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ORIGINAL RESEARCH

A common variant in the adiponectin gene on weight loss and body composition under sibutramine therapy in obesity

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Abstract: In this study, we aimed to explore whether a common single nucleotide polymorphism (SNP), rs266729 (–11,377C > G), in the adiponectin C1Q and collagen domain containing (ADIPOQ) gene could influence weight reduction and fat change under sibutramine therapy in an obese population. There were 131 obese Taiwanese patients, including 44 in the placebo group and 87 in the sibutramine (10 mg daily) group. We assessed the measures of weight loss and body fat reduction at the end of the 12-week treatment period by analysis of covariance (ANCOVA) models using gender, baseline weight, and baseline percent body fat as covariates. By comparing the placebo and sibutramine groups with ANCOVA, our data revealed a strong effect of sibutramine on percent body fat loss (1.9 ± 0.3 vs $4.6 \pm 0.5\%$; $P < 0.001$) and on weight reduction (2.8 ± 2.0 vs 7.9 ± 1.6 kg; $P < 0.001$) for subjects with the CC genotype. On the contrary, sibutramine had no significant effect on percent body fat loss or on weight loss in the GG and GC individuals. The results suggest that the SNP rs266729 of the ADIPOQ gene may contribute to weight reduction and fat loss in response to sibutramine therapy in Taiwanese obese patients.

Keywords: body fat, obesity, sibutramine, single nucleotide polymorphisms, weight loss

Introduction

Sibutramine is one of the two agents currently approved for the long-term management of obesity in Taiwan and was recently withdrawn from the European market (through the European Medicines Agency) due to safety issues. Sibutramine reduces food intake and induces weight loss by selectively inhibiting the neuronal reuptake of serotonin and norepinephrine within the hypothalamus.[1,2] Several studies[3–7] in pharmacogenetics have revealed that some genetic variants, such as the C-1291G (rs1800544) single nucleotide polymorphism (SNP) in the adrenergic alpha-2A-receptor (ADRA2A) gene, the C825T (rs5443) SNP in the guanine nucleotide binding protein beta polypeptide 3 (GNB3) gene, the serotonin transporter gene-linked polymorphic region (5-HTTLPR) variant in the solute carrier family 6 member 4 (SLC6A4; serotonin neurotransmitter transporter) gene, and the G-866A (rs659366) SNP in the uncoupling protein 2 (UCP2) gene, were associated with weight reduction and body composition with sibutramine treatment in obese patients in different populations.

Adiponectin is an adipose-derived plasma protein, which is known to modulate insulin sensitivity and glucose homeostasis, and has been well known to be linked with metabolic syndrome.[8] It has been shown that serum adiponectin levels were increased during sibutramine treatment in obese nondiabetic subjects.[9,10] Furthermore,

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it has been reported that serum adiponectin was elevated in rats which received sibutramine with high fat diet in a recent animal study.[11] Adiponectin is encoded by the adiponectin C1Q and collagen domain containing (ADIPOQ) gene, which locates on chromosome 3q27.[12] A common SNP, rs266729 (−11,377C > G), in the proximal promoter region of the ADIPOQ gene has drawn much attention. The ADIPOQ rs266729 variant has been identified to be associated with obesity, body mass index (BMI), type 2 diabetes, diabetic nephropathy, and insulin sensitivity.[13–19] Moreover, evidence indicates that the ADIPOQ rs266729 polymorphism functionally regulates adiponectin promoter activity and its protein levels in blood.[20,21] In addition, ADIPOQ rs266729 has been found to be correlated with circulating adiponectin levels in diabetes and obesity.[13,22–24]

Our previous findings[6,7] mainly reported of the association studies of sibutramine with the GNB3 rs5443 and UCP2 rs659366 polymorphisms. In this work, we extended the previous research to test the hypothesis that ADIPOQ rs266729 may influence weight loss and fat change in response to sibutramine treatment amongst Taiwanese obese individuals.

Patients and methods

Patients

Our patient cohort was original to the previous study by Hsiao and colleagues[6] and was described in detail elsewhere.[6] Briefly, obese Taiwanese patients were recruited from the Taipei Medical University Hospital in Taipei, Taiwan in 2008. All the recruited patients fulfilled the following inclusion criteria: (1) aged between 18 and 65 years old; (2) a BMI $\geq$ 25 kg/m^2. We used Asian-adapted definitions[25,26] of obesity based on BMI: nonobese (BMI $<$ 25 kg/m^2) and obese (BMI $\geq$ 25 kg/m^2). Subjects with cardiovascular diseases or with concomitant medications were excluded from the study. The intent-to-treat population consisted of 131 individuals in a randomized clinical trial, including 87 in the sibutramine (10 mg daily) group and 44 in the placebo group. Five subjects in the sibutramine group and seven in the placebo group dropped out before the study period was completed. Before conducting the study, approval was obtained from the Internal Review Board of the Taipei Medical University Hospital. The approved informed consent form was signed by each subject.

The first endpoint was percent body fat loss after 12 weeks versus baseline.[6] The second endpoint was weight loss at the end of 12 weeks compared to baseline. Total body fat was measured by dual energy x-ray absorptiometry (Lunar Corp, Madison, WI, USA).

Laboratory methods

DNA was isolated from blood samples using QIAamp® DNA blood kit following the manufacturer's instructions (Qiagen, Valencia, CA, USA). To extract DNA, we used 200 µL of blood which was further solved in 200 µl of distilled water.[19] Before polymerase chain reaction (PCR), part of the extracted DNA was diluted into a concentration of 10 µg/µL. The qualities of isolated genomic DNAs were checked using the agarose gel electrophoresis and the quantities determined using spectrophotometry.

All SNP genotypings were performed using the Taqman SNP genotyping assay (Applied Biosystems [ABI], Foster City, CA, USA).[6] The primers and probes of SNPs were from the ABI Assays-on-Demand™ kit. Reactions were carried out according to the manufacturer's protocol. The probe fluorescence signal detection was performed using the ABI Prism 7900® Real-Time PCR System.

Statistical analysis

We assessed the categorical data at baseline using the χ^2 test and compared differences for continuous variables at baseline using analysis of variance (ANOVA). Genotype frequencies were evaluated for Hardy-Weinberg equilibrium using a χ^2 goodness-of-fit test. The measures of weight loss and body fat reduction at the end of the treatment period were analyzed by analysis of covariance (ANCOVA) models using gender, baseline weight, and baseline percent body fat as covariates.[6] For each endpoint (percent body fat loss or weight loss), three separate ANCOVA models were used and stratified for the CC, GG, and GC groups, respectively. The criterion for significance was set at $P < 0.05$ for all tests.

Results

Tables 1 and 2 present the demographic characteristics of the study population for the sibutramine group and the placebo group, respectively. In the sibutramine group, the GG, GC, and CC genotypes had similar distribution of sex, baseline weight, and baseline percent body fat (Table 1; $P = 0.478$, 0.586, and 0.575, respectively). Similarly, the distribution of sex, baseline weight, and baseline percent body fat in the GG, GC, and CC genotypes was well matched in the placebo group (Table 2; $P = 0.093$, 0.299, and 0.42, respectively). ADIPOQ rs266729 genotype frequency distributions were in Hardy-Weinberg equilibrium ($P = 0.21$).

Table 1 Demographic characteristics of study subjects for the sibutramine group

	GG	GC	CC	*P* value[a]
Number	7 (9%)	28 (34%)	47 (57%)	
Age, years	27.7 ± 2.9	32.5 ± 5.1	31.7 ± 4.8	0.582
Gender, % male	28.6	50.0	53.2	0.478
Height, cm	165.2 ± 8.3	166.6 ± 9.6	167.2 ± 7.7	0.568
Weight at baseline, kg	82.4 ± 22.9	79.8 ± 11.4	82.8 ± 13.4	0.586
BMI at baseline, kg/m^2	29.9 ± 6.8	28.7 ± 3.0	29.5 ± 3.3	0.964
Percent body fat at baseline, %	35.1 ± 8.6	32.5 ± 7.0	32.7 ± 6.4	0.575

Data are presented as mean ± standard deviation.
[a]*P* values refer to ANOVA analyses for continuous variables and the χ^2 test for the categorical data.
Abbreviation: BMI, body mass index.

First, we analyzed influence of ADIPOQ genotype on effect of 12-week sibutramine treatment on body fat composition by ANCOVA models, adjusting for gender, baseline weight, and baseline percent body fat as covariates. By comparing the sibutramine and placebo groups, a strong effect of sibutramine on percent body fat loss was indicated for subjects with the CC genotype (Table 3; 4.6 ± 0.5 vs 1.9 ± 0.3%; $P < 0.001$). On the contrary, sibutramine had no significant effect on percent body fat loss in subjects with the GG and GC genotypes (Table 3; $P = 0.383$ and 0.814, respectively). We further considered putting GG and GC individuals together in the analysis, and sibutramine showed no significant effect on percent body fat loss in this combined GG and GC group ($P = 0.638$).

Additionally, there was no significant difference on percent body fat loss among the GG, GC, and CC individuals in either the sibutramine group ($P = 0.061$) or the placebo group ($P = 0.725$).

Furthermore, we investigated influence of ADIPOQ genotype on effect of sibutramine treatment on weight loss using ANCOVA after covariate adjustment with gender, baseline weight, and baseline percent body fat. By comparing the sibutramine and placebo groups, a strong effect of sibutramine on weight reduction was observed in individuals with the CC genotype (Table 4; 7.9 ± 1.6 vs 2.8 ± 2.0 kg; $P < 0.001$). In contrast, sibutramine caused no significant effect on weight loss in subjects with the GG and GC genotypes (Table 4; $P = 0.417$ and 0.055, respectively). Furthermore, we considered combining GG and GC subjects together in the analysis, and sibutramine showed no significant effect on weight loss in this combined GG and GC group ($P = 0.054$).

In addition, a genotype-dependent difference was not observed in weight loss amongst the GG, GC, and CC individuals within either the sibutramine ($P = 0.205$) or placebo ($P = 0.277$) groups.

Discussion

Our study is the first to date to have examined whether ADIPOQ rs266729 is significantly associated with weight reduction and body composition under sibutramine therapy amongst Taiwanese obese individuals. Our analyses showed that treatment with sibutramine resulted in significantly greater reduction of body fat and weight for specific ADIPOQ rs266729 CC genotype as compared to the placebo group with the same genotype. As mentioned in the Introduction,

Table 2 Demographic characteristics of study subjects for the placebo group

	GG	GC	CC	*P* value[a]
Number	4 (11%)	13 (35%)	20 (54%)	
Age, years	34.8 ± 9.8	31.5 ± 6.2	30.1 ± 4.5	0.145
Gender, % male	25.0	76.9	45.0	0.093
Height, cm	162.0 ± 7.4	168.2 ± 8.1	166.6 ± 9.4	0.631
Weight at baseline, kg	76.6 ± 10.8	82.4 ± 15.1	85.2 ± 15.8	0.299
BMI at baseline, kg/m^2	29.1 ± 1.6	28.9 ± 3.1	30.5 ± 3.8	0.128
Percent body fat at baseline,%	36.3 ± 4.0	31.8 ± 3.9	35.6 ± 5.7	0.420

Data are presented as mean ± standard deviation.
[a]*P* values refer to ANOVA analyses for continuous variables and the χ^2 test for the categorical data.
Abbreviation: BMI, body mass index.

Table 3 Percent body fat loss after sibutramine treatment by ADIPOQ genotype

	Sibutramine	Placebo	*P* value[a]
CC	4.6% ± 0.5%	1.9% ± 0.3%	<0.001
GG	3.5% ± 0.6%	1.8% ± 0.4%	0.383
GC	3.2% ± 0.4%	3.0% ± 0.3%	0.814

Data are presented as mean ± standard deviation (adjusted for covariates from ANCOVA analyses).
[a]*P* values are based on ANCOVA models.
Abbreviation: ADIPOQ, adiponectin C1Q and collagen domain containing.

weight reduction with sibutramine treatment in obese subjects has previously been shown to be associated with some variations in other candidate genes, including the rs1800544 (C-1291G) SNP in the ADRA2A gene,[5] the rs5443 (C825T) SNP in the GNB3 gene,[3,5,6] the 5-HTTLPR variant in the SLC6A4 gene,[4,5] and the rs659366 (G-866A) SNP in the UCP2 gene.[7] Thus, a promising finding reported for the first time was that ADIPOQ rs266729 may play a key role in modulating treatment outcomes with sibutramine in Taiwanese obese subjects.

One may concern the potential biological mechanism under the strong dependency of the sibutramine effect between the ADIPOQ genotype and body fat. ADIPOQ encodes adiponectin expressed exclusively in both white and brown adipose tissues.[27] Recent evidence has indicated that the G allele of ADIPOQ rs266729 alters the sequence for one of transcriptional stimulatory protein binding sites and subsequently reduces adiponectin promoter activity.[20,28] Furthermore, several studies have demonstrated that there was an association between adiponectin and adipose tissue mass in adults, and suggested that adiponectin secretion and circulating levels were inversely proportional to body fat.[29–31] It has been shown that adiponectin expression from adipose tissue was lower in obese subjects, and there was an overall significant decrease in plasma adiponectin with increasing body fat.[30] Moreover, it has been reported that body weight reduction increased the plasma levels of adiponectin in obese patients who received gastric partition surgery, implicating that the expression of adiponectin may be under a strict feedback regulation in obesity and body fat mass.[29] In addition, an animal study revealed that adiponectin was decreased in obesity and was completely absent in mice without adipose tissues.[32] In that animal study, adiponectin was also indicated to prevent the accumulation of lipids in insulin target tissues by stimulating oxidation of fatty acids primarily in muscle and liver.[32]

Table 4 Weight loss after sibutramine treatment by ADIPOQ genotype

	Sibutramine	Placebo	*P* value[a]
CC	7.9 ± 1.6 kg	2.8 ± 2.0 kg	<0.001
GG	6.7 ± 1.6 kg	4.4 ± 0.6 kg	0.417
GC	6.7 ± 1.0 kg	4.8 ± 0.7 kg	0.055

Data are presented as mean ± standard deviation (adjusted for covariates from ANCOVA analyses).
[a]*P* values are based on ANCOVA models.
Abbreviation: ADIPOQ, adiponectin C1Q and collagen domain containing.

Another concern involves whether the results reported here were influenced by a nonrandomized patient selection for genotyping. However, it seems unlikely that this is the case because allele frequencies for ADIPOQ rs266729 were in accordance with HapMap database entries[33] and with previous studies.[13–24] Furthermore, we did not observe significant deviations from Hardy-Weinberg equilibrium ($P = 0.21$). Our findings should be confirmed by regenotyping in nonobese controls to detect genotype-specific differences.

There were several limitations to this study as follows. First, the contributions of other markers in ADIPOQ should be further examined in future work. As discussed previously, the selected SNP rs266729 has been suggested by previous studies as positive associations with metabolism.[13–24] We assumed that an SNP, which has been investigated in several studies, might be a good candidate to explore the genetic role of the ADIPOQ gene tested in the current pilot study.[19] There were some SNPs in ADIPOQ shown to be associated with metabolism. However, ADIPOQ rs266729 was one of the most mentioned SNPs in previous reports.[13–24] Second, our results could be different after a longer time of intervention with sibutramine.[34] Third, by chance findings could not be excluded because a small group was investigated, and large prospective clinical trials are necessary in future work. In addition, the side effects of sibutramine and a follow up study after 12 weeks should be further investigated. Future research is also needed to check if ADIPOQ rs266729 changes any binding sites in the promoter region of the human adiponectin. Moreover, these findings may not be generalizable to other populations. Ethnically-matched studies would be necessary to know if such association is found in non-Taiwanese subjects.

Conclusion

In conclusion, our findings support the hypothesis that ADIPOQ rs266729 may help predict weight reduction and fat loss in response to sibutramine therapy together with other markers found in some previous studies.[3–7] Independent

replications are needed to confirm the role of the ADIPOQ rs266729 polymorphism found in this study.

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Disclosure

The authors report no conflicts of interest in this work.

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