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SHORT REPORT

Effects of lifestyle intervention on weight and metabolic parameters in patients with impaired glucose tolerance related to beta-3 adrenergic receptor gene polymorphism Trp64Arg(C/T): Results from the Japan Diabetes Prevention Program

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Keywords
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ABSTRACT

The beta-3 adrenergic receptor (ADRB3), primarily expressed in adipose tissue, is involved in the regulation of energy metabolism. The present study hypothesized that ADRB3 (Trp64Arg, rs4994) polymorphisms modulate the effects of lifestyle intervention on weight and metabolic parameters in patients with impaired glucose tolerance. Data were analyzed from 112 patients with impaired glucose tolerance in the Japan Diabetes Prevention Program, a lifestyle intervention trial, randomized to either an intensive lifestyle intervention group or usual care group. Changes in weight and metabolic parameters were measured after the 6-month intervention. The ADRB3 polymorphisms were determined using the polymerase chain reaction restriction fragment length polymorphism method. Non-carriers showed a greater weight reduction compared with the carriers in both the lifestyle intervention group and usual care group, and a greater increase of high-density lipoprotein cholesterol levels than the carriers only in the lifestyle intervention group. ADRB3 polymorphisms could influence the effects of lifestyle interventions on weight and lipid parameters in impaired glucose tolerance patients.

INTRODUCTION

The prevalence of diabetes in the Western Pacific Region was reported to be 8.6% of adults, or 138 million, in 2013, and it has been estimated that it will rise to 11.1%, or 201 million, in 2035[1]. Intensive lifestyle interventions to modify dietary and physical activity habits leads to weight reduction, delaying or preventing the onset of type 2 diabetes mellitus[2]. Weight changes through lifestyle modifications might depend on the

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interaction of environmental, behavioral and genetic factors. Interindividual variation in weight reduction in response to different types of intervention has been observed[3]. The beta-3 adrenergic receptor (ADRB3), primarily expressed in adipose tissue, is involved in the regulation of energy metabolism[4]. The polymorphism of ADRB3 in codon 64 (Trp64Arg: rs4994) is associated with abdominal obesity and insulin resistance syndrome[5,6]. Obese diabetic and non-diabetic subjects with this polymorphism were found to be resistant to a low-calorie diet and exercise[7,8]. Lifestyle interventions generally improve lipid profiles and reduce the risk of cardiovascular disease, but the effects are variable, and genetic factors[9] might be involved. In the Finnish Diabetes Prevention Study, the −501A/C (rs26802) polymorphism in preproghrelin, but not ADRB3, modified the effect of total and moderate-to-vigorous physical activity on change in high-density lipoprotein cholesterol[10]. It remained unclarified whether ADRB3 polymorphism modifies the effect of lifestyle intervention on weight reduction and metabolic parameters in subjects with impaired glucose tolerance. The aim of the present study was to evaluate the effects of gene–treatment interactions on weight and serum lipids in subjects with impaired glucose tolerance.

MATERIALS AND METHODS

Study design and participants

The study design, protocol, recruitment and interim results of the Japan Diabetes Prevention Program were described in detail previously[11,12]. In short, the study was an unmasked, multicenter, randomized controlled trial carried out at 32 public health centers throughout Japan. Individuals with impaired glucose tolerance and aged 30–60 years were recruited through health checkups carried out at each health center. The definition of impaired glucose tolerance using the 75-g oral glucose tolerance test was based on the World Health Organization criteria[13]. The exclusion criteria were as previously described[11,12]. Participants were randomly assigned to either an intensive lifestyle intervention group (ILG) or a usual care group (UCG). Among a total of 304 patients recruited, just 110 patients (53 in the control group and 57 in the intervention group), who agreed to deoxyribonucleic acid analysis of ADRB3 polymorphism, were available for the present study.

Ethics

The study was approved by the ethical committee at the National Hospital Organization Kyoto Medical Center, Kyoto, Japan.

Intervention

The intervention program was described previously[12]. Briefly, public health nurses or dieticians at each health center carried out lifestyle interventions individually. The goals of intervention were: (i) to reduce the initial bodyweight by 5% in overweight and obese participants, and (ii) to increase energy expenditure through promoting leisure time physical activity by 700 kcal per week. The participants in the UCG received only one group session providing advice on a healthy lifestyle for the prevention of type 2 diabetes mellitus at the outset. No individual guidance was given to the UCG during the study period.

Measures

Body mass index was calculated as the weight (kg)/height^2 (m^2), measured with the participants wearing light clothes without shoes. Blood pressure was measured in the upper arm of seated participants. Waist circumference was measured at the umbilical level. After fasting for ≥12 h, blood was drawn from an antecubital vein. Plasma glucose, serum insulin and serum lipids, including high-density lipoprotein cholesterol (HDL-C) were measured at a nationally-certified central laboratory (SRL Inc., Tokyo, Japan). Genomic deoxyribonucleic acid was extracted from peripheral blood leukocytes. The Mva I polymorphisms (Trp64Arg, rs4994) of the ADRB3 gene were determined by polymerase chain reaction restriction fragment length polymorphism analysis, as previously described[14].

Statistical analysis

All data are presented as the mean ± standard deviation, and categorical variables are expressed as numbers counted. The three possible genotypic frequencies were evaluated by χ^2-tests, and found to be in Hardy–Weinberg equilibrium. Differences in the baseline characteristics between participants in the control and intervention groups were evaluated by independent *t*-tests. Changes in each parameter from the baseline until after the 6-month intervention were evaluated using paired *t*-tests. The participants in each group were divided into two subgroups: carriers (Trp64/Arg64 and Arg64/Arg64) and non-carriers (Trp64/Trp64). Two main effects of interest (gene, intervention) and one interaction (gene × intervention) were tested. A P-value <0.05 was considered significant. Statistical analysis was carried out using the SPSS program version 20.0 (IBM SPSS, Tokyo, Japan).

RESULTS

The mean age and percentage of men were 51 ± 6 years and 40%, respectively. The distributions of Trp64/Trp64 homozygous, Trp64/Arg64 heterozygous, and Arg64/Arg64 homozygous were 80, 28 and 4, respectively. The frequencies were in Hardy–Weinberg equilibrium and consistent with a previous report on different Japanese populations[15]. The allelic frequencies were similar across the ILG and UCG.

At the baseline (Table 1), there were no significant differences in bodyweight, body mass index, waist circumference, blood pressure, blood glucose or serum lipids between carriers and non-carriers. The non-carriers showed significantly greater reductions of weight and body mass index than the carriers. There was a significant interaction of lifestyle intervention on HDL-C level; that is, the non-carriers showed a significantly greater increase of HDL-C levels than carriers only in the ILG (P = 0.001). Except for weight and HDL-C, changes of other parameters were not significantly affected by Trp64Arg polymorphisms (Table 1).

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Table 1 | Baseline and 6-month follow-up data on anthropometric and metabolic values in the control and intervention groups by beta-3 adrenergic receptor polymorphism

Parameters	Control group					Intervention group					Gene-treatment interaction		
	Baseline‡	6 months	Change	*n*	*P*†	Baseline	6 months	Change	*n*	*P*	Carrier	Intervention	Interaction
Weight (kg)													
Non-carrier	64.4 ± 11.1	63.3 ± 10.5	−1.1 ± 2.0	37	0.001	61.2 ± 12.8	59.0 ± 12.6	−2.2 ± 2.3	41	<0.001	0.043	0.100	0.496
Carrier	64.3 ± 13.2	63.9 ± 12.7	−0.4 ± 2.1	16	0.301	62.1 ± 11.6	61.1 ± 12.0	−1.0 ± 2.2	16	0.102			
Body mass index (kg/m^2)													
Non-carrier	25.1 ± 3.3	24.7 ± 3.2	−0.4 ± 1.1	37	0.002	24.2 ± 3.8	23.4 ± 2.8	−0.9 ± 0.9	41	<0.001	0.039	0.055	0.55
Carrier	24.5 ± 4.3	24.3 ± 4.3	−0.2 ± 0.8	16	0.368	24.1 ± 2.8	23.7 ± 2.8	−0.4 ± 0.8	16	0.081			
Waist circumference (cm)													
Non-carrier	86.3 ± 9.0	84.6 ± 8.7	−1.7 ± 4.3	37	0.025	83.3 ± 10.7	80.8 ± 10.7	−2.4 ± 4.7	41	0.002	0.542	0.810	0.545
Carrier	84.8 ± 9.5	83.2 ± 8.0	−1.9 ± 4.5	16	0.297	83.9 ± 8.9	81.6 ± 8.8	−2.4 ± 3.9	16	0.028			
Systolic blood pressure (mmHg)													
Non-carrier	127 ± 15	128 ± 17	1 ± 16	36	0.833	132 ± 15	128 ± 17	−4 ± 15	39	0.081	0.520	0.539	0.719
Carrier	134 ± 22	135 ± 19	1 ± 14	16	0.745	138 ± 16	134 ± 20	−3 ± 17	16	0.487			
Diastolic blood pressure (mmHg)													
Non-carrier	78 ± 9	77 ± 9	−0 ± 9	36	0.774	81 ± 10	78 ± 10	−3 ± 10	39	0.051	0.542	0.828	0.874
Carrier	83 ± 11	82 ± 13	−1 ± 9	16	0.700	84 ± 11	83 ± 11	−2 ± 6	16	0.253			
Fasting plasma glucose (mmol/L)													
Non-carrier	109 ± 10	106 ± 10	−3 ± 8	37	0.020	106 ± 9	103 ± 11	−4 ± 9	42	0.011	0.902	0.173	0.257
Carrier	109 ± 11	108 ± 10	−1 ± 11	16	0.666	109 ± 8	103 ± 10	−6 ± 11	16	0.045			
2-h plasma glucose (mmol/L)													
Non-carrier	160 ± 15	142 ± 41	−18 ± 41	37	0.009	165 ± 16	132 ± 28	−33 ± 27	42	<0.001	0.354	0.176	0.492
Carrier	167 ± 18	150 ± 23	−17 ± 29	16	0.034	160 ± 12	139 ± 35	−22 ± 33	16	0.020			
Total cholesterol (mmol/L)													
Non-carrier	210 ± 34	207 ± 34	−3 ± 26	37	0.451	221 ± 34	214 ± 30	−7 ± 25	42	0.087	0.091	0.364	0.764
Carrier	214 ± 29	222 ± 34	8 ± 26	16	0.249	219 ± 35	207 ± 34	1 ± 33	16	0.887			
HDL cholesterol (mmol/L)													
Non-carrier	59 ± 18	57 ± 19	−2 ± 11	37	0.220	58 ± 14	61 ± 18	3 ± 8	42	0.016	0.867	0.458	0.038
Carrier	59 ± 16	61 ± 18	2 ± 7	16	0.272	56 ± 16	55 ± 13	0 ± 8	16	0.837			
Triglycerides (mmol/L)													
Non-carrier	134 ± 96	137 ± 97	4 ± 93	37	0.774	125 ± 71	106 ± 72	−19 ± 60	42	0.041	0.058	0.725	0.134
Carrier	128 ± 59	135 ± 74	7 ± 61	16	0.647	100 ± 43	120 ± 70	21 ± 51	16	0.124			

Data are means ± standard deviaton. †Baseline vs 6 months. ‡There were no significant differences in any of the baseline variables between the control and intervention groups. HDL, high-density lipoprotein.

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DISCUSSION

The present study suggests that Trp64Arg polymorphism might mediate the HDL-C levels in a minimal intervention with modest weight loss in patients with impaired glucose tolerance. Difficulties in weight reduction seen in the carriers in the present study are consistent with previous reports on obese subjects with or without type 2 diabetes mellitus[16]. Defects in ADRB binding, signal transduction or regulatory mechanisms could result in a lower resting metabolic rate and diminished lipolysis in visceral adipose tissue[17,18], explaining the poor response to lifestyle intervention. However, there were some studies that failed to observe difficulties in weight reduction in carriers[19,20]. Although the reason for the discrepancies among the studies is not clear, differences in the study participants (obesity alone, obesity with impaired glucose tolerance and type 2 diabetes mellitus) and study design might be associated.

The present study also showed a gene–treatment interaction on HDL-C levels. The Arg64 allele was cross-sectionally associated with a decreased HDL-C level in obese Japanese people[6] and a Kyrgyz population[21], although a few studies described conflicting data – no association with HDL-C[22] or association with higher HDL-C levels was found in Caucasian-Brazilian patients with type 2 diabetes[23]. An increase of HDL-C levels is important for preventing the development of diabetes mellitus and atherosclerosis[24]. Thus, the present findings could be valuable in providing an effective strategy to increase HDL-C in impaired glucose tolerance patients.

The strengths of the present study include its real-world setting and it being a randomized controlled trial. However, the study had several limitations, including the small sample size and the multiple hypothesis testing. These limitations should be addressed in future research.

In conclusion, these findings suggest that Tp64Arg polymorphism modulates weight change and the HDL-C response to lifestyle intervention in patients with impaired glucose tolerance. This genetic information could help identify individuals who require intensive lifestyle intervention.

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DISCLOSURE

The authors declare no conflict of interest.

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