Nutrition, Metabolism & Cardiovascular Diseases (2014) 24, 83–90

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

Interactions between *ADIPOQ* gene variants and dietary monounsaturated: saturated fatty acid ratio on serum lipid levels in Korean children

J.Y. Park [a,1], H.-J. Lee [a,1], H.B. Jang [a], J.-Y. Hwang [c], J.H. Kang [b], B.-G. Han [c], J.-Y. Lee [c], J. Song [a,*]

[a] *Division of Metabolic Diseases, Center for Biomedical Sciences, National Institute of Health, Cheongwon-gun, Chungcheongbuk-do, Republic of Korea*
[b] *Department of Family Medicine, Obesity Research Institute, Seoul Paik Hospital, College of Medicine, Inje University, Seoul, Republic of Korea*
[c] *Center for Genome Science, National Institute of Health, Cheongwon-gun, Chungcheongbuk-do, Republic of Korea*

Received 9 August 2012; received in revised form 2 April 2013; accepted 16 April 2013
Available online 24 June 2013

KEYWORDS
ADIPOQ;
MUFA/SFA ratio;
Serum lipid levels;
Children

Abstract *Background and aims:* Adiponectin plays important roles in the regulation of insulin action and metabolism of glucose and lipids. We investigated whether *ADIPOQ* genetic variants are associated with serum lipid levels in Korean children and whether those influences might be modulated by dietary factors such as dietary monounsaturated fatty acid to saturated fatty acid ratio (MUFA:SFA).
Method and results: The study included a population-based sample of 687 children aged 7–11 years in Gwacheon city, Kyunggi Province, Korea. Anthropometric and biochemical measurements and *ADIPOQ* genotype (−11377 C/G, +45 T/G, and +276 G/T) were determined. Dietary intake was estimated with a self reported 3-day food diary. The −11377 G allele carriers had significantly higher serum total cholesterol and LDL cholesterol compared to non-carriers. When dietary MUFA:SFA ratio was dichotomized (MUFA:SFA ≥1 or <1), the aggravating effects of the minor allele on serum total and LDL cholesterol were only present when the MUFA:SFA ratio was <1. Additionally, we observed that the *ADIPOQ* haplotype influenced serum total and LDL cholesterol levels. G–T–G haplotype carriers had higher total and LDL cholesterol levels than non-G–T–G carriers. The deleterious effect of *ADIPOQ* G–T–G haplotype to increase serum total and LDL cholesterol could be seen only when the MUFA:SFA ratio was <1.

* Corresponding author. Tel.: +82 43 719 8690; fax: +82 43 719 8602.
E-mail addresses: jhsong10@korea.kr, jihyun_s@yahoo.com (J. Song).
[1] Both authors contributed equally to this article.

0939-4753/$ - see front matter
http://dx.doi.org/10.1016/j.numecd.2013.04.007

Conclusion: In this present study, we found interaction effects between *ADIPOQ* genetic variants and dietary MUFA:SFA ratio on serum lipid levels in Korean children. These results suggest that individual genetic information and dietary fatty acid intake information should be assessed together to achieve an effective outcome for reducing the atherogenic lipid profile.

Introduction

High serum lipid levels in childhood are significantly associated with the development of atherosclerosis and metabolic syndrome in adolescence and adulthood. Thus, diagnosis and management of lipid levels at an early stage are important in preventing cardiovascular disease and its complications [1,2].

The serum lipid level is influenced by genetic variants and environmental factors, including response to dietary fatty acid intake, and their interactions in European [3,4] and South African [5]. Among the reported genetic factors associated with serum lipid level, *ADIPOQ* is considered as a candidate gene. *ADIPOQ,* the gene coding for adiponectin, is located on chromosome 3q27 and expressed in adipose tissue exclusively. *ADIPOQ* single-nucleotide polymorphisms (SNPs) have been extensively studied with respect to risk of cardiovascular disease, type 2 diabetes, and metabolic syndrome in almost ethnic group including East Asian [6—8].

Recent studies have focused on the effect of the interaction between *ADIPOQ* genetic variants and dietary factors on body-mass index, insulin sensitivity, and metabolic syndrome [9,10]. Since dietary fatty acids play a key role in glucose and lipid metabolism, the development of metabolic disorder could be modulated through the effects of dietary fatty acids on serum lipid profile and insulin sensitivity [11]. Based on the effects on metabolic disorder, several studies have reported interaction effects between dietary fatty-acid intake and *ADIPOQ* genetic variants. CC allele homozygotes of *ADIPOQ* −11377 had lower glucose concentrations when changing from a saturated fatty acid (SFA)-rich to a monounsaturated fatty acid (MUFA)-rich diet than did minor G allele carriers [9]. In another study, among subjects with MUFA intake above the median, −11391 A allele carriers had lower body mass index and decreased obesity risk [10].

Previous studies reported that *ADIPOQ* genetic variation or gene—diet interaction is associated with metabolic disorder. There have been few studies of the effect of *ADIPOQ* genetic variants on serum lipid profile [12,13]. No previous study of the association and interaction of *ADIPOQ* genetic variants and dietary fatty acid intake on serum cholesterol level has been reported, especially in children. Therefore, we investigated whether *ADIPOQ* genetic variants have an association with serum lipid levels in Korean children and whether those influences might be modulated by dietary factors such as dietary monounsaturated fatty acid to saturated fatty acid ratio (MUFA:SFA).

Methods

Study subjects

This study was conducted as part of the Korea children-adolescent cohort study from Seoul and Kyunggi province, Korea. The overall objective of the cohort study was to identify early risk factors for obesity and associated metabolic disease in Korean children. The study subjects consisted of 687 children (365 boys and 322 girls) from 7 to 11 years of age. Subjects were excluded if they were taking any medications or using weight-loss medication. The study protocol was approved by the Institutional Review Board of the Korea Center for Disease Control and Prevention (KCDC) and Seoul-Paik Hospital, Inje University. Informed consent was obtained from the children and their parents.

Anthropometric parameters

Height was measured using an automatic stadiometer (DS-102; Jenix, Seoul, Korea). Weight and body fat percentage were measured using a body composition analyzer (BC41B; Tanita, Tokyo, Japan). Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Waist circumference was measured at the midpoint between the lower border of the ribcage and the iliac crest using a non-elastic tape measure. We defined overweight status in children using Cole's cutoff point, corresponding to 25 kg/m^2 at 18 years of age for each sex and each age proposed by the body mass index (BMI) references established in an international survey [14].

Assessment of dietary intake

The study subjects for the assessment of dietary intake consisted of 439 children (235 boys and 204 girls). The typical dietary intake of each child was estimated from modified 3-day (2 weekdays, 1 weekend day) food records that were maintained by each child with help from his or her parents. Recipes for school meals (lunches) were provided to the parents, and parents confirmed the amount of food intake of their children. Nutrient intakes were determined from food intakes using the Computer-Aided Nutritional Analysis for Professionals, version 3.0 (CAN-pro 3.0, Korean Nutrition Society, Seoul, Korea) software program. Macronutrient (carbohydrate, fat, and protein) and fatty acid (SFA, MUFA, and PUFA) intake data for each individual were obtained in terms of estimated amounts (g/d), and expressed as percentages of total energy intake. To investigate interaction effects between *ADIPOQ* and dietary fatty acid intake, we divided the subjects into two groups according to dietary MUFA to SFA ratio. In the dietary guidelines of the Korean Nutrition Society, a fatty acid intake ratio of 1.0—1.5:1 of MUFA:SFA is recommended. The mean dietary MUFA:SFA ratio was 1.11 ± 0.01 in this study population. Therefore, dietary fatty acid intake was classified into two groups (MUFA:SFA < 1 and MUFA:SFA ≥ 1)

with reference to the dietary guidelines and fatty acid intake distribution.

Blood collection and biochemical analysis and genotyping

After overnight fasting, venous blood specimens were collected for biochemical measurements, including total cholesterol, triglycerides, and high-density lipoprotein cholesterol, and for DNA extraction.

Serum total cholesterol, HDL cholesterol, and triglycerides (TG) were measured using enzymatic assays and an auto-analyzer (Hitachi 7180, Tokyo, Japan). In study participants with serum TG concentration below 400 mg/dL, LDL cholesterol was indirectly estimated using the Friedewald equation. Fasting adiponectin concentration was measured using an enzyme immunoassay (Bio-Vender, Australia). The genomic DNA of participants was extracted from whole blood using an Accuprep genomic DNA extraction kit (Bioneer, Daejeon, Korea), according to the manufacturer's protocol. Primers and probes were designed for TaqMan (Applied Biosystems, Foster City, CA). Information regarding the primers is available on the following website: http://www.snp-genetics.com/user/additional_list.asp. SNPs of *ADIPOQ* satisfied the following criteria: a minimum call rate of 90%, no duplicate error, and Hardy–Weinberg equilibrium $P > 0.05$.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences software, version 15.0 (SPSS 15.0, SPSS Inc., Chicago, IL, USA). The data are presented as means ± standard deviation (S.D.). Variables with skewed distributions were log-transformed before statistical analysis. Hardy–Weinberg equilibrium and linkage disequilibrium tests were examined using the Haploview 4.1 (Broad Ins., Cambridge, MA, USA). 95% confidence interval (CI) for comparisons among groups was calculated by Student's *t*-test and ANOVA. Linear regression analyses of associations between genotypes and phenotypes were performed assuming the additive model (minor allele homozygotes vs. heterozygotes vs. major allele homozygotes) and adjusted for age, gender, BMI and waist circumference. The interactions between *ADIPOQ* genotype and dietary MUFA:SFA were tested in the general linear model using interaction terms and controlled confounding factors, including age, gender, BMI, waist circumference, and total energy intake. *P* values <0.05 were considered to indicate a statistical significance.

Results

General characteristics of the study population and genotype distribution

The anthropometric and biochemical characteristics of the 687 Korean children classified by their weight status are listed in Table 1. The prevalence of children who were overweight based on the Cole's cutoff was 19.65%. Mean BMI, waist circumference, and serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride) levels were all within reference ranges. Significant differences in height, weight, BMI, waist size, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and adiponectin level were observed between normal weight and overweight children (Table 1). Total energy intake was not different between the normal weight and overweight groups but obese children little more took in total protein than normal weight children. These genotype distributions were in Hardy–Weinberg equilibrium ($P > 0.05$). From the LD test, SNP +45 and SNP +276 were found to be highly linked ($D' = 1.0$), even though r^2 was not high ($r^2 = 0.204$). SNP +45 and SNP −11377 were also found to be linked ($D' = 0.708$, $r^2 = 0.074$).

Serum lipid level according to *ADIPOQ* genotype and haplotype

Table 2 shows the serum lipid levels of the study population according to the genotypes of *ADIPOQ* −11377 C/G, +45 T/G, and +276 G/C, respectively. At position −11377, there was a significant genotype-related difference in serum total cholesterol level after adjustment for age, gender, BMI, and waist circumference ($P = 0.023$). Serum LDL cholesterol level had a tendency to be different for SNP −11377. However, there were no significant genotype-related differences with respect to serum total cholesterol, LDL cholesterol, HDL cholesterol, or triglyceride level at SNP +45 and SNP +276.

Additionally, we investigated serum lipid levels of the study population according to the haplotype (*ht*: G–T–G) of *ADIPOQ* (Table 3). The haplotype analysis was performed for SNP −11377 combined with SNP +45 and SNP +276. In the haplotype analysis, G–T–G haplotype carrier (*ht*/*ht* + *ht*/−) subjects showed significantly higher serum total cholesterol ($P = 0.017$) and LDL cholesterol ($P = 0.052$) levels than G–T–G non-carrier (−/−) subjects. Serum HDL cholesterol and triglyceride levels did not differ according to *ADIPOQ* haplotype.

Interaction effects between *ADIPOQ* polymorphisms and dietary MUFA:SFA ratio on serum lipid levels

The interaction effects between *ADIPOQ* genetic variants and dietary MUFA:SFA on serum lipid level after adjustment for age, gender, BMI, waist circumference, and total energy intake are presented in Table 4. There was an interaction effect between the SNP −11377 and dietary fatty acid intake on serum total cholesterol (*P* for interaction = 0.005) and LDL cholesterol level (*P* for interaction = 0.026). In the MUFA:SFA < 1 group, serum total cholesterol ($P = 0.009$) and LDL cholesterol level ($P = 0.016$) showed genotype-related differences. However, there was no significant genotype-related difference in the MUFA:SFA ≥1 group. SNP +45 and SNP +276 did not show interaction effects between genetic variants and dietary fatty acid intake.

Interaction effects between *ADIPOQ* haplotype and dietary MUFA:SFA ratio on serum lipid levels

Figure 1 shows the interaction effects between *ADIPOQ* genetic variants and dietary MUFA:SFA on serum total

Table 1 General characteristics of the study population.

	Children (n = 687)	Normal (n = 552)	Overweight[a] (n = 135)
Age (years)	8.38 ± 0.50	8.40 ± 0.86	8.31 ± 0.97
Male/females (%)	53.1/46.9	50.4/49.6	64.4/35.6
Height (cm)	130.3 ± 7.26	129.7 ± 7.05	132.5 ± 7.70*
Weight (kg)	29.0 ± 6.21	27.3 ± 4.64	36.3 ± 6.56*
Body mass index (kg/m^2)	17.0 ± 2.38	16.1 ± 1.49	20.5 ± 2.05*
Waist circumference (cm)	57.6 ± 6.71	55.4 ± 4.64	66.7 ± 6.12*
Total cholesterol (mg/dL)	168.3 ± 26.66	166.7 ± 26.83	174.8 ± 25.02*
LDL cholesterol (mg/dL)	96.3 ± 23.74	95.0 ± 23.82	101.8 ± 22.68*
HDL cholesterol (mg/dL)	58.3 ± 11.61	59.0 ± 11.60	55.1 ± 11.16*
Triglycerides (mg/dL)	66.0 ± 34.14	62.0±29.83	82.9 ± 44.50*
Adiponectin (μg/mL)	12.0 ± 4.34	12.3 ± 4.41	10.8 ± 3.85*
Estimated dietary intake	N = 439	N = 365	N = 74
Total energy intake (kcal)	1780.3 ± 16.0	1787.0 ± 332.3	1747.2 ± 350.53
Carbohydrate (% of energy)	58.9 ± 0.23	59.0 ± 4.71	58.2 ± 5.10
Fat (% of energy)	25.7 ± 0.21	25.8 ± 4.41	25.5 ± 4.07
Protein (% of energy)	16.4 ± 0.09	16.3 ± 1.87	16.9 ± 2.15
SFA (% of energy)	4.96 ± 0.10	4.93 ± 2.01	5.09 ± 2.17
MUFA (% of energy)	5.18 ± 0.06	5.15 ± 1.81	5.33 ± 1.87
PUFA (% of energy)	4.14 ± 0.06	4.10 ± 1.19	4.36 ± 1.05
MUFA/SFA	1.11 ± 0.01	1.12 ± 0.26	1.12 ± 0.25
Polymorphism of *ADIPOQ* (MAF/HWE)			
−11377 C/G	0.239/0.074	0.242/0.622	0.226/0.081
+45 T/G	0.320/0.161	0.317/0.124	0.333/0.432
+276 G/T	0.304/0.071	0.302/0.841	0.311/0.069

Data are expressed as the means ± S.D. SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

[a] Children were defined as overweight on the basis of the age- and sex-appropriate international BMI cutoffs proposed by Cole's method. *$P < 0.05$.

cholesterol and LDL cholesterol levels after adjustment for age, gender, BMI, waist circumference, and total energy intake. The *ADIPOQ* haplotype interacted with dietary MUFA:SFA in association with serum total cholesterol (P for interaction = 0.002) and LDL cholesterol (P for interaction = 0.021) levels. G–T–G haplotype carriers had higher total cholesterol (P = 0.006) and LDL cholesterol (P = 0.019) levels than did G–T–G non-carriers (−/−) when the ratio of MUFA:SFA was <1. Also, subjects with dietary MUFA:SFA <1 who were carrying the G–T–G haplotype had higher serum total cholesterol (P = 0.030) and LDL cholesterol (P = 0.093) levels than did MUFA:SFA ≥1 subjects. There were no differences in serum HDL cholesterol and triglyceride levels according to interactions between *ADIPOQ* haplotype and dietary fatty acid intake.

Discussion

In the present study, we observed that *ADIPOQ* −11377 G allele carriers had significantly higher serum total cholesterol and LDL cholesterol levels compared to non-carriers; these differences were found only in children in the low dietary MUFA:SFA ratio group. Additionally, we found interaction effects between the haplotype of *ADIPOQ* and dietary MUFA:SFA on serum total cholesterol and LDL cholesterol levels. G–T–G haplotype carriers had higher total cholesterol and LDL cholesterol levels than did G–T–G non-carriers within the MUFA:SFA <1 group.

Interaction effects between *ADIPOQ* genetic variants and fatty acids were previously reported with regard to serum adiponectin level, obesity, and type 2 diabetes-related phenotypes. AlSaleh et al. [15] reported that treatment with a high MUFA diet for 4 weeks in G allele homozygotes of *ADIPOQ* −10066 increased serum adiponectin concentration. Warodomwichit et al. [10] showed that −11391 A carriers had a lower BMI and decreased obesity risk in subjects with a MUFA intake above the median. Ferguson et al. [16] showed that the *ADIPOQ* −11377 C/G SNPs interact with plasma SFA to alter insulin resistance in healthy subjects and metabolic syndrome patients. These results suggest that *ADIPOQ* SNPs and fatty acids are linked to obesity and insulin resistance.

However, the associations between *ADIPOQ* genetic variants and lipid metabolism and the biological mechanisms underlying adiponectin and lipid metabolism have not yet been elucidated. One potential pathway involves the activation of peroxisome proliferator-activated receptor-γ (PPAR-γ), a transcriptional regulator that interacts directly with the *ADIPOQ* promoter. Dietary fatty acid intake leads to increased expression of the *ADIPOQ* gene and serum adiponectin concentration though increased availability of PPAR-γ activating ligands [17]. The biological functions of adiponectin depend primarily on the activation of

Table 2 Serum lipid level according to *ADIPOQ* polymorphism.

	Genotype			*P*-value[a]
Children				
−11377 C/G	CC (n = 407)	CG (n = 232)	GG (n = 48)	
Total cholesterol (mg/dL)	166.7 ± 26.9 (164.1−169.3)	169.3 ± 25.0 (166.1−172.6)	176.8 ± 31.2 (167.8−185.9)	0.023
LDL cholesterol (mg/dL)	95.1 ± 23.9 (92.8−97.4)	97.5 ± 21.9 (94.6−100.3)	101.2 ± 29.7 (92.6−109.9)	0.165
HDL cholesterol (mg/dL)	58.0 ± 11.8 (56.8−59.1)	58.2 ± 11.7 (56.7−59.7)	60.1 ± 9.5 (58.1−63.6)	0.148
Triglycerides (mg/dL)[b]	65.3 ± 34.2 (61.9−68.7)	66.7 ± 34.5 (62.2−71.1)	69.0 ± 32.0 (59.6−78.4)	0.711
+45 T/G	TT (n = 324)	TG (n = 282)	GG (n = 78)	
Total cholesterol (mg/dL)	168.0 ± 27.0 (165.0−171.0)	168.7 ± 27.1 (165.5−170.1)	167.7 ± 24.1 (162.3−173.1)	0.873
LDL cholesterol (mg/dL)	96.3 ± 24.2 (93.6−98.9)	96.9 ± 24.0 (94.0−100.0)	94.6 ± 21.1 (89.8−99.4)	0.655
HDL cholesterol (mg/dL)	58.0 ± 11.9 (56.9−59.3)	58.3 ± 11.6 (57.0−60.0)	59.1 ± 10.7 (56.8−61.5)	0.765
Triglycerides (mg/dL)[b]	66.5 ± 34.2 (62.8−70.3)	65.1 ± 32.5 (61.3−68.9)	67.4 ± 40.3 (58.2−76.5)	0.239
+276 G/T	GG (n = 322)	GT (n = 310)	TT (n = 53)	
Total cholesterol (mg/dL)	168.8 ± 25.8 (166.0−171.6)	167.6 ± 27.6 (164.5−170.7)	169.1 ± 26.9 (161.7−176.5)	0.890
LDL cholesterol (mg/dL)	96.6 ± 22.7 (94.1−99.0)	96.1 ± 24.4 (93.4−98.8)	96.7 ± 26.5 (89.4−104.0)	0.987
HDL cholesterol (mg/dL)	58.8 ± 11.3 (57.6−60.0)	57.5 ± 12.0 (56.2−58.8)	59.5 ± 11.3 (56.3−62.6)	0.211
Triglycerides (mg/dL)[b]	65.8 ± 35.5 (61.9−69.7)	66.5 ± 33.0 (62.8−70.2)	64.6 ± 33.5 (55.3−73.8)	0.806

Data are expressed as the means ± S.D (95% confidence interval).
[a] *P* value of the additive models was calculated by linear regression analysis with adjustment for age, gender, BMI and waist circumference.
[b] Tested by logarithmic transformation.

AMP-activated protein kinase, thereby reducing lipid accumulation [18]. Adiponectin enhances the transcription of other genes involved in fatty acid metabolism, most notably PPAR-α. Activation of PPAR-α leads to an increase in levels of molecules involved in the fatty acid transporter, energy dissipation, and fatty acid oxidation. The adiponectin level was lower in subjects with a high risk of T2DM than in control subjects. Total energy expenditure, especially under hyperinsulinemic conditions, increases with elevated adiponectin [19,20]. In the present study *ADIPOQ* genetic variant, −11377 C/G SNPs, showed the significant association with total cholesterol and its G−T−G haplotype carriers had higher LDL cholesterol levels than non-carriers with a marginal statistical significance. Increased cholesterol levels get the catalytic domain of HMG CoA reductase susceptible to destruction by the proteosome to be oligomerized. The phosphorylation by an AMP-activated protein kinase can also reduce the activity of HMG CoA reductase [21]. AMP produced by ATP hydrolyzation activates this kinase. It may be that *ADIPOQ* gene is related to the regulation of hepatic cholesterol synthesis through AMP-activated protein kinase. Similar to our research, recent studies have reported the effect of *ADIPOQ* genetic variants on serum cholesterol according to BMI status. Riestra et al. [12] showed a significant association between *ADIPOQ* 276 G/T and lipid parameters in overweight children, in whom the 276 T allele carrier was associated with lower serum total cholesterol, LDL cholesterol, and apoA-I levels. Vasseur et al. [13] reported that BMI modulates the effects of *ADIPOQ* haplotypes on serum LDL cholesterol level. Based on previous reports, we suggest that *ADIPOQ* genetic variants affect adiponectin itself and its related proteins and thereby influence serum lipid level.

Many studies have shown that a higher intake of SFA is associated with an atherogenic profile, whereas the contrary is true for MUFA. Bos et al. [22] showed that replacing a high SFA diet with a high MUFA diet improved serum lipid levels. The high MUFA diet reduced serum total cholesterol and LDL cholesterol, and also increased HDL cholesterol and reduced the total cholesterol:HDL cholesterol ratio. Rivellese et al. and Campos et al. [23,24] showed that high-SFA diets negatively influence LDL cholesterol by causing a

Table 3 Serum lipid level according to the *ADIPOQ* haplotype G−T−G (−11377 C/G, +45 T/G and +276 G/T).

	G−T−G carrier	G−T−G non-carrier	*P*-value[a]
	(n = 250)	(n = 434)	
Total cholesterol (mg/dL)	171.5 ± 26.4 (168.2−174.7)	166.5 ± 26.7 (164.0−169.0)	0.017
LDL cholesterol (mg/dL)	98.8 ± 23.5 (95.9−101.7)	94.9 ± 23.8 (92.7−97.2)	0.052
HDL cholesterol (mg/dL)	58.6.1 ± 11.5 (57.1−60.0)	58.1 ± 11.7 (57.0−59.2)	0.371
Triglycerides (mg/dL)[b]	68.2 ± 34.3 (63.9−72.5)	64.7 ± 34.1 (61.5−68.0)	0.762

Data are expressed as the means ± S.D. (95% confidence interval).
[a] *P* value of the additive models was calculated by linear regression analysis with adjustment for age, gender, BMI and waist circumference.
[b] Tested by logarithmic transformation.

Table 4 Interaction between *ADIPOQ* polymorphism and dietary monounsaturated fatty acid (MUFA)/saturated fatty acid (SFA) ratio in the context of serum lipid level.

	Genotype*diet intake								*P*-value[b] for interaction
	MUFA/SFA < 1			*P*-value[a]	MUFA/SFA ≥ 1			*P*-value[a]	
Children									
−11377 C/G	CC ($n = 95$)	CG ($n = 62$)	GG ($n = 10$)		CC ($n = 168$)	CG ($n = 84$)	GG ($n = 20$)		
Total cholesterol (mg/dL)	165.7 ± 24.8	178.2 ± 27.3	187.4 ± 36.2	0.009	165.4 ± 27.4	166.0 ± 24.8	172.6 ± 32.1	0.591	0.005
LDL cholesterol (mg/dL)	92.0 ± 21.9	104.7 ± 24.0	107.0 ± 35.2	0.016	94.2 ± 24.3	93.8 ± 22.8	100.1 ± 31.4	0.878	0.026
HDL cholesterol (mg/dL)	60.9 ± 10.7	60.3 ± 11.2	65.8 ± 9.4	0.571	58.0 ± 11.5	58.9 ± 11.4	59.5 ± 9.5	0.713	0.189
Triglycerides (mg/dL)[c]	63.7 ± 33.9	63.2 ± 31.2	73.5 ± 32.0	0.234	62.7 ± 31.3	61.7 ± 28.0	65.5 ± 37.5	0.993	0.779
+45 T/G	TT ($n = 79$)	TG ($n = 66$)	GG ($n = 22$)		TT ($n = 126$)	TG ($n = 116$)	GG ($n = 30$)		
Total cholesterol (mg/dL)	175.0 ± 28.8	169.7 ± 27.8	167.1 ± 19.8	0.463	164.2 ± 27.3	168.4 ± 26.9	165.1 ± 25.9	0.483	0.133
LDL cholesterol (mg/dL)	99.9 ± 25.5	97.2 ± 24.7	92.6 ± 19.0	0.434	93.4 ± 25.0	96.5 ± 24.2	91.3 ± 22.9	0.393	0.306
HDL cholesterol (mg/dL)	61.3 ± 11.9	60.4 ± 9.8	61.6 ± 10.1	0.895	57.3 ± 11.6	59.3 ± 11.1	59.4 ± 11.1	0.360	0.256
Triglycerides (mg/dL)[c]	66.8 ± 34.2	60.6 ± 30.6	65.0 ± 33.7	0.445	63.5 ± 30.6	60.9 ± 28.1	65.3 ± 41.2	0.991	0.508
+276 G/T	GG ($n = 87$)	GT ($n = 68$)	TT ($n = 12$)		GG ($n = 123$)	GT ($n = 129$)	TT ($n = 20$)		
Total cholesterol (mg/dL)	170.4 ± 25.3	173.2 ± 29.8	175.3 ± 30.0	0.771	166.7 ± 25.9	165.9 ± 28.3	164.1 ± 25.7	0.899	0.344
LDL cholesterol (mg/dL)	96.6 ± 22.9	98.9 ± 25.8	101.7 ± 29.4	0.734	95.1 ± 22.8	94.7 ± 25.7	89.5 ± 26.2	0.493	0.539
HDL cholesterol (mg/dL)	60.7 ± 10.8	61.3 ± 11.2	60.8 ± 9.9	0.883	59.1 ± 11.4	57.4 ± 11.4	60.3 ± 10.6	0.344	0.223
Triglycerides (mg/dL)[c]	63.4 ± 31.3	65.0 ± 34.9	64.5 ± 32.4	0.953	60.7 ± 29.9	63.1 ± 30.3	71.3 ± 38.1	0.488	0.770

Data are expressed as the estimated means ± S.D.

[a] *P* value of the additive models was calculated by linear regression analysis with adjustment for age, gender, BMI and waist circumference.

[b] *P* value of the mixed-effect models by generalized linear regression analysis with adjustment for age, gender, BMI, waist circumference, and total energy intake.

[c] Tested by logarithmic transformation.

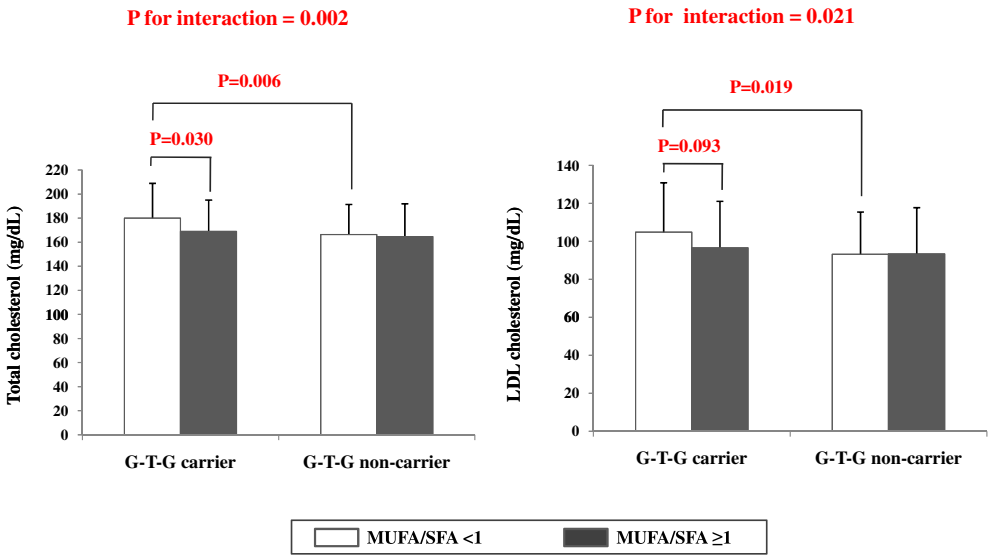

Figure 1 Interaction of *ADIPOQ* haplotype and dietary MUFA:SFA ratio on serum total cholesterol and LDL cholesterol level data was expressed as estimated means ± S.D. Performed by general linear model analysis with adjustment for age, gender, BMI, waist circumference and total energy intake.

change in the distribution of LDL particles and that, on the contrary, high MUFA diets have beneficial effects on LDL cholesterol level.

Since *ADIPOQ* genetic variants may affect serum total cholesterol and LDL cholesterol levels, they may also affect serum lipid levels, which are dependent on dietary fatty acid composition. Although the high energy and fat intake when compared with the 2007 Korean National Health and Nutrition Examination Survey (6—11 years: 1592.8 kcal, 37.8 g), our children's dietary intake meets the proper ratio of energy of 3—18 years old by the Dietary Reference Intakes for Koreans (Carbohydrate:Protein:Fat = 55—70:7—20:15—30). After adjustment for age, gender, BMI, waist circumference, and total energy intake, the MUFA:SFA <1 group showed an influence of the *ADIPOQ* polymorphism on serum total cholesterol and LDL cholesterol levels in our study. G—T—G haplotype carriers had higher serum total cholesterol and LDL cholesterol levels than did G—T—G non-carriers with a lower MUFA:SFA intake ratio. However, no genotype or haplotype related differences were detected in the MUFA:SFA ≥1 group. These findings suggest that the influence of the *ADIPOQ* −11377 G allele and G—T—G haplotype on serum cholesterol is associated with the MUFA:SFA ratio.

Despite a small sample size, we showed interaction effects between the genetic variants of *ADIPOQ* and dietary MUFA:SFA ratio on serum total cholesterol and LDL cholesterol levels in Korean children. These findings showed the necessity of integration of multiple types of information, such as dietary fatty acid intake, SNPs, and metabolic traits. This integrated information could help suggest effective prevention methods for atherogenic lipid profile and cardiovascular disease at an early stage.

Conflict of interest

There are no potential conflicts of interest.

Acknowledgments

We thank all the participating schools, children, and parents. This work was supported by intramural grants from the Korea National Institute of Health, and Korea Center for Disease Control (project no: 4845-302-210-13).

References

[1] Berenson GS, Srinivasan SR, Bao W, Newman 3rd WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. N Engl J Med 1998;338(23):1650—6.

[2] McGill Jr HC, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Bol 2000;20(8):1998—2004.

[3] Standl M, Lattka E, Stach B, Koletzko S, Bauer CP, von Berg A, et al. *FADS1 FADS2* gene cluster, PUFA intake and blood lipids in children: results from the GINIplus and LISAplus studies. PLoS One 2012;7(5):e377801.

[4] Wu K, Bowman R, Welch AA, Luben RN, Wareham N, Khaw KT, et al. Apolipoprotein E polymorphism, dietary fat and fiber, and serum lipids: the EPIC Norfolk Study. Eur Heart J 2007; 28(23):2390—6.

[5] Joffe YT, van der Merwe L, Collins M, Carstens M, Evans J, Lambert EV, et al. The -308 G/A polymorphism of the tumor necrosis factor-α gene modifies the association between saturated fat intake and serum total cholesterol levels in white South African women. Genes Nutr 2011;6(4):353—9.

[6] Gable DR, Hurel SJ, Humphries SE. Adiponectin and its gene variant as risk factors for insulin resistance, the metabolic syndrome, and cardiovascular disease. Atherosclerosis 2006; 188(2):231—44.

[7] Francke S, Manraj M, Lacquemant C, Lecoeur C, Lepretre F, Passa P, et al. A genome-wide scan for coronary heart disease suggests in Indo-Mauritians a susceptibility locus on

chromosome 16p13 and replicates linkage with the metabolic syndrome on 3q27. Hum Mol Genet 2001;10(24):2751—65.
[8] Vionnet N, Hani EH, Dupont S, Gallina S, Francke S, Dotte S, et al. Genomewide search for type 2 diabetes-susceptibility genes in French whites: evidence for a novel susceptibility locus for early-onset diabetes on chromosome 3q27-qter and independent replication of a type 2-diabetes locus on chromosome 1q21-q24. Am J Hum Genet 2000;67(6):1470—80.
[9] Perez-Martinez P, Lopez-Miranda J, Cruz-Teno C, Delgado-Lista J, Jimenez-Gomez Y, Fernandez JM, et al. Adiponectin gene variants are associated with insulin sensitivity in response to dietary fat consumption in Caucasian men. J Nutr 2008;138:1609—14.
[10] Warodomwichit D, Shen J, Arnett DK, Tsai MY, Kabagambe EK, Peacock JM, et al. The monounsaturated fatty acid intake modulates the effect of *ADIPOQ* polymorphisms on obesity. Obesity 2009;17(3):510—7.
[11] Gillingham LG, Harris-Janz S, Jones PJ. Dietary monounsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. Lipids 2011; 46(3):209—28.
[12] Riestra P, Garcia-Anguita A, Lasuncion MA, Mangas A, de Oya M, Garces C. Influence of the interaction between the adiponectin G276T polymorphism and body mass index on lipid levels in healthy children. Mol Biol Rep 2012;39(4):4831—5.
[13] Vasseur F, Caeyseele T, Barat-Houari M, Lobbens S, Meirhaeghe A, Meyre D, et al. Concordance of two multiple analytical approaches demonstrate that interaction between BMI and ADIPOQ haplotypes is a determinant of LDL cholesterol in a general French population. J Hum Genet 2010;55(4): 227—31.
[14] Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. Br Med J 2000;320(7244):1240—3.
[15] AlSaleh A, O'Dell SD, Frost GS, Griffin BA, Lobegrove JA, Jebb SA, et al. Single nucleotide polymorphisms at the *ADIPOQ* gene locus interact with age and dietary intake of fat to determine serum adiponectin in subjects at risk of the metabolic syndrome. Am J Clin Nutr 2011;94(1):262—9.
[16] Ferguson JF, Phillips CM, Tierney AC, Perez-Martinez P, Cefoort C, Helal O, et al. Gene-nutrient interactions in the metabolic syndrome: single nucleotide polymorphisms in *ADIPOQ* and *ADIPOR1* interact with plasma saturated fatty acids to modulate insulin resistance. Am J Clin Nutr 2010; 91(3):794—801.
[17] AlSaleh A, Sanders TA, O'Dell SD. Effect of interaction between PPARG, PPARA, and *ADIPOQ* gene variants and dietary fatty acids on plasma lipid profile and adiponectin concentration in a large intervention study. Proc Nutr Soc 2012;71(1): 141—53.
[18] Fu Y, Luo N, Klein RL, Garvey WT. Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation. J Lipid Res 2005;46(7):1369—79.
[19] Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423(6941):762—9.
[20] Salmenniemi U, Zacharova J, Ruotsalainen E, Vauhkonen I, Pihlajamaki J, Kainulainen S, et al. Association of adiponectin level and variants in the adiponectin gene with glucose metabolism, energy expenditure, and cytokines in offspring of type 2 diabetic patients. J Clin Endocrinol Metab 2005;90(7): 4216—23.
[21] Hardie DG. New roles for the LKB1AMPK pathway. Curr Opin Cell Biol 2005;17(2):167—73.
[22] Bos MB, de Vries JH, Feskens EJ, va Dijk SJ, Hoelen DW, Siebelink E, et al. Effect of a high monounsaturated fatty acids diet and a Mediterranean diet in serum lipids and insulin sensitivity in adults with mild abdominal obesity. Nutr Metab Cardiovasc Dis 2010;20(8):591—8.
[23] Rivellese AA, Maffettone A, Vessby B, Uusitupa M, Hermansen K, Berglund L, et al. Effects of dietary saturated, monounsaturated and n-3 fatty acids on fasting lipoproteins, LDL size and post-prandial lipid metabolism in healthy subjects. Atherosclerosis 2003;167(1):149—58.
[24] Campos H, Dreon DM, Krauss RM. Associations of hepatic and lipoprotein lipase activities with changes in dietary composition and low density lipoprotein subclasses. J Lipid Res 1995; 36(3):462—72.