratio in both genders and with decreases in HDL-C in the men, followed by a relatively lesser magnitude of correlation with increases in LDL-C in both genders.

Further analysis using multiple linear regression was carried out to verify whether the correlations between triglyceride and the 18:1/18:0 ratio or n-3 PUFAs were independent of gender, age, BMI, HOMA-IR, and FFAs (**Table 4**, model 1). Such analysis, with triglyceride as the dependent variable, showed that the 18:1/18:0 ratio, n-3 PUFAs, age, gender, BMI, HOMA-IR, and FFAs were determinants explaining more than 50% of the variance in triglyceride for the Japanese and Mongolians and 28% of the variance in triglyceride for the Koreans. For the Japanese and Koreans, increases in triglyceride had a great magnitude of correlation with increases in the 18:1/18:0 ratio, followed by relatively lesser magnitudes of correlation with increases in BMI and HOMA-IR, but FFAs and n-3 PUFAs did not remain significant. For the Mongolians, increases in triglyceride showed a great magnitude of correlation with decreases in n-3 PUFAs, followed by relatively lesser magnitudes of correlation with increases in HOMA-IR, the 18:1/18:0 ratio, and gender, but age, BMI, and FFAs did not remain significant. To investigate the relationship between triglyceride and the 18:1/18:0 ratio or n-3 PUFAs for the subjects in the low range of n-3 PUFA levels, we selected those Japanese and Korean subjects who were within the range of the Mongolians for n-3 PUFA levels (<8.0% n-3 PUFAs) and conducted an analysis using multiple linear regression. Among these subjects, in the Japanese, increases in triglyceride had a relatively lesser magnitude of correlation with decreases in n-3 PUFAs ($\beta = -0.116$, $P = 0.029$) compared with the Mongolians and did not remain significant for the Koreans ($\beta = -0.005$). LNA, EPA, and DHA, major components of n-3 PUFAs, were also analyzed instead of total n-3 PUFAs as determinants explaining the variance in triglyceride using a multiple linear regression model for the three ethnic groups (Table 4, model 2). Increases in triglyceride showed a significant correlation with decreases in DHA for the Japanese and Mongolians ($\beta = -0.132$ and -0.560, respectively) and with increases in LNA for the Japanese and Koreans ($\beta = 0.117$ and 0.116, respectively), but EPA did not remain significant in all groups.

DISCUSSION

Graded increases in BMI were positively associated with the prevalence of HTG in both genders of all three ethnic

TABLE 4. Standard regression coefficients (β) for triglyceride using multiple regression analysis

Model and Ethnicity	Independent Variables	R^2	F	β	P
Model 1					
Japanese		0.523	65.0		<0.001
	Gender			−0.181	<0.001
	Age			0.195	<0.001
	BMI			0.160	<0.001
	HOMA-IR			0.162	<0.001
	FFAs			0.039	NS
	n-3 PUFAs (%)			−0.042	NS
	18:1/18:0 ratio			0.502	<0.001
Koreans		0.282	24.4		<0.001
	Gender			−0.031	NS
	Age			0.012	NS
	BMI			0.235	<0.001
	HOMA-IR			0.167	<0.001
	FFAs			−0.070	NS
	n-3 PUFAs (%)			0.031	NS
	18:1/18:0 ratio			0.383	<0.001
Mongolians		0.565	47.4		<0.001
	Gender			−0.136	0.002
	Age			−0.048	NS
	BMI			0.064	NS
	HOMA-IR			0.295	<0.001
	FFAs			0.039	NS
	n-3 PUFAs (%)			−0.416	<0.001
	18:1/18:0 ratio			0.296	<0.001
Model 2					
Japanese		0.557	55.7		<0.001
	Gender			−0.186	<0.001
	Age			0.208	<0.001
	BMI			0.170	<0.001
	HOMA-IR			0.161	<0.001
	FFAs			0.055	NS
	LNA (%)			0.117	0.001
	EPA (%)			0.060	NS
	DHA (%)			−0.132	0.016
	18:1/18:0 ratio			0.479	<0.001
Koreans		0.308	20.2		<0.001
	Gender			−0.056	NS
	Age			0.030	NS
	BMI			0.236	<0.001
	HOMA-IR			0.162	<0.001
	FFAs			−0.069	NS
	LNA (%)			0.116	NS
	EPA (%)			−0.087	NS
	DHA (%)			0.074	NS
	18:1/18:0 ratio			0.348	<0.001
Mongolians		0.686	58.4		<0.001
	Gender			−0.076	NS
	Age			−0.064	NS
	BMI			0.039	NS
	HOMA-IR			0.253	<0.001
	FFAs			0.027	NS
	LNA (%)			0.025	NS
	EPA (%)			−0.024	NS
	DHA (%)			−0.560	<0.001
	18:1/18:0 ratio			0.224	<0.001

Analyses were performed for logarithmically transformed values for triglyceride and HOMA-IR. Model 1 analyzed interrelationships between triglyceride, gender, age, BMI, HOMA-IR, FFAs, n-3 PUFAs, and the 18:1/18:0 ratio. Model 2 analyzed interrelationships between triglyceride, gender, age, BMI, HOMA-IR, FFAs, LNA, EPA, DHA, and the 18:1/18:0 ratio.

groups in the present investigation. As adiposity is characterized by increased hepatic lipogenesis that could contribute to excessive fat mass (9), obesity is thought to be primarily responsible for HTG. Because BMI as well as waist circumference was correlated with obesity-related parameters in Japanese and Mongolians in our previous study (25), obesity was specified as BMI ⩾ 25.0 (17) in the present study. A higher prevalence of HTG in all of the Japanese and Korean subjects was observed for both nonobese (BMI < 25.0) and obese (BMI ⩾ 25.0) subjects than in the Mongolians, despite comparatively lower BMI values for the Japanese and Koreans. As the relationship between BMI and HTG was gender and ethnicity specific, HTG in different ethnic populations should be investigated with a view toward a possible linkage with obesity, insulin resistance, lipogenesis, and diet.

Plasma fatty acid composition is a reflection of the fatty acid composition of one's usual diet and is a valuable marker to determine actual fat intake (26, 27). The Japanese had three times the EPA and two times the DHA and n-3 PUFA levels as did the Mongolians. Plasma EPA, DHA, and n-3 PUFA levels of the Koreans fell between those of the Japanese and Mongolians. The remarkably higher values for plasma n-3 PUFAs, particularly EPA and DHA, in the present study clearly reflect the differences in marine fish consumption among the three ethnic groups (28). Because the Mongolians showed the highest values for LNA levels, the Mongolian diet appears to have LNA in its soybean, canola flaxseed, and perilla seed oils, which convert to EPA and DHA in small amounts and can be substituted for fish oil (29).

We demonstrated that an increase in plasma n-3 PUFAs was independently related to a decrease in triglyceride in the Mongolians and in those Japanese subjects with a low range of n-3 PUFAs. In contrast, the Japanese in the high range of n-3 PUFAs and all of the Koreans had weak correlations between plasma triglyceride levels and plasma n-3 PUFAs, but the favorable effects of n-3 PUFAs disappeared after the adjustment for gender, age, BMI, HOMA-IR, and the 18:1/18:0 ratio. Our present results indicate that n-3 PUFAs affected triglyceride levels independently in the Mongolians and in those Japanese subjects with a lower range of n-3 PUFAs, all with low fish intake. A study group of Caucasians with low levels of n-3 PUFAs similar to those in our Mongolian subjects was given as little as 3 g supplement of dietary n-3 PUFAs, which reduced serum triglyceride by 30% and demonstrated a dose-related effect on HTG when average daily supplementation ranged between 1 and 9 g (30). The Japanese general population has an average daily intake of 2.4–2.9 g of n-3 PUFAs (31), similar to the reported therapeutic intake for Caucasians with low n-3 PUFA histories. Possible reasons for the divergent hypotriglyceridemic effect of n-3 PUFAs in our Japanese and Korean subjects may be a reduced effect at higher levels and/or a diminishing effect as a result of long-term administration of n-3 PUFAs (32). Of the major components of n-3 PUFAs, DHA was identified by multiple linear regression modeling as a determinant explaining the variance in triglyceride in the Japanese and Mongolians, and EPA and LNA did not demonstrate beneficial effects on HTG. The Lyon Diet Heart Study clearly demonstrated the protective effect from cardiovascular disease of the Mediterranean dietary pattern, which is character-

ized by high levels of LNA (33); however, our data suggested that DHA was the effective component for HTG.

The multivariate analyses revealed that the increase in triglyceride had a great magnitude of correlation with increases in the 18:1/18:0 ratio for the Japanese and Mongolians but had no correlation for the Koreans. Our results for the Japanese and Mongolians support a previously reported significant correlation between the 18:1/18:0 ratio and plasma triglyceride levels in Caucasians (11). Because the 18:1/18:0 ratio has been validated in mice and humans as a plasma marker of SCD activity (11), SCD activity is thought to relate to HTG in our Japanese and Mongolian subjects.

SCD gene expression is extensively regulated; it is very sensitive to dietary lipids and carbohydrates, insulin, developmental processes, temperature changes, thiazolidinediones, metals, alcohol, peroxisomal proliferators, and phenolic compounds. Recently, SREBP-1c has emerged as a master regulator of the conversion of carbohydrate to fatty acid, and SCD is extremely sensitive to SREBP-1c regulation (34). Interestingly, both SCD activity and n-3 PUFAs affect lipogenesis through the common SREBP-1c gene expression (10). As the hypotriglyceridemic effects of n-3 PUFAs have been reported to act through increased lipoprotein lipase-mediated triglyceride clearance in combination with the reduction of VLDL synthesis by reduced SREBP-1c and SCD gene expression (7, 30), we believe that the 18:1/18:0 ratio and n-3 PUFAs in plasma acted independently on triglyceride levels in the present study.

Recent evidence indicates that a high-carbohydrate diet induces an increase in plasma levels of triglyceride by induction of SCD activity in the livers of mice (6). In humans, a high-carbohydrate diet has induced an increase in the 18:1/18:0 ratio, and in some subjects, it has increased triglyceride levels (11). Japanese and Koreans take in large amounts of dietary carbohydrate (35), whereas Mongolians use large quantities of protein and fat from meat and dairy products (36). The Korean subjects with the richest carbohydrate diet showed the highest 18:1/18:0 ratio of the three ethnic groups but did not show a significant association between HTG and the 18:1/18:0 ratio. Therefore, carbohydrate intake would appear to contribute to increased SCD activity, but the influence of SCD activity seems to be weak for HTG.

The obese Mongolians had lower triglyceride and LDL-C levels but higher insulin levels in plasma than the obese Japanese and Koreans. These ethnic differences in dyslipidemia remained even after adjustment for BMI. A similar discrepancy between HTG and obesity was observed in ethnic comparative studies between Pima Indians and Caucasians (37). Acylation-stimulating protein (ASP) has recently been shown to be a principal determinant of the rate of triglyceride synthesis and the rate of fatty acid uptake by adipocytes (38). Plasma ASP levels are closely related to HTG, higher FFA levels, insulin resistance, and adiposity (39), and the ethnic difference in dyslipidemia between Pima Indians and Caucasians was partially explained by such ASP activities (37, 38). Our present study investigated HTG in the three ethnic groups from the aspect of SCD activity and n-3 PUFAs, which affected the assembly and secretion of VLDL.

The 18:1/18:0 ratio, n-3 PUFAs, age, gender, BMI, HOMA-IR, and FFAs can explain more than 50% of the variance in triglyceride for the Japanese and Mongolians but only 28% of the variance in triglyceride for the Koreans. The slope of the regression line of the Korean men for the relationship between triglyceride and the 18:1/18:0 ratio or n-3 PUFAs was similar to that for the Japanese and Mongolian men. However, the Korean women demonstrate a unique relationship between triglyceride and the 18:1/18:0 ratio or n-3 PUFAs relative to the Japanese and Mongolian women. Although the explanation for the low rate of variance for the Koreans is unclear, the Korean women may have unique lifestyle influences on HTG. Plasma levels of triglyceride are determined by rates of assembly and secretion from the intestine and liver as well as by rates of catabolism, which are influenced by estrogen, smoking, and exercise (40, 41). Future studies of HTG should incorporate additional factors, such as diet, ASP, catabolic factors, and hepatic uptake influence.

In conclusion, our results indicate a link between HTG and obesity, insulin resistance, age, the 18:1/18:0 ratio in plasma, and n-3 PUFAs in three ethnic northeast Asian groups. Multivariate analyses revealed that an increase in plasma n-3 PUFAs was independently related to a decrease in triglyceride in the Mongolian subjects, whereas the Japanese and Koreans had no correlation between plasma triglyceride levels and plasma n-3 PUFAs. An increase in the 18:1/18:0 ratio in plasma was associated with increased triglyceride for Japanese and Mongolians but not for the Koreans. HTG is ethnicity-specifically associated with an increase in the 18:1/18:0 ratio or a decrease in n-3 PUFAs in plasma for Japanese, Koreans, and Mongolians.

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REFERENCES

1. Hokanson, J. E., and M. A. Austin. 1996. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J. Cardiovasc. Risk.* **3:** 213–219.
2. Haynes, W. G. 2003. Triglyceride-rich lipoproteins and vascular function. *Arterioscler. Thromb. Vasc. Biol.* **23:** 153–155.
3. Reaven, G. M. 1988. Role of insulin resistance in human disease. *Diabetes.* **37:** 1595–1607.
4. Adeli, K., C. Taghibiglou, S. C. Van Iderstine, and G. F. Lewis. 2001. Mechanisms of hepatic very low-density lipoprotein overproduction in insulin resistance. *Trends Cardiovasc. Med.* **11:** 170–176.
5. Ginsberg, H. N. 2002. New perspectives on atherogenesis: role of abnormal triglyceride-rich lipoprotein metabolism. *Circulation.* **106:** 2137–2142.
6. Ntambi, J. M. 1992. Dietary regulation of stearoyl-CoA desaturase 1 gene expression in mouse liver. *J. Biol. Chem.* **267:** 10925–10930.
7. Ntambi, J. M. 1999. Regulation of stearoyl-CoA desaturase by polyunsaturated fatty acids and cholesterol. *J. Lipid Res.* **40:** 1549–1558.
8. Parks, E. J., R. M. Krauss, M. P. Christiansen, R. A. Neese, and M. K. Hellerstein. 1999. Effects of a low-fat, high-carbohydrate diet

on VLDL-triglyceride assembly, production, and clearance. *J. Clin. Invest.* **104:** 1087–1096.
9. Diraison, F., E. Dusserre, H. Vidal, M. Sothier, and M. Beylot. 2002. Increased hepatic lipogenesis but decreased expression of lipogenic gene in adipose tissue in human obesity. *Am. J. Physiol. Endocrinol. Metab.* **282:** E46–E51.
10. Miyazaki, M., and J. M. Ntambi. 2003. Role of stearoyl-coenzyme A desaturase in lipid metabolism. *Prostaglandins Leukot. Essent. Fatty Acids.* **68:** 113–121.
11. Attie, A. D., R. M. Krauss, M. P. Gray-Keller, A. Brownlie, M. Miyazaki, J. J. Kastelein, A. J. Lusis, A. F. Stalenhoef, J. P. Stoehr, M. R. Hayden, and J. M. Ntambi. 2002. Relationship between stearoyl-CoA desaturase activity and plasma triglycerides in human and mouse hypertriglyceridemia. *J. Lipid Res.* **43:** 1899–1907.
12. Harris, W. S. 1997. n-3 fatty acids and serum lipoproteins: human studies. *Am. J. Clin. Nutr.* **65 (Suppl.):** 1645S–1654S.
13. Bene, H., D. Lasky, and J. M. Ntambi. 2001. Cloning and characterization of the human stearoyl-CoA desaturase gene promoter: transcriptional activation by sterol regulatory element binding protein and repression by polyunsaturated fatty acids and cholesterol. *Biochem. Biophys. Res. Commun.* **284:** 1194–1198.
14. Nakatani, T., H. J. Kim, Y. Kaburagi, K. Yasuda, and O. Ezaki. 2003. A low fish oil inhibits SREBP-1 proteolytic cascade, while a high-fish-oil feeding decreases SREBP-1 mRNA in mice liver: relationship to anti-obesity. *J. Lipid Res.* **44:** 369–379.
15. Katoh, T., S. Mano, T. Ikuta, B. Munkhbat, K. Tounai, H. Ando, N. Munkhtuvshin, T. Imanishi, H. Inoko, and G. Tamiya. 2002. Genetic isolates in East Asia: a study of linkage disequilibrium in the X chromosome. *Am. J. Hum. Genet.* **71:** 395–400.
16. Suvd, J., B. Gerel, H. Otgooloi, D. Purevsuren, H. Zolzaya, G. Roglic, and H. King. 2002. Glucose intolerance and associated factors in Mongolia: results of a national survey. *Diabetes Med.* **19:** 502–508.
17. Shiwaku, K., E. Anuurad, E. Byambaa, A. Nogi, K. Kitajima, K. Shimono, Y. Yamane, and T. Oyunsuren. 2004. Overweight Japanese with body mass indexes of 23.0–24.9 have higher risks for obesity-associated disorders: a comparison of Japanese and Mongolians. *Int. J. Obes. Relat. Metab Disord.* **28:** 152–158.
18. Moon, O. R., N. S. Kim, S. M. Jang, T. H. Yoon, and S. O. Kim. 2002. The relationship between body mass index and the prevalence of obesity-related diseases based on the 1995 National Health Interview Survey in Korea. *Obes. Rev.* **3:** 191–196.
19. Kim, S., S. Moon, and B. M. Popkin. 2000. The nutrition transition in South Korea. *Am. J. Clin. Nutr.* **71:** 44–53.
20. Friedewald, W. T., R. I. Levy, and D. Fredrickson. 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin. Chem.* **18:** 499–502.
21. Matthews, D. R., J. P. Hosker, A. S. Rudenski, B. F. Naylor, D. F. Treacher, and R. C. Turner. 1985. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* **28:** 412–419.
22. Lepage, G., and C. C. Roy. 1986. Direct transestification of all classes of lipids in a one-step reaction. *J. Lipid Res.* **27:** 114–120.
23. Hashimoto, M., K. Shinozuka, S. Gamoh, Y. Tanabe, M. S. Hossain, Y. M. Kwon, N. Hata, Y. Misawa, M. Kunitomo, and S. Masumura. 1999. The hypotensive effect of docosahexaenoic acid is associated with the enhanced release of ATP from the caudal artery of aged rats. *J. Nutr.* **129:** 70–76.
24. National Institutes of Health. 2001. Third Report of the National Cholesterol Educational Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary. National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD.
25. Shiwaku, K., E. Anuurad, E. Byambaa, K. Kitajima, and Y. Yamane. 2004. Appropriate BMI for Asian populations. *Lancet.* In press.
26. Ma, J., A. R. Folsom, J. H. Eckfeldt, L. Lewis, and L. E. Chambless. 1995. Short- and long-term repeatability of fatty acid composition of human plasma phospholipids and cholesterol esters. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Am. J. Clin. Nutr.* **62:** 572–578.
27. Hasegawa, T., and M. Oshima. 1999. Serum fatty acid composition as a marker of eating habits in normal and diabetic subjects. *Diabetes Res. Clin. Pract.* **46:** 115–120.
28. Hojo, N., T. Fukushima, A. Isobe, T. Gao, K. Shiwaku, K. Ishida, N. Ohta, and Y. Yamane. 1998. Effect of serum fatty acid composition on coronary atherosclerosis in Japan. *Int. J. Cardiol.* **66:** 31–38.
29. Pauletto, P., M. Puato, M. G. Caroli, E. Casiglia, A. E. Munhambo, G. Cazzolato, G. Bittolo Bon, M. T. Angeli, C. Galli, and A. C. Pessina. 1996. Blood pressure and atherogenic lipoprotein profiles of fish-diet and vegetarian villagers in Tanzania: the Lugalawa study. *Lancet.* **348:** 784–788.
30. Roche, H. M., and M. J. Gibney. 2000. Effect of long-chain n-3 polyunsaturated fatty acids on fasting and postprandial triacylglycerol metabolism. *Am. J. Clin. Nutr.* **71 (Suppl.):** 232S–237S.
31. Yamada, T., J. P. Strong, T. Ishii, T. Ueno, M. Koyama, H. Wagayama, A. Shimizu, T. Sakai, G. T. Malcom, and M. A. Guzman. 2000. Atherosclerosis and omega-3 fatty acids in the populations of a fishing village and a farming village in Japan. *Atherosclerosis.* **153:** 469–481.
32. von Schacky, C., P. Angerer, W. Kothny, K. Theisen, and H. Mudra. 1999. The effect of dietary ω-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.* **130:** 554–562.
33. de Lorgeril, M., P. Salen, J. L. Martin, I. Monjaud, J. Delaye, and N. Mamelle. 1999. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation.* **99:** 779–785.
34. Shimano, H. 2001. Sterol regulatory element-binding proteins (SREBPs): transcriptional regulators of lipid synthetic genes. *Prog. Lipid Res.* **40:** 439–452.
35. Nakamura, M., S. Tajima, and N. Yoshiike. 2002. Nutrient intake in Japanese adults—from The National Nutrition Survey, 1995–99. *J. Nutr. Sci. Vitaminol.* **48:** 433–441.
36. Gill, M. 1999. Meat production in developing countries. *Proc. Nutr. Soc.* **58:** 371–376.
37. Weyer, C., and R. E. Pratley. 1999. Fasting and postprandial plasma concentrations of acylation-stimulation protein (ASP) in lean and obese Pima Indians compared to Caucasians. *Obes. Res.* **7:** 444–452.
38. Sniderman, A. D., K. Cianflone, P. Arner, L. K. Summers, and K. N. Frayn. 1998. The adipocyte, fatty acid trapping, and atherogenesis. *Arterioscler. Thromb. Vasc. Biol.* **18:** 147–151.
39. Cianflone, K., Z. Xia, and L. Y. Chen. 2003. Critical review of acylation-stimulating protein physiology in humans and rodents. *Biochim. Biophys. Acta.* **1609:** 127–143.
40. Walsh, B. W., I. Schiff, B. Rosner, L. Greenberg, V. Ravnikar, and F. M. Sacks. 1991. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N. Engl. J. Med.* **325:** 1196–1204.
41. Rashid, S., T. Watanabe, T. Sakaue, and G. F. Lewis. 2003. Mechanisms of HDL lowering in insulin resistant, hypertriglyceridemic states: the combined effect of HDL triglyceride enrichment and elevated hepatic lipase activity. *Clin. Biochem.* **36:** 421–429.