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Original Article

Changes in Physiological Parameters after Combined Exercise according to the I/D Polymorphism of hUCP2 Gene in Middle-Aged Obese Females

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Abstract

Background: The purpose of this study was to determine whether a 45 bp insertion/deletion (I/D) polymorphism in human uncoupling protein 2 (hUCP2) gene was associated with changes in several cardiovascular risk and physical fitness factors in response to combined exercise during 12 weeks in Korean middle-aged women. The changes in physiological parameters after combined exercise during 12 weeks were compared between each genotype subgroups of hUCP2 gene to clarify the inter-individual differences in exercised-induced changes according to genetic predisposition.

Methods: A total of 185 women aged over 40 years living in Seoul, Korea were participated in this study, and analyzed before and after 12 weeks on combined exercise including aerobic exercise and strength training for body composition, hemodynamic parameters, physical fitness and metabolic variables. A 45 bp I/D polymorphism in hUCP2 gene was genotyped by polymerase chain reaction (PCR) amplification and agarose gel electrophoresis method.

Results: Combined exercise program during 12 weeks indicated the significant health-promoting effects for our participants on multiple body composition, hemodynamic parameters, physical fitness factors and metabolic parameters, respectively. With respect to a 45 bp I/D polymorphism in hUCP2 gene, this polymorphism was significantly associated with baseline %body fat of our participants ($P<.05$). Moreover, this polymorphism was significantly associated with the changes in %body fat and serum triglyceride(TG) level after combined exercise program during 12 weeks($P<.05$).

Conclusion: Our data suggest that a 45 bp I/D polymorphism in hUCP2 gene may at least in part contribute to the inter-individual differences on the changes in some clinical and metabolic parameters following combined exercise in middle-aged women.

Keywords: Cardiovascular risk factors, Combined exercise, Korea, hUCP2 and Polymorphism

Introduction

Obesity is known as a metabolic disease that is symptomatic of body fat accumulation caused by an imbalance between energy intake and energy expenditure, which is involved with a variety of genetic and environmental factors (1). In the past, this disease was regarded as a problem limited to industrialized and advanced countries, e.g., European countries, but now its morbidity has been increasing steadily even in Asian countries including Korea that adopted the western lifestyle on the course of industrialization (2,3). The remarkable advancement of molecular biotechnology, in particular, has recently made noteworthy progress in research for genetic predispositions to obesity

(4).The results so far show that genes, which regulate energy metabolism, are likely to cause obesity, and the gene that encodes uncoupling protein (UCP gene) is regarded as a principal gene related to the regulation of human's basic metabolic rate (BMR) or the onset of obesity, for uncoupling protein has a thermogenetic function when proton ions, enriched in mitochondrial intermembrane space, leak in a process of oxidation and reduction under the electron transport system (ETS) (5,6). In this regard, many researches are underway into the UCP gene regarding obesity and its complications (7, 8).

So far, there are at least 5 kinds of human uncoupling protein (hUCP) genes, i.e., hUCP1, hUCP2, hUCP3, hUCP4 and hUCP5, and that the hUCP genes are somewhat different with respect to internal tissues or their functions though they are considerably homologous in relation to DNA nucleotide sequence or protein amino acid sequence (9).

Unlike hUCP1 or hUCP3 genes, hUCP2 genes are widely distributed in various tissues such as white adipose tissue, skeletal muscles, the pancreas and the central nervous system, and that they have a variety of genetic variations such as -866G/A polymorphism in the promoter region, Ala55Val polymorphism in the exon 4 region and 45bp insertion/deletion (I/D) polymorphism in the 3'-untranslated region (10-12). Accordingly, the above-mentioned genetic polymorphisms are used for researches on the influence of the candidate genes on obesity or various phenotypes (12, 13).

Meanwhile, there are many evidences that active physical activity or regular exercise is effective not only against obesity but against chronic degenerative diseases; hereat, various exercise programs have been developed to prevent obesity and to improve chronic degenerative diseases (14). However, such exercise programs showed wide inter-individual differences with respect to the reduction in these parameters (15). One cause of inter-individual differences may be explained by genetic background, which seems in part to influence the difference (16). Many studies have been conducted on causative genes known to be significantly associated with obesity, but there have been few studies on the identification of causative genes of inter-individual differences regarding changes in obesity or obesity-related metabolic parameters (17). The situation is very much the same with hUCP2 genes (18-20). Many studies have been conducted to analyze the clinical significance of genetic variances in hUCP2 genes, but there have been very few studies on the influence of genetic variations on inter-individual differences with respect to changes in obesity or the metabolic parameters in the obese subjects who followed exercise programs (21).

Because the prevalence of obesity is high, it is clinically important to design the precise personalized exercise program according to the genetic information of each individual. Therefore, this study was conducted on middle-aged obese Korean women who completed an exercise program that combined aerobic exercise and strength exercise, and an analysis was made of whether 45bp I/D polymorphism, located in the 3'-untranslated region, exerted significant influence on inter-individual differences regarding changes in obesity or metabolic parameters.

Materials and Methods

Study subjects

This study was performed to clarify the inter-individual differences in exercise-induced changes of each physiological parameter according to genetic predisposition.

A total of 185 middle-aged obese Korean females over 40 years (mean age 48.4 ± 11.6 years and mean % body fat 34.0 ± 5.6%) living in Seoul, Korea were recruited in this study from January, 2003 to March, 2003, and only 108 subjects of all participants completed the combined exercise program including aerobic and strength trainings during 12 weeks. To be eligible, the participants of this study are free of each metabolic disease including NIDDM, hypertension and cardiovascular diseases, and thus, they were in good health. A separate written informed consent was obtained for registration from all participants in this study, and signed in the form approved by ethical institution.

Combined exercise program

The combined exercise program during 12 weeks was performed for 3 days for week. In the case of aerobic exercise, the walking in treadmill with intensity of about 50~60% of maximum oxygen consumption (VO_{2max}) was performed for 30 min in a day. With regards to strength exercise, dumbbell exercise was performed at the level of about 50~60% of 1 repetition maximum (1 RM) for 30 min in a day. The frequency of strength exercise increases from initial 20 times, setting repeating set as 2 sets for first 2 weeks and later as 3 sets. There were about 3~5 min rest between each set. All participants performed this exercise program under the instruction and supervision of at least two professional trainers.

Measurements of various anthropometrical parameters

The measurement of body composition was achieved by using InBody 720 analyzer (Biospace, Co. Ltd., Korea). Systolic blood pressure (SBP) and diastolic blood pressure(DBP) were also measured by using mercury sphygmomanometer in supine position. Also, the physical fitness factors such as muscular strength, muscular endurance, power, flexibility and agility were measured by using basic fitness measurement system (Helmas system, Korea).

Biochemical assay

After fasting for 12 h, peripheral blood samples were taken from the participants before and after 12 weeks combined exercise program, and various biochemical parameters measured using an automatic analyzer in professional clinical medical center. Each biochemical parameters were measured twice, respectively. Serum glucose level was measured by glucose oxidase test. Serum total cholesterol (TC) and triglyceride (TG) levels were measured by automatic colorimetry methods with commercial kit (Boehringer Mannheim, Germany), and serum HDL-cholesterol level was determined by centrifugation after adding magnesium chloride ($MgCl_2$) to serum. In the case of LDL-cholesteol level, the concentration was calculated using the following formula suggested by Friedewald *et al.,* (1972) (22): LDL-C level (mg/dl) = TC level (mg/dl) – (HDL-C level (mg/dl) + 1/5 X TG level (mg/dl)).

Analysis of a 45 bp I/D polymophism in the hUCP2 gene

In order to analyze a 45 bp I/D polymorphism in the hUCP2 gene, total genomic DNA was prepared from peripheral blood of the participants, and polymerase chain reaction(PCR) method used for this study. To amplify the region including hUCP2 I/D polymorphism, total 50 μl of the reaction mixture was perpared as follows; 10 pmol of each primer pair, 10 nmol of dNTPs(dATP, dTTP, dCTP and dGTP), 10X buffer recommended by the manufacturer, and 1.5 U of *Taq* DNA polymerase(Promega Corp., USA). The primer sequences for this polymorphism were also as follows;

forward, 5'-CAG TGA GGG AAG TGG GAG G-3',

reverse, 5'-GGG GCA GGA CGA AGA TTC-3' (12).

PCR amplificarion reaction was performed on automated thermocycler, and the reaction product was analyzed by the 1.5% agarose gel electrophoresis with ethidium bromide(EtBr) staining.

Statistical Analysis

Deviation in observed genotype distribution from that expected for Hardy-Weinberg equilibrium was tested using χ^2–test. The significance of the changes in quantitative parameters following 12 weeks combined exercise was tested using paired t-test. The significance of difference in quantitative parameters between each genotype was tested using unpaired *t*-test. Statistical significance level was set at $\alpha = 0.05$, and all statistical analyses were performed by using SPSSWIN version 18.0 software (SPSS Inc, Chicago, IL, USA).

Results

Characteristics of participants

Table 1 shows demographic and clinical characteristics of our subjects.

Table 1: Clinical characteristics of participants

Variables	No.	Mean ± SD
Age (yr)	185	48.4 ± 11.6
Height (cm)	185	156.4 ± 6.2
Weight (kg)	164	66.1 ± 11.5
BMI (kg/m²)	164	28.6 ± 22.8
%Body fat (%)	164	34.0 ± 5.6
SBP (mmHg)	153	127.5 ± 17.5
DBP (mmHg)	153	77.7 ± 12.1
MAP (mmHg)	153	61.1 ± 11.8
Pulse pressure (mmHg)	153	49.8 ± 10.4
Mus. Strength (kg)	108	28.7 ± 5.8
Mus. end. (count/min)	103	9.5 ± 8.8
Power (cm)	99	17.0 ± 7.5
Flexibility (cm)	152	12.1 ± 7.7
Agility (msec)	108	380.4 ± 123.1
TC (mg/dL)	183	208.5 ± 39.1
TG (mg/dL)	151	134.3 ± 81.5
HDL-Chol. (mg/dL)	157	56.5 ± 10.4
LDL-Chol. (mg/dL)	126	123.1 ± 35.2
Glucose (mg/dL)	153	97.5 ± 31.1

Effects of combined exercise program

A total of 108 middle-aged obese women were participated in combined exercise program during 12 weeks, and various clinical characteristics including body composition, hemodynamic parameters, physical fitness factors and metabolic and biochemical parameters measured before and after each intervention (Table 2).

Table 2: The changes in body composition and clinical parameters following 12 wk combined training

Variables	Mean±SD(No.)		*t*-value	*P*-value
	Pre	Post		
Height (cm)	156.4 ± 5.7(108)	156.6 ± 5.6(108)	-3.955	<0.001*
Weight (kg)	65.2 ± 12.2(108)	63.8 ± 11.4(108)	4.263	<0.001*
BMI (kg/m²)	26.6 ± 4.6(108)	26.0 ± 4.3(108)	6.266	<0.001*
%Body fat (%)	33.1 ± 5.9(108)	32.0 ± 6.4(108)	5.542	<0.001*
SBP (mmHg)	128.7 ± 17.7(96)	123.1 ± 16.2(96)	4.207	<0.001*
DBP(mmHg)	78.5 ± 11.7(96)	74.7 ± 10.4(96)	3.533	0.001*
MAP(mmHg)	61.8 ± 11.5(96)	58.6 ± 10.0(96)	2.742	0.007*
Pulse pressure (mmHg)	50.1 ± 11.0(96)	48.4 ± 9.9(96)	1.832	0.070*
Mus. Strength (kg)	28.5 ± 6.1(60)	29.4 ± 5.0(60)	-1.587	0.118
Mus. end. (count/min)	9.1 ± 5.9(58)	12.1 ± 5.5(58)	-6.153	<0.001*
Power (cm)	16.2 ± 6.4(53)	18.6 ± 7.4(53)	-4.514	<0.001*
Flexibility (cm)	12.2 ± 8.0(97)	18.8 ± 23.8(97)	-2.980	0.004*
Agility (msec)	403.9 ± 128.2(61)	339.9 ± 91.5(61)	4.000	<0.001*
TC (mg/dL)	207.4 ± 42.8(109)	202.5 ± 39.7(109)	1.387	0.168
TG (mg/dL)	132.0 ± 68.7(95)	113.9 ± 50.9(95)	3.557	0.001*
HDL-Chol. (mg/dL)	54.6 ± 10.1(83)	53.2 ± 9.6(83)	1.696	0.094
LDL-Chol. (mg/dL)	123.9 ± 37.9(70)	126.1 ± 36.6(70)	-0.561	0.577
Glucose (mg/dL)	98.9 ± 26.5(96)	99.0 ± 20.3(96)	-0.011	0.991

*$P < 0.05$.

In the case of body composition, our combined exercise program significantly decreased weight, BMI, and %body fat ($P<.05$). Also, there was significant decrease in SBP, DBP, MAP and pulse pressure ($P<.05$). Thus, our combined exercise program significantly improved the body composition and hemodynamic parameters of the subjects participated in our combined exercise program. In addition, various physical fitness factors including muscular strength, muscular endurance, power, flexibility and agility were also significantly improved after combined exercise program during 12 weeks, suggesting the beneficial effect of our combined exercise program on the improvement of physical fitness($P<.05$). With respect to metabolic and biochemical parameters, our combined exercise program indicated the significant decrease in uric acid and TG level of our subjects, suggesting the positive effect of our combined exercise program on the prevention and improvement of metabolic syndrome($P<.05$). Taken together, our combined exercise program showed various health-promoting effects on body composition, hemodynamic parameters, physical fitness, metabolic and biochemical parameters of our subjects.

The distribution of a 45 bp I/D polymorphism in the hUCP2 gene

The distribution of the genotype and allele frequencies of a 45 bp I/D polymorphism in the hUCP2 gene were displayed in Table 3. The observed genotype distribution of this polymorphism was not in Hardy-Weinberg equilibrium ($\chi^2 = 4.3080$, df = 1, $P = 0.0380$). The observed frequencies of TT, TC, and CC genotypes were 9.2, 31.9, and 58.9% in our subjects, respectively. The derived allele frequencies were 25.1% for I allele, and 74.9% for D allele, respectively.

Effects of hUCP2 I/D polymorphism on the change of body composition

Table 4 indicates the influence of hUCP2 I/D polymorphism on the changes of body composition following the combined exercise program. There were no significant differences in height, weight, BMI, fat mass and muscular mass at baseline and in response to combined exercise program between each genotype.

Table 3: The genotype and allele frequencies of the I/D polymorphism in the UCP2 gene

Genotype	No.(%)	Allele	No. (%)
II	17(9.2)	I	93(25.1)
ID	59(31.9)	D	277(74.9)
DD	109(58.9)		
Total	185(100.0)		370(100.0)

Observed genotype distribution were not in Hardy-Weinberg equilibrium ($X^2 = 4.3080$, df =1, $P = 0.0380$).

Table 4: Body composition parameters at baseline and in changes following a 12 wk combined training program according to the genotypes of the I/D polymorphism in the UCP2 gene

Variable	Mean ± SD(No.)		t-value	*P*-value
	II+ID	DD		
Height (cm)				
Baseline	155.6 ± 5.2(43)	156.9 ± 6.0(65)	-1.202	0.232
Change	0.2 ± 0.5(43)	0.2 ± 0.6(65)	-0.174	0.863
Weight (kg)				
Baseline	63.0 ± 10.2(43)	66.7 ± 13.2(65)	-1.559	0.122
Change	-1.2 ± 1.8(43)	-1.5 ± 4.0(65)	0.393	0.695
BMI (kg/m^2)				
Baseline	26.0 ± 4.0(43)	26.9 ± 4.9(65)	-0.997	0.321
Change	-0.6 ± 0.7(43)	-0.5 ± 1.1(65)	-0.343	0.732
%Body fat (%)				
Baseline	31.4 ± 6.2(43)	34.2 ± 5.4(65)	-2.479	0.015(< 0.05.)
Change	-2.0 ± 2.4(43)	-0.6 ± 1.8(65)	-3.249	0.002*(< 0.05.)

But, baseline %body fat was significantly different between each genotype (t = -2.479, *P* = .015, 95%CI of the difference -5.0316 ~ -0.5602). Especially, I allele carriers (31.4±6.2%) indicated the significantly greater %body fat value than those with DD genotype (34.2±5.4%). Also, there was significant difference in the change of %body fat following combined exercise program across each genotype (t = -3.249, *P* = .002, 95%CI of the difference -40.6062 ~ -0.3119). I allele carriers (-2.0±2.3%) showed a significantly greater reduction in %body fat than those with DD genotype (-0.6±1.8%).

Effects of hUCP2 I/D polymorphism on the change of hemodynamic parameters

Table 5 shows the influence of hUCP2 I/D polymorphism on the changes of hemodynamic parameters after the combined exercise program. However, there were no statistically significant differences in any other hemodynamic parameters in response to combined exercise program as well as at baseline between each genotype.

Effects of hUCP2 I/D polymorphism on the change of physical fitness factors

The changes in physical fitness factors following the combined exercise program were displayed in Table 6. There were no significant differences in any physical fitness factors in response to combined exercise program as well as at baseline between each genotype.

Effects of hUCP2 I/D polymorphism on the change of biochemical parameters

When the changes in biochemical parameters related to blood lipid and carbohydrate metabolism after the combined exercise program were investigated in each genotype group, there were no significant differences in the changes of blood TC, LDL-cholesterol, HDL-cholesterol and glucose levels following the combined exercise program as well as blood TG, TC, LDL-cholesterol, HDL-cholesterol and glucose levels at baseline(Table 7). However, significant difference in the change of blood TG level following the combined exercise between each genotype were observed in this study(t = -3.965, *P* < .001, 95%CI of the difference -40.6062 ~ -0.3119). Especially, the participants with DD genotype(5.9±45.9 mg/dl) indicated the increase in blood TG level after the combined exercise program, while the decrease in blood TG level was observed in I allele carriers(-33.7±51.0 mg/dl).

Table 5: Hemodynamic parameters at baseline and in changes following a 12 wk combined training program according to the genotypes of the I/D polymorphism in the UCP2 gene

Variable	Mean ± SD(No.)		t-value	*P*-value
	II+ID	DD		
SBP (mmHg)				
Baseline	128.3 ± 17.0(40)	128.9 ± 18.3(56)	-0.154	0.878
Change	-6.1 ± 12.0(40)	-5.1 ± 13.6(56)	-0.341	0.734
DBP (mmHg)				
Baseline	78.7 ± 11.7(40)	78.4 ± 11.8(56)	0.084	0.934
Change	-2.6 ± 8.9(40)	-4.6 ± 11.5(56)	0.914	0.363
MAP (mmHg)				
Baseline	62.1 ± 11.9(40)	61.6 ± 11.3(56)	0.193	0.847
Change	-1.5 ± 9.8(40)	-4.4 ± 12.4(56)	1.253	0.213
Pulse pressure (mmHg)				
Baseline	49.7 ± 11.1(40)	50.4 ± 11.0(56)	-0.339	0.736
Change	-3.5 ± 9.1(40)	-0.5 ± 9.5(56)	-1.501	0.137

*$P < 0.05$.

Table 6: Physical fitness factors at baseline and in changes following a 12 wk combined training program according to the genotypes of the I/D polymorphism in the UCP2 gene

Variable	Mean ± SD(No.)		*t*-value	*P*-value
	II+ID	DD		
Mus. Strength (kg)				
Baseline	27.7 ± 7.0(15)	28.7 ± 5.8(45)	-0.561	0.577
Change	0.9 ± 6.3(15)	0.9 ± 3.8(45)	0.051	0.960
Mus. end. (count/min)				
Baseline	9.3 ± 6.2(16)	9.0 ± 5.9(42)	0.192	0.849
Change	3.3 ± 3.4(16)	2.9 ± 3.9(42)	0.291	0.772
Power (cm)				
Baseline	15.6 ± 6.0(14)	16.5 ± 6.6(39)	-0.458	0.649
Change	3.2 ± 4.9(14)	2.1 ± 3.4(39)	0.806	0.431
Flexibility (cm)				
Baseline	11.1 ± 7.0(42)	13.0 ± 8.6(55)	-1.180	0.241
Change	5.8 ± 4.3(42)	7.2 ± 28.9(55)	-0.138	0.751
Agility (msec)				
Baseline	419.5 ± 142.5(17)	397.8 ± 123.5(44)	0.590	0.558
Change	-101.4 ± 131.1(17)	-49.5 ± 120.8(44)	-1.467	0.148

*$P < 0.05$.

Table 7: Biochemical parameters at baseline and in changes following a 12 wk combined training program according to the genotypes of the I/D polymorphism in the UCP2 gene

Variable	Mean ± SD(No.)		t-value	*P*-value
	II+ID	DD		
TC (mg/dl)				
Baseline	207.1 ± 48.8(45)	207.6 ± 38.5(64)	-0.055	0.956
Change	-11.8 ± 39.5(45)	-0.3 ± 34.3(64)	-1.617	0.109
TG (mg/dl)				
Baseline	147.9 ± 79.7(40)	120.5 ± 57.5(55)	-1.948	0.054
Change	-33.7 ± 51.0(40)	5.9 ± 45.9(55)	-3.965	<0.001*
LDL-chol (mg/dl)				
Baseline	120.0 ± 38.0(19)	125.3 ± 38.1(51)	-0.524	0.602
Change	1.6 ± 28.6(19)	2.5 ± 36.1(51)	-0.105	0.917
HDL-chol (mg/dl)				
Baseline	53.7 ± 8.0(23)	54.9 ± 10.8(60)	-0.455	0.651
Change	-0.6 ± 7.2(23)	-1.7 ± 7.5(60)	0.582	0.562
Glucose (mg/dl)				
Baseline	104.9 ± 28.0(41)	94.5 ± 24.7(55)	1.880	0.064
Change	10.1 ± 19.2(41)	3.9 ± 15.4(55)	1.731	0.087

*$P < 0.05$.

Discussion

Effects by combined exercise program

This study was conducted on a total of 185 middle-aged obese Korean women who completed a 12-week combined exercise program, and an analysis was made of their physical and metabolic changes. In subjects who completed a 12-week exercise program, there were general improvements in body composition, hemodynamics, physical fitness factors and metabolic parameters, which was similar to the results of other studies that reported the complementary effects between aerobic exercise and strength exercise, instancing the improvement in cardiovascular function resulting from aerobic exercise, the increase in

muscle mass resulting from strength exercise, the ensuing improvement in physical fitness factors, etc. (23-24).
However, all subjects did not show such improvements but showed inter-individual differences. One cause of inter-individual differences may be explained by genetic predispositions, which are known to affect in part. The problem is that genes, which are causative of inter-individual differences in exercise effects, have not been identified yet. In this study, the hUCP2 gene was putted up as a candidate, whereof 45 bp I/D polymorphism was used as a genetic marker to identify whether it is causative of inter-individual differences in exercise effects (21).

I/D polymorphism in the hUCP2 gene

In a total of 185 middle-aged obese Korean women, genotypes and alleles constituting I/D polymorphism located in the hUCP2 gene were similar in frequencies to those of Korea general population (25). However, genotype frequencies, observed in those subjects, got out of the Hard-Weinberg equilibrium. The reason might be that subjects' clinical status, such as age and gender, were limited, unlike Korea general population. In addition, this study showed a very low frequency of I-allele in I/D polymorphism, which was similar to the results of other studies conducted on Korea general population (26).

Effects on body composition according to each genotype

An analysis, made of the influence of I/D polymorphism located in the hUCP2 gene (hUCP2-I/D polymorphism) on subjects' body compositions, showed that percentage body fat was higher in DD-genotype carriers than in I-allele carriers. With reference to the influence of hUCP2-I/D polymorphism on obesity-related parameters, Walder et al. (1998) reported that the sleeping metabolic rate was the highest in Pima Indians having ID genotypes, not in ones having other genotypes, and that subjects aged 45 or older showed the highest BMI (12). Yanovski et al. reported that total body fat or percentage body fat was significantly higher in Asians, Africans, Americans and Caucasians having ID genotypes than in ones having other genotypes. Their reports were inconsistent with this study (27). Also, Lee et al. conducted a study on Korean population and reported that I-allele carriers were significantly superior to DD-genotype carriers in BMI and waist circumference, which was inconsistent with this study (25). In the case of Tonga population, it was reported that there was no significant association between this genetic polymorphism and obesity-related parameters including body composition, which presented a great contrast to other previous studies (28).
An analysis was made of the influence of hUCP2-I/D polymorphism on inter-individual differences regarding changes in the body compositions of subjects who completed the combined exercise program. The percentage body fat decreased less in DD-genotype carriers than in I-allele carriers. These results are worthy of notice, in that the combined exercise program enables I-allele carriers to cut down on the fat in their bodies much further than DD-genotype carriers.

Effects on hemodynamics according to each genotype

Diastolic blood pressure (DBP) and mean arterial pressure were significantly higher in the obese having DD genotypes than in ones having ID genotypes (29). But such an association was not observed in non-obese subjects. However, there was no any significant association between hUCP2-I/D polymorphism and hemodynamic changes in subjects who completed a combined exercise program. Therefore, hUCP2-I/D polymorphism is not presumed to be a genetic marker that significantly influences the inter-individual difference in hemodynamic changes caused by a combined exercise program.

Effects on physical fitness according to each genotype

Physical fitness factors are closely associated with energy metabolism, and thus an analysis was made of the influence of hUCP2-I/D polymorphism on changes in the physical fitness factors of subjects who completed a combined exercise pro-

gram. The results showed that there was no any significant association between hUCP2-I/D polymorphism and changes in physical fitness factors. There are not many studies on the influence of hUCP2-I/D polymorphism on physical fitness factors. In a study of Lee et al. (2004a), male college students in their 20s to 30s who were having ID genotypes was superior in cardiopulmonary fitness to ones having DD genotypes, which was somewhat different from this study (26). It might be because subjects differed from each other in age, gender and physical fitness factors (15-16).

Effects on biochemical parameters according to each genotype

An analysis, made of the influence of hUCP2-I/D polymorphism on biochemical parameters such as serum glucose level and lipid profiles showed that significant differences were observed only in the blood TG levels of subjects who completed a combined exercise program; the blood TG levels slightly rose in DD-genotype carriers who completed the exercise program, whereas they considerably fell in I-allele carriers. These results imply that in subjects who completed a combined exercise program, hUCP2-I/D polymorphism caused inter-individual differences in the blood TG level, one of cardiovascular risk factors relevant to cardiovascular diseases. Specifically, the combined exercise program is presumed to lower the blood TG level much further in I-allele carriers than in DD-genotype carriers. Lee et al. (2004a) conducted a study on non-obese men in their 20s to 30s and reported that the blood TG level was lower in ID-genotype carriers than in DD-genotype carriers (26). Ann and Lee (2005), who conducted a study on men in their 20s to 30s who took endurance exercise, reported that in comparison with DD-genotype carriers, ID-genotype carriers had lower levels of blood TG before taking endurance exercise and for 60 minutes during the recovery period (30). It is problematic to compare this study to the foregoing two studies, given that they are different in subjects' gender, age, exercise, exercise method, *etc.*, In men in their 20s to 30s, hUCP2-I/D polymorphism significantly influenced the baseline blood TG level. In middle-aged women, however, the genetic polymorphism was significantly associated with inter-individual differences regarding changes in the blood TG level measured after the combined exercise, rather than with the baseline blood TG level. Such results suggest that the influence, which the genetic polymorphism has on the blood TG level, may vary in different factors, *e.g.*, age, gender, exercise, etc.

Limitation

This study has some limitation. Firstly, as the sample size in this study was not large enough to conduct a genetic epidemiological study, it is unavoidable to have low statistical power. Secondly, no exact mechanism for the association between this genetic marker and the parameters measured was determined in this study. Thus, further studies using larger sample size will be required to clarify the causality on the association between these genetic markers and the exercise-induced changes of some parameters.

Conclusion

This study conducted on middle-aged obese women who completed a combined exercise program, showed improvements in body composition, hemodynamics, physical fitness factors and blood biochemical parameters, but at the same time, showed inter-individual differences in exercise-induced effects. It suggests that the inter-individual differences might be affected in part by I/D polymorphism located in the hUCP2 gene. Thus, it requires that the exercise program should be designed with consideration for subjects' genetic backgrounds in order to develop the personalized combined exercise program.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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