Adiponectin Gene Polymorphisms Are Associated with Long-Chain ω3-Polyunsaturated Fatty Acids in Serum Phospholipids in Nondiabetic Koreans

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Context: Hypoadiponectinemia is caused by interactions between genetic and environmental factors, including the quality of dietary fats.

Objective: We investigated the association of single-nucleotide polymorphisms (SNPs) in the adiponectin gene (*ADIPOQ*) with dietary fat intake or fatty acid (FA) composition in serum phospholipids, plasma adiponectin, and insulin resistance.

Methods: Nondiabetic subjects (n = 1194) were genotyped for three *ADIPOQ* SNPs (−11377C>G; 45T>G; 276G>T) after screening of eight sites. Dietary fat intake, FA composition in serum phospholipids, adiponectin, and homeostasis model assessment of insulin resistance (HOMA-IR) were also measured.

Results: The 276G carriers (n = 1082) showed lower high-density lipoprotein cholesterol ($P = 0.024$) and adiponectin ($P < 0.001$) but higher glucose ($P = 0.015$) and HOMA-IR ($P = 0.005$) than 276T/T subjects (n = 112). No associations were found in other SNPs. After adjusted for age, sex, body mass index, and the proportion of 18:2ω6 and 18:3ω3 (biomarkers of long term essential FA intake), the 276G carriers showed lower proportions of total ω3FA ($P = 0.026$), 20:5ω3 ($P = 0.021$), and 22:5ω3 ($P = 0.024$) in serum phospholipids. Among FAs in serum phospholipids, 18:2ω6 highly correlated with ω3-polyunsaturated FA (PUFA) intake ($r = 0.260$, $P < 0.001$) and adiponectin ($r = 0.150$, $P < 0.001$). The 276G carriers with a higher proportion of 18:2ω6 (≥12.5%) exhibited more pronounced characteristics, *i.e.* lower adiponectin ($P < 0.001$), lower high-density lipoprotein cholesterol ($P = 0.004$), higher HOMA-IR ($P = 0.013$), and lower long-chain ω3PUFAs (20:5ω3, 22:5ω3, and 22:6ω3, $P < 0.001$). Additionally, the effect of 276G>T on the relationship between adiponectin and HOMA-IR was modified by 18:2ω6 proportion.

Conclusion: *ADIPOQ* 276G is associated with reduced proportion of long-chain ω3PUFAs in serum phospholipids in nondiabetic Koreans. **(*J Clin Endocrinol Metab* 95: E347–E351, 2010)**

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Abbreviations: *ADIPOQ*, Adiponectin gene; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; FA, fatty acid; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of IR; IR, insulin resistance; PPAR, peroxisomal proliferator-activated receptor; PUFA, ω3-polyunsaturated FA; SFA, saturated fatty acid; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

Low circulating adiponectin, the protein produced by *adipocyte C1q*, and *collagen domain-containing gene* (*ADIPOQ*), are associated with type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (1, 2). Among the single-nucleotide polymorphisms (SNPs) in the *ADIPOQ* gene, 276G>T is associated with reduced circulating adiponectin, greater insulin resistance (IR), and the increased risk of T2DM (3) or the early onset of coronary artery disease (CAD) (4). Menzaghi *et al.* (5) also showed that 276G>T, either independently or as a haplotype with 45T>G, is associated with several features of IR in nondiabetic Italians. In French subjects, a GG haplotype from SNPs −11391G>A/−11377C>G is significantly associated with hypoadiponectinemia, despite no association with IR and T2DM (6). The reasons for these partially discrepant results are unknown but may result from the different genetic background and potential gene-diet interactions in the different ethnicities.

Hypoadiponectinemia is caused by interactions between genetic and environmental factors, including the quality of dietary fats. Previous studies have reported significant association between circulating adiponectin and plasma fatty acids (FAs) (7, 8). In rodents, a diet rich in ω3-polyunsaturated FAs (PUFAs) increases adiponectin concentration and up-regulates adipocytes (7, 8), whereas saturated fat down-regulates *ADIPOQ* expression (9). However, there are no studies on the association between *ADIPOQ* polymorphisms and serum FA composition, even though FA composition was a reasonably accurate biochemical marker of long-term proportionate FA intake, especially for PUFAs and essential FAs (10).

Therefore, we examined whether *ADIPOQ* genetic variation and dietary fat intake or FA composition of serum phospholipids may modulate plasma adiponectin and contribute to CVD risk, including the IR index.

Subjects and Methods

Study subjects

Study participants were recruited during routine check-ups at a health promotion center at Yonsei University Hospital (580 men, 614 women). Exclusion criteria were clinical or electrocardiographic evidence of CAD, stroke, myocardial infarction, or peripheral arterial occlusive disease; diabetes mellitus (or fasting glucose ≥ 126 mg/dl); abnormal liver or renal function; thyroid or pituitary disease; acute or chronic inflammatory disease; and regular use of any medications. The purpose of the study was carefully explained to all participants, and their informed consent was obtained. The study protocol was approved by the Institutional Review Board of Yonsei University.

Anthropometric parameters and blood collection

Body mass index (BMI; kilograms per square meter) was calculated with body weight and height. Waist to hip ratio was calculated with waist and hip circumferences. Blood pressure was measured in the left arm of the patient after a 20-min rest (TM-2654; A&D, Tokyo, Japan). Fasting venous blood specimens (12 h) were collected in EDTA-treated and plain tubes, centrifuged to give plasma or serum, and stored at −70 C until analysis.

Genotyping

Genomic DNA was extracted using a commercially available DNA isolation kit (WIZARD Genomic DNA purification kit; Promega, Madison, WI). Previously reported eight *ADIPOQ* SNPs (−11391G>A; −11377C>G; H241P; Y111H;G90S; R221S; 45T>G; 276G>T) were prescreened to see the minor allele frequency of each SNP (11). Each genotyping reaction was performed with SNP-IT assays (SNPstream 25K system; Orchid Biosystems, Princeton, NJ).

Glucose, insulin, homeostasis model assessment for IR (HOMA-IR), and lipid profile

Fasting glucose was measured by a glucose oxidase method (Beckman glucose analyzer; Beckman Instruments, Irvine, CA). Insulin was measured by RIAs with commercial kits (Immuno Nucleo Corp., Stillwater, MN). IR was calculated with the homeostasis model assessment. Fasting total cholesterol and triglycerides were measured using commercially available kits (Hitachi 7150 autoanalyzer; Hitachi Ltd., Tokyo, Japan). High-density lipoprotein (HDL) cholesterol in the supernatant was measured by an enzymatic method and low-density lipoprotein cholesterol was indirectly estimated in subjects with serum triglyceride less than 400 mg/ml using the Friedewald formula.

Plasma adiponectin and FA composition in serum phospholipids

Plasma adiponectin was measured using an enzyme immunoassay (human adiponectin ELISA kit; B-Bridge International Inc., San Jose, CA) and a Victor^2 (PerkinElmer Life Sciences, Turku, Finland). Serum phospholipid FA composition was analyzed using the modified method of Folch *et al.* (12) and Lepage and Roy (13) with gas chromatography (Hewlett Packard 5890A; Palo Alto, CA).

Dietary intervention program and assessment of dietary intake/physical activity level

Subjects' diets were assessed using a 24-h recall method (3 d dietary records). Dietary energy values and nutrient content were calculated using CAN-pro 2.0 (Korean Nutrition Society, Seoul, Korea). Total energy expenditures (kilocalories per day) were also calculated.

Statistical analysis

Statistical analyses were performed with SPSS version 12.0 (SPSS Inc., Chicago, IL). Executive SNP analyzer (http://www.istech.info/silicosnp/index.html?) was used for the Hardy-Weinberg equilibrium test and linkage disequilibrium test. One-way ANOVA with the Bonferroni correction was used to test the genotype effect. General linear models approach was also used for the comparison with adjustment for confounding factors. Pearson and partial correlation coefficients were used to determine the relationship between variables. Each variable was examined for normal distribution, and skewed variables were log transformed. For descriptive purposes, mean values are presented using untransformed values.

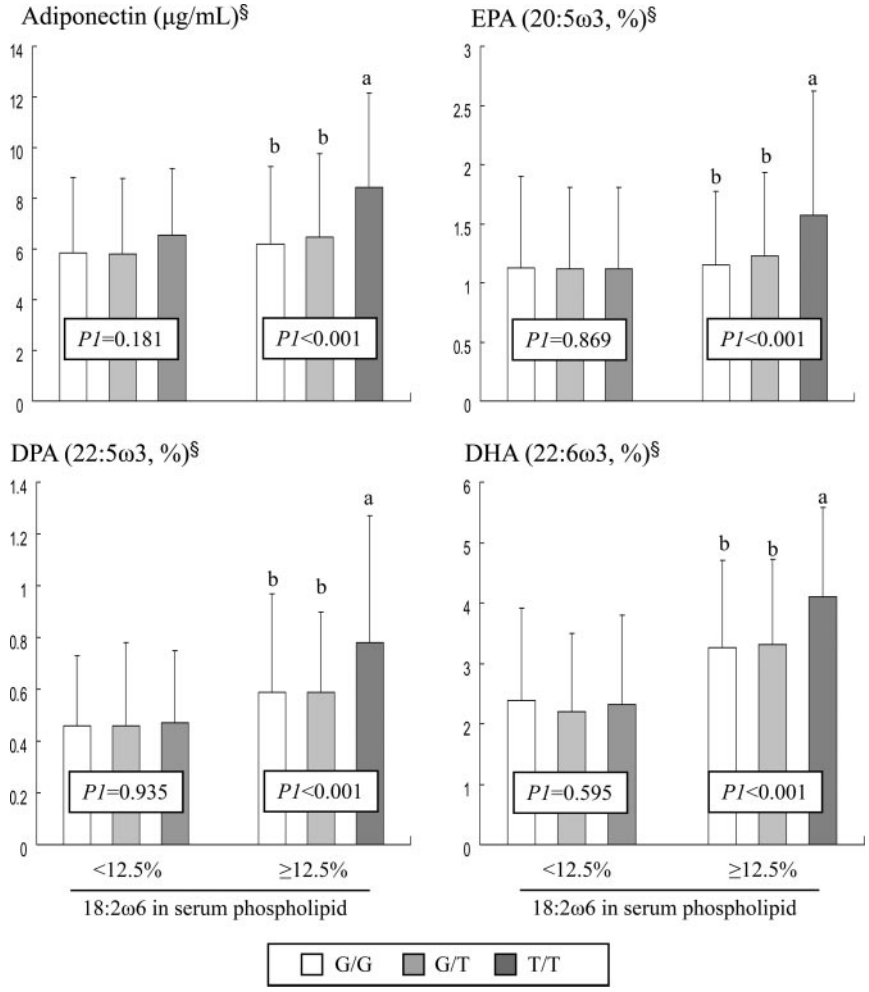

FIG. 1. Effect of *ADIPOQ* 276 G>T on plasma adiponectin and the proportions of long-chain ω3PUFAs in serum phospholipids according to the proportion of 18:2ω6 in serum phospholipids (below or above the median level, 12.5%). Data are mean ± SD.§, Tested by logarithmic transformation. Tested by one-way ANOVA followed by Bonferroni method (P0, unadjusted) and generalized linear model with adjustment for age, sex, BMI, and proportions of 18:2ω6 and 18:3ω3 in serum phospholipids (P1, adjusted). Sharing the same alphabet indicates no significant difference (P1 < 0.05) in mean values. EPA, Eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid.

Results are expressed as mean ± SD. A two-tailed value of $P < 0.05$ was considered statistically significant.

Results

Distribution of −11377C>G, 45T>G, and 276G>T genotype in the entire population

Among eight SNPs in *ADIPOQ*, the minor allele frequencies of −11391G>A, H241P, Y111H, G90S, and R221S were less than 2%; therefore, only SNPs −11377C>G, 45T>G, and 276G>T were further analyzed. Genotype distributions did not deviate from the Hardy-Weinberg equilibrium, and the minor allele frequency of each SNP was consistent with previous reports in Korean populations (11). Among the three SNPs, 45T>G and 276G>T were found highly linked ($D' = -1$; $R^2 = 0.195$, $P < 0.001$). However, haplotype analysis did not provide information beyond that revealed by each SNP; therefore, we presented the results of individual *ADIPOQ* polymorphisms.

Clinical characteristics and dietary intakes according to *ADIPOQ* SNP genotypes

No significant genotype-associated differences were observed in age, sex distribution, BMI, waist to hip ratio, cigarette smoking, alcohol consumption, blood pressure, lipid profile except HDL cholesterol, and total energy intake and energy intake percent derived from macronutrients (data not shown). Compared with 276T/T subjects, 276G carriers showed lower concentrations of HDL cholesterol ($P = 0.024$) and adiponectin ($P < 0.001$), higher levels of glucose ($P = 0.015$), insulin ($P = 0.006$), and HOMA-IR ($P = 0.005$) and lower intake of PUFAs with lower PUFA/saturated fatty acid (SFA). None of the other SNPs were significantly associated with these variables (data not shown).

Effect of *ADIPOQ* 276G>T on plasma adiponectin, long-chain ω3PUFAs in serum phospholipids, and insulin resistance according to the proportion of linoleic acid

SNP276G>T was significantly associated with FA proportion in serum phospholipids. After adjusting for age, sex, BMI, and the proportion of 18:2ω6 and 18:3ω3 (biomarkers of long term essential FA intake), 276G>T was still associated with the proportion of total ω3 ($P = 0.026$), 20:5ω3 ($P = 0.021$), and 22:5ω3 ($P = 0.024$), adiponectin ($P = 0.001$), glucose ($P = 0.002$) and insulin ($P = 0.035$), and HOMA-IR ($P = 0.030$). Further adjustment for the proportion of total ω3PUFA in serum phospholipids still maintained the significant association of 276G>T with HDL cholesterol ($P = 0.029$), adiponectin ($P < 0.001$), and glucose ($P = 0.002$). On the other hand, the significant effect on insulin and HOMA-IR turned to a tendency after the further adjustment.

Among the FAs in serum phospholipids, 18:2ω6 highly correlated with PUFA intake ($r = 0.260$, $P < 0.001$) and plasma adiponectin ($r = 0.150$, $P < 0.001$). Therefore, subjects were divided into two subgroups according to the median value of 18:2ω6 (<12.5% *vs.* ≥ 12.5%). In subjects

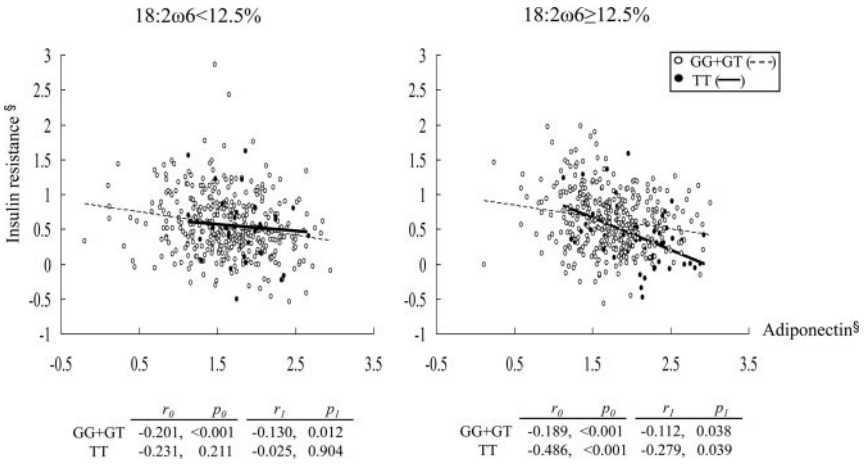

FIG. 2. Relationship between adiponectin and IR according to *ADIPOQ* 276G>T polymorphism and the proportion of 18:2ω6 in serum phospholipids (below or above the median level, 12.5%). §, Tested by logarithmic transformation and tested by Pearson correlation (r_0) or partial correlation analysis (r1). r_0, Correlation coefficient, unadjusted; r_1, correlation coefficient after adjusted for age, sex, BMI, and proportions of 18:2ω6 and 18:3ω3 in serum phospholipids.

with a higher proportion of 18:2ω6, 276G carriers showed lower levels of adiponectin ($P < 0.001$), 20:5ω3 ($P = 0.005$), 22:5ω3 ($P = 0.003$), and 22:6ω3 ($P = 0.012$) than 276T/T subjects after the adjustment (Fig. 1). The 276G carriers also showed higher levels of glucose (G/G: 92.1 ± 9.49, G/T: 90.2 ± 9.38, T/T: 85.4 ± 11.1 mg/dl; $P < 0.001$) and HOMA-IR (G/G: 2.03 ± 1.10, G/T: 2.10 ± 1.08, T/T: 1.72 ± 0.85; $P = 0.013$) and lower levels of HDL cholesterol ($P = 0.004$) and adiponectin ($P = 0.001$). Further adjustment for the proportion of long-chain ω3PUFA in serum phospholipids still maintained the significant association (glucose, $P < 0.001$; HOMA-IR, $P = 0.002$; HDL cholesterol, $P < 0.001$; adiponectin, $P < 0.001$). In contrast, in lower 18:2ω6, 276G>T was not associated with adiponectin, glucose, HOMA-IR, or FA composition in serum phospholipids.

Figure 2 shows the relationship between adiponectin levels and HOMA-IR according to 276G>T and the levels of 18:2ω6 proportion. The 276G carriers had the negative relationship between the two variables, regardless of 18:2ω6 proportion. On the other hand, TT subjects showed the significant negative correlation in higher proportion of 18:2ω6 after the adjustment

Discussion

This study shows a significant association of *ADIPOQ* 276G>T with plasma adiponectin and long-chain ω3PUFAs in serum phospholipids after adjustment for the proportions of 18:2ω6 and 18:3ω3, biomarkers of long-term essential FA intake (14). Interestingly, the association of 276G>T with plasma adiponectin, long-chain ω3PUFAs, and IR was more pronounced in subjects with higher proportion of 18:2ω6 in serum phospholipids.

Circulating adiponectins is modulated by ingestion of certain FAs or by changes in serum FA composition (7, 8). Lower proportions of serum phospholipid total ω3FAs in our 276 G carrier might reflect a dietary intake with lower PUFA and lower PUFA/pSFA because macronutrient energy intake percent was not different according to 276G>T. Moreover, the higher 20:5ω3 and 22:5ω3 in 276T/T subjects after adjustment for proportions of 18:2ω6 and 18:3ω3 could indicate a close link between ω3FAs and adiponectin. Fernández-Real *et al.* (15) also showed that ω3FA proportion in plasma FA profiles is highest in individuals with increased circulating adiponectin, and this association persists after controlling for age, BMI, and remaining individual FAs.

In this study, the association between *ADIPOQ* SNPs, adiponectin, and IR was found only for SNP276, consistent with previous findings that the 276G allele is associated with lower circulating adiponectin and is an independent contributor for the increased CVD risk in Koreans (11) and the early onset of CAD (4). The major biological functions of adiponectin depend on the activation of AMP-activated protein kinase primarily in skeletal muscles, which increases FA oxidation and glucose uptake, thereby improving insulin sensitivity (16). The mechanism whereby serum phospholipid ω3PUFAs might impact peripheral adiponectin concentration, or vice versa, was not elucidated in this study. One potential pathway involves activation of peroxisomal proliferator-activated receptor (PPAR)-γ, a transcriptional regulator that interacts directly with the *ADIPOQ* promoter. In fact, eicosapentaenoic acid and docosahexaenoic acid may up-regulate *ADIPOQ* by acting as ligands of PPAR-γ (17), and pharmacological activation with PPAR-γ agonists leads to increased adiponectin (18).

Circulating adiponectin levels are known to be highly heritable (~50%). Additionally, dietary FAs and gene-diet interactions were found to modulate plasma adiponectin and contribute to IR, a risk factor for T2DM and CVD (19). Our results indicate associations between dietary PUFAs or serum phospholipid PUFAs, 276G>T, circulating adiponectin, and HOMA-IR, despite a much lower percentage of fat energy intake in the study subjects and in the general Korean population than in white populations (20). Recently Koreans have the increased fat energy percent in their diets and rapidly increased mortality rate of ischemic heart disease (20). It may suggest that the Korean population is genetically predisposed to be negatively affected by adverse dietary changes at a lower threshold than whites.

Our results suggest that when low intake of PUFA or PUFA/SFA are superimposed on a high-risk 276G carrier background, the lower proportion of PUFAs, especially long-chain ω3PUFAs in serum phospholipids, could result in more pronounced hypoadiponectinemia and IR than for other genotypes, thus accounting for the increased CVD risk. Therefore, substitution of soy, vegetable, or fish oil for saturated fat, even in a low-fat diet, might be beneficial for 276G allele carriers (19).

Our results have the limitations of all cross-sectional and observational studies; thus, cause-effect relationships and the mechanistic interactions between *ADIPOQ* genetic variability, adiponectin concentration, dietary fat, and other biochemical factors cannot be easily established. Despite these limitations, it confirmed the relationship between *ADIPOQ* 276G>T and circulating adiponectin and IR shown in multiple independent populations (3–5, 11, 19) and identified an interesting association of the 276G allele with reduced proportion of long-chain ω3PUFAs in serum phospholipids after adjustment for long-term essential fatty acid intake.

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