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Impact of *ENPP1* K121Q on Change of Insulin Resistance after Web-Based Intervention in Korean Men with Diabetes and Impaired Fasting Glucose

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Ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (*ENPP1*) gene has been studied in relation to type 2 diabetes mellitus (T2DM) and insulin resistance (IR). We hypothesized that the difference in genotype may be one of the factors that affect the outcome of intervention. We genotyped 448 men with fasting glucose ≥ 5.6 mM/L, including 371 in subjects with K allele (KK) (69 control group [CG]; and 302 intervention group [IG]) and 77 in subjects with Q allele (KQ+QQ) (13 CG and 64 IG). The web-based intervention based on a lifestyle modification was delivered by e-mail once a month for 10 months. In the KK, IG demonstrated significantly decreased levels of fasting serum insulin (FSI) as compared to CG and homeostasis model of assessment of insulin resistance (HOMA-IR). In the KQ+QQ IG group, hemoglobin A1c (HbA1c), FSI and HOMA-IR were significantly decreased, and showed further reduction in the HOMA-IR than KQ+QQ CG. After analysis of covariance, K121Q did significantly influence the change of HbA1c in CG after appropriate adjustment. In a multivariate model, BMI change predicted HOMA-IR change (adjusted $\beta = 0.801$; $P = 0.022$) in KK IG subjects with T2DM. *ENPP1* K121Q did not influence the change in IR. However, individuals with T2DM carrying the K121 variant are very responsive to the effect of BMI reduction on HOMA-IR.

Keywords: Ectoenzyme Nucleotide Pyrophosphate Phosphodiesterase 1; Diabetes Mellitus; Web-Based Lifestyle Intervention; Insulin Resistance

INTRODUCTION

Type 2 diabetes (T2DM) is a complex disorder due to the combination of genetic and environmental factors (diet, physical activity, etc.). Impaired pancreatic β-cell function and insulin resistance (IR) in muscle, fat and liver are pathogenic for T2DM (1). Recent genetic and genome-wide association studies have identified the DNA sequence differences (polymorphisms/mutations) in genes that encode proteins contributing to either insulin biosynthesis/secretion or insulin action. Among the genes related to T2DM, ectoenzyme nucleotide pyrophosphate phosphodiesterase 1 (*ENPP1*), also known as plasma cell membrane glycoprotein 1 (*PC-1*), reduces insulin signaling by inhibiting the insulin receptor tyrosine kinase activity (2). Costanzo et al. (3) showed that the human Q121 allele has more potent inhibitory effects on IR autophosphorylation than the K121 allele in vitro. Abate et al. (4) and Wang et al. (5) reported the association of the Q121 allele with diabetes in South-Asian and Han Chinese. However, no association was reported in the other Asians including Korean (6), Japanese (7) and Chinese (8). There are a few epidemiologic data associating *ENPP1* K121Q polymorphism with the risk of T2DM among Koreans.

The discipline of nutrigenomics focuses on the effects of ingested nutrients and other food components on gene expression and gene regulation (9). The epidemic rise in the incidence of T2DM has fuelled research on the complex interplay between genes and environmental factors in the pathogenesis of the hyperglycemic diabetic state (10). Nutrigenomics has emerged as a multidisciplinary field that focuses on studying the interactions.

Lifestyle intervention can prevent or delay T2DM (11). Stefan et al. (12) investigated the influence of different polymorphisms on the effects of lifestyle intervention. In another study, the Q allele in the *ENPP1* gene was significantly associated with an impaired increase in OGTT-derived insulin sensitivity after lifestyle intervention (13). Also, Moore et al. (14) reported that the K121Q polymorphism modulated the efficacy of lifestyle intervention on the incidence of T2DM. Therefore, Weyrich et al. (15) suggested that general methodological approaches to study gene-lifestyle interactions are needed. However, recent studies addressing the role of *ENPP1* K121Q on lifestyle intervention have not demonstrated gene-by-dietary change-by-weight loss interaction.

In this study, we aimed to demonstrate a potential interac-

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tion between K121Q and web-based lifestyle intervention, and to verify whether the improvement of glucose metabolism observed after weight loss was associated with *ENPP1* K121Q polymorphism.

MATERIALS AND METHODS

Subjects and study design

Flow chart of Participants during the study is shown in Fig. 1. The subjects were recruited from industrial male workers by screening members of the T2DM risk group who participated in annual regular health check-ups in 2010. Exclusion criteria were previously diagnosed T2DM, dyslipidemia, hypertension, cardiovascular disease, and any therapy known to affect glucose and lipid metabolism at basal screening. A total of 477 eligible individuals with newly diabetes (diagnosis of T2DM [fasting plasma glucose (FPG) ≥ 7.0 mM/L] or impaired fasting glucose [IFG] [FPG 5.6-6.9 mM/L]) were called to participate in the web-based lifestyle intervention via e-mail, and 380 individuals accepted the intervention protocol (intervention group [IG]). The control group (CG, n = 97) agreed to participate in post-examination, but received no e-mail on healthy lifestyle to improve T2DM. 448 (CG: 82, IG: 366) of 477 individuals who participated in a health follow-up in 2011, were included in the final analyses.

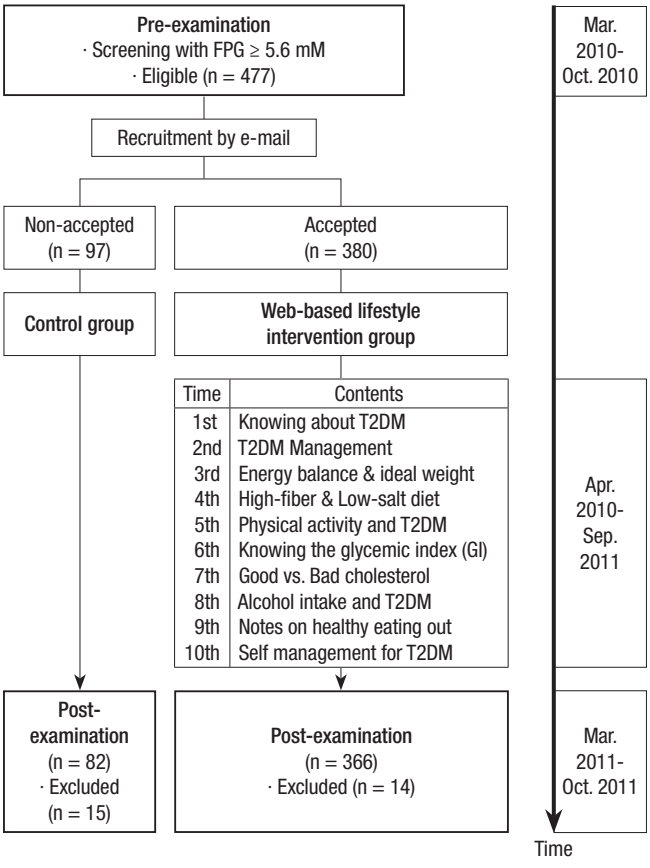

Fig. 1. Flowchart of study participants. FPG, Fasting plasma glucose; T2DM, Type 2 diabetes mellitus.

The web-based lifestyle intervention was developed based on a previous study (16) and guidelines (17, 18). It is detailed in Fig. 1. Participants were encouraged to change unhealthy lifestyle behaviors and eating habits. Each e-mail included information regarding healthy eating habits and lifestyle. After sending each e-mail, the research staff checked within 3 days whether the e-mail had been read. If not read, e-mail material was sent again and short messaging services (SMS) messages were sent to motivate participation.

Measurements

Body height and weight were measured with each subject standing straight wearing light clothing using InBody 720 (Biospace, Seoul, Korea). Body mass index (BMI) was calculated using the body weight (kg)/height (m^2). Waist circumference (WC) was measured at the midpoint between the iliac crest and the lower ribs. Blood pressures was measured in duplicate using an electronic sphygmomanometer (FT-700R; Jawon Medical, Seoul, Korea) in a sitting position after a ≥ 10 min stabilization prior to blood sampling and results were averaged.

Prior to blood sampling, all subjects fasted overnight (more than 10 hr). Blood analysis was performed in a central laboratory (Radiation Health Research Institute). FPG was analyzed by enzymatic methods using commercially available kits and an automatic analyzer (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany). Fasting serum insulin (FSI) was analyzed by radioimmunoassay methods using Irma kit (RALS system, DS8150; ITC Edison, NJ, USA). Hemoglobin A1c (HbA1c) was determined on whole blood samples by VARIANT™ II TURBO HbA1c kit 2.0 and VARIANT™ II TURBO Reagents analyzer (BIO-RAD, CA, USA). The formula for calculating the homeostasis model of insulin resistance (HOMA-IR) was (FSI [μU/mL] × FPG [mM/L]) ÷ 22.5 (19). Dietary intakes were analyzed using a computerized food frequency questionnaire (FFQ) originally developed by the Korea Centers for Disease Control and Prevention and modified by our institution for industrial workers. The FFQ consisted of 7 food groups including 108 food items. It was designed to collect information regarding the usual food intake over the past one year.

ENPP1 genotyping

We separated the buffy coat from the blood sample of each subject. Genomic DNA was extracted from the above samples using the GENErALL™ Blood SV kit (General Biosystem, Seoul, Korea). Genotyping used to identify the K121Q polymorphism in *ENPP1* exon 4 was by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). PCR was carried out in a final volume of 10 μL containing 50 mM KCl, 10 mM Tris (pH 8.3), 1.5 mM $MgCl_2$, 75 ng of each primer, 100 μM de-

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oxy-NTP, and 1 U *Taq* polymerase. All genotyping was carried out in duplicate for each individual, and the investigator was unaware of the sample origin. In this study sample genotype distribution obeyed the Hardy-Weinberg equilibrium.

Statistical analyses

Power calculations were performed using the G*Power program version 3.0.10 (Franz Faul, Universität Kiel, Germany). A total of 400 subjects were calculated as a sample size for $\alpha = 0.05$ and 95% power among two groups in a two-sided ANCOVA model.

Deviations from Hardy-Weinberg equilibrium at *ENPP1* codon 121 were tested by a chi-square goodness of fit test. All the statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Data were presented as the mean ± standard deviation. Variables with a non-normal distribution were submitted to logarithmic transformation. To compare the differences between CG and IG by *ENPP1* polymorphism and differences of changes between KK and KQ+QQ by type of group, independent *t*-test for continuous variables was applied. In addition, pre-post comparisons were carried out using the paired *t*-test. ANCOVA was used to compare the clinical and laboratory characteristics of subjects according to genotypes and type of group. Adjustment of changes during intervention comprised the respective pre-values to correct for potential ceiling effects. Multivariate analyses were performed using linear models for gene-by-BMI change interaction in modulating insulin resistance. All two-tailed *P* values of 0.05 were regard as indicating statistical significance.

Ethics statement

This study was approved by the institutional review board of the Asan Medical Center (IRB No. 2007-0119). Informed written consent was obtained from all study subjects.

RESULTS

Effects of web-based lifestyle intervention on KK genotype

In KK genotype, analytical results in two groups at baseline and 12 months after intervention are shown in Table 1. There were no significant differences between CG and IG except for age, FPG and HbA1c at baseline (Table 1). No differences in anthropometrics, metabolic measurements and nutrient intake at baseline and after intervention were evident for KK CG. However, in the KK IG group, BMI ($P = 0.022$), HbA1c ($P < 0.001$), FSI ($P < 0.001$), HOMA-IR ($P < 0.001$) and intakes of total energy ($P = 0.019$) and protein ($P = 0.007$) were significantly decreased after intervention. Comparison of change of FSI levels between the two groups showed a greater improvement in the KK IG after appropriate adjustment ($P = 0.033$).

Effects of web-based lifestyle intervention on KQ+QQ genotype

The baseline characteristics and nutrient intakes of the two groups in the KQ+QQ genotype are shown in Table 2. BMI, FSI and intakes of total energy, carbohydrate and total fat were greater in KQ+QQ IG than in KQ+QQ CG at baseline. Intake of carbohydrate was significantly increased in KQ+QQ CG after interven-

Table 1. Analysis of the effects of web-based intervention program in the KK genotype

Parameters	KK (n = 371)						P^1	P^2
	CG (n = 69)			IG (n = 302)				
	Pre	Post	Δ	Pre	Post	Δ		
Glucose metabolism								
IFG	55 (79.7)	56 (81.2)	-	205 (67.9)	206 (68.2)	-	0.059	-
T2DM	14 (20.3)	13 (18.8)		97 (32.1)	96 (31.8)			
Age (yr)	50.35 ± 6.47	-	-	48.49 ± 5.86	-	-	0.031	-
BMI (kg/m^2)	24.75 ± 2.53	24.63 ± 2.60	-0.13 ± 0.70	24.80 ± 2.75	24.68 ± 2.73	-0.12 ± 0.89*	0.927	0.872
WC (cm)	84.65 ± 6.24	84.32 ± 6.70	-0.32 ± 4.25	85.32 ± 6.73	84.99 ± 6.88	-0.33 ± 4.07	0.456	0.809
SBP (mmHg)	128.86 ± 13.87	130.67 ± 14.64	1.81 ± 14.70	127.09 ± 16.00	126.76 ± 13.55	-0.23 ± 14.12	0.272	0.087
DBP (mmHg)	84.20 ± 9.32	84.72 ± 10.33	0.52 ± 10.09	83.94 ± 10.95	83.25 ± 9.58	-0.65 ± 10.72	0.728	0.385
FPG (mM/L)	6.49 ± 1.16	6.46 ± 2.03	-0.03 ± 2.04	7.01 ± 2.24	6.97 ± 2.17	-0.04 ± 2.03	0.011	0.243
HbA1c (%)	5.93 ± 0.96	6.01 ± 0.81	0.08 ± 0.62	6.51 ± 1.43	6.18 ± 1.17	-0.33 ± 1.08***	< 0.001	0.225
FSI (μU/mL)	8.53 ± 6.07	8.17 ± 5.03	-0.36 ± 5.85	8.37 ± 6.33	6.74 ± 5.79	-1.63 ± 6.01***	0.615	0.033
HOMA-IR	2.51 ± 2.01	2.39 ± 1.68	-0.12 ± 1.58	2.63 ± 2.22	2.14 ± 2.30	-0.48 ± 2.37***	0.862	0.269
Total energy (kcal)	2,332.19 ± 904.26	2,391.99 ± 1,019.02	59.80 ± 864.61	2,406.06 ± 802.65	2,293.57 ± 761.00	-112.48 ± 828.60*	0.534	0.173
Carbohydrate (g)	328.62 ± 118.03	349.72 ± 151.16	21.10 ± 146.86	347.77 ± 114.37	336.25 ± 105.87	-11.52 ± 122.06	0.224	0.144
Protein (g)	96.48 ± 47.95	93.76 ± 48.31	-2.72 ± 47.63	94.31 ± 41.03	88.24 ± 35.81	-6.07 ± 39.12**	0.729	0.376
Total fat (g)	48.92 ± 41.49	56.10 ± 41.47	7.18 ± 44.30	58.41 ± 37.82	56.41 ± 36.18	-2.00 ± 44.56	0.085	0.658
Total cholesterol (mg)	189.03 ± 152.41	171.26 ± 157.67	-17.77 ± 164.33	170.46 ± 136.27	157.53 ± 116.84	-12.93 ± 142.32	0.354	0.784
Alcohol (g)	36.02 ± 51.97	30.62 ± 43.14	-5.40 ± 48.27	27.86 ± 34.73	24.59 ± 26.87	-3.27 ± 30.24	0.218	0.354

Data are expressed as no. (%) or mean ± SD. Significantly different within group between pre and post by paired *t*-test at $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. P^1 values measured by independent *t*-test between CG and IG at pre values. P^2 values measured by ANCOVA with adjusted by pre values, age, and changes in BMI, total energy intake and caloric nutrients. Δ, Post-Pre. CG, control group; IG, intervention group; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSI, fasting serum insulin, HOMA-IR: homeostasis model of insulin resistance.

Table 2. Analysis of the effects of web-based intervention program in KQ+QQ genotype

Parameters	KQ+QQ (n = 77)						P^1	P^2
	CG (n = 13)			IG (n = 64)				
	Pre	Post	Δ	Pre	Post	Δ		
Glucose metabolism								
IFG	9 (69.2)	10 (76.9)	-	46 (71.9)	46 (71.9)	-	0.847	-
T2DM	4 (30.8)	3 (23.1)		18 (28.1)	18 (28.1)			
Age (yr)	44.77 ± 7.38	-	-	48.09 ± 6.02	-	-	0.148	
BMI (kg/m^2)	22.78 ± 2.67	22.88 ± 2.66	0.10 ± 0.42	25.21 ± 3.05	25.02 ± 2.95	-0.19 ± 1.10	0.012	0.817
WC (cm)	82.23 ± 8.53	81.02 ± 6.39	-1.21 ± 6.60	86.16 ± 8.17	85.25 ± 8.37	-0.90 ± 5.24	0.157	0.122
SBP (mmHg)	125.08 ± 12.05	128.85 ± 16.35	3.77 ± 12.28	128.77 ± 14.17	129.42 ± 14.11	0.66 ± 15.31	0.374	0.294
DBP (mmHg)	79.62 ± 6.01	79.00 ± 9.69	-0.62 ± 7.03	83.52 ± 11.07	84.70 ± 10.38	1.19 ± 11.02	0.119	0.377
FPG (mM/L)	7.45 ± 2.90	6.95 ± 2.18	-0.50 ± 2.10	6.87 ± 1.66	6.75 ± 1.95	-0.12 ± 1.25	0.575	0.794
HbA1c (%)	5.74 ± 0.67	6.35 ± 0.42	0.61 ± 1.47	6.38 ± 1.15	6.15 ± 1.03	-0.23 ± 0.82***	0.057	0.084
FSI (μU/mL)	5.37 ± 2.69	8.20 ± 12.66	2.83 ± 10.85	9.15 ± 6.42	6.76 ± 4.27	-2.39 ± 5.62***	0.011	0.102
HOMA-IR	1.80 ± 1.12	3.19 ± 6.52	1.39 ± 5.76	2.86 ± 2.19	2.11 ± 1.58	-0.75 ± 1.91***	0.061	0.049
Total energy (kcal)	1,954.72 ± 432.71	2,239.90 ± 527.58	285.18 ± 501.73	2,476.73 ± 842.43	2,180.29 ± 657.47	-296.44 ± 727.85**	0.002	0.110
Carbohydrate (g)	254.73 ± 72.73	329.37 ± 106.40	74.64 ± 99.87*	347.72 ± 121.55	308.91 ± 100.00	-38.81 ± 112.13**	0.001	0.066
Protein (g)	87.22 ± 32.62	102.78 ± 66.97	15.56 ± 82.70	94.27 ± 36.80	80.57 ± 28.85	-13.70 ± 33.94**	0.496	0.048
Total fat (g)	38.26 ± 21.80	74.22 ± 129.08	35.96 ± 136.56	59.79 ± 39.76	51.90 ± 33.89	-7.89 ± 35.50	0.010	0.134
Total cholesterol (mg)	204.85 ± 116.89	163.55 ± 49.19	-41.30 ± 117.01	171.88 ± 118.96	141.45 ± 92.54	-30.43 ± 118.36*	0.368	0.666
Alcohol (g)	38.27 ± 25.23	36.64 ± 35.30	-1.63 ± 29.97	35.02 ± 55.37	32.08 ± 39.33	-2.94 ± 50.84	0.743	0.663

Data are expressed as mean ± SD. Significantly different within group between pre and post by paired *t*-test at *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. P^1 values measured by independent *t*-test between CG and IG at pre values. P^2 values measured by ANCOVA with adjusted by pre values, age, and changes in BMI, total energy intake and caloric nutrients. Δ, Post-Pre; CG, control group; IG, intervention group; IFG, impaired fasting glucose; T2DM, type 2 diabetes mellitus; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSI, fasting serum insulin, HOMA-IR: homeostasis model of insulin resistance.

Table 3. Comparisons of changes between pre and post web-based intervention program

Parameters	Total subjects (n = 448)						P^2
	CG (n = 82)			IG (n = 366)			
	KK (n = 69)	KQ+QQ (n = 13)	P^1	KK (n = 302)	KQ+QQ (n = 64)	P^1	
Δ BMI	-0.13 ± 0.70	0.10 ± 0.42	0.334	-0.12 ± 0.89	-0.19 ± 1.10	0.852	0.981
Δ WC	-0.32 ± 4.25	-1.21 ± 6.60	0.589	-0.33 ± 4.07	-0.90 ± 5.24	0.384	0.770
Δ SBP	1.81 ± 14.70	3.77 ± 12.28	0.970	-0.23 ± 14.12	0.66 ± 15.31	0.593	0.680
Δ DBP	0.52 ± 10.09	-0.62 ± 7.03	0.340	-0.65 ± 10.72	1.19 ± 11.02	0.185	0.538
Δ FPG	-0.03 ± 2.04	-0.50 ± 2.10	0.494	-0.04 ± 2.03	-0.12 ± 1.25	0.731	0.931
Δ HbA1c	0.08 ± 0.62^{a,b}	0.61 ± 1.47^{a,c}	0.038	-0.33 ± 1.08^{b}	-0.23 ± 0.82^{b}	0.674	0.050
Δ FSI	-0.36 ± 5.85^{a,b}	2.83 ± 10.85^{b}	0.116	-1.63 ± 6.01^{a,c}	-2.39 ± 5.62^{a,c}	0.437	0.026
Δ HOMA-IR	-0.12 ± 1.58^{a,b}	1.39 ± 5.76^{b}	0.161	-0.48 ± 2.3^{a,c}	-0.75 ± 1.91^{a,c}	0.470	0.039

Data are expressed as mean ± SD. P^1 values measured by ANCOVA with adjusted by pre values, age, and changes in total energy intake and caloric nutrients between KK and KQ+QQ genotypes. P^2 values measured by ANCOVA with adjusted by pre values, age, and changes in total energy intake and caloric nutrients among four groups. ^{a,b,c}Means with different superscript letter are significantly different among four groups. Δ, Post-Pre; CG, control group; IG, intervention group; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSI, fasting serum insulin, HOMA-IR: homeostasis model of insulin resistance.

tion ($P = 0.020$). In KQ+QQ IG, HbA1c ($P < 0.001$), FSI ($P < 0.001$), HOMA-IR ($P < 0.001$) and intakes of total energy ($P = 0.002$), carbohydrate ($P = 0.007$), protein ($P = 0.002$) and total cholesterol ($P = 0.044$) were significantly decreased after intervention. The web-based lifestyle intervention resulted in significant decrease in HOMA-IR in KQ+QQ IG as compared to KQ+QQ CG after appropriate adjustment ($P = 0.049$).

Magnitude of effect on genotype and web-based lifestyle intervention

When adjusting for confounders, HbA1c was significantly increased in KQ+QQ CG compared to the KK CG ($P = 0.038$) (Table 3). The reductions in FSI and HOMA-IR were significantly greater in KQ+QQ IG subjects compared to the CG. Similarly, the reductions in KK IG subjects were significantly greater compared to the CG subjects (respectively, FSI: $P = 0.026$, HOMA-IR: $P = 0.039$), and HbA1c reduction were marginally significant ($P = 0.050$).

Relationship between HOMA-IR and BMI changes in IG subjects with T2DM

The relationship between HOMA-IR and BMI was analyzed in IG subjects with T2DM (Fig. 2). When assessed across the two genotypes, the positive correlation was highly significant among 97 KK subjects (adjusted $\beta = 0.801$; $P = 0.022$) and was not significant among the 18 KQ+QQ subjects (adjusted $\beta = -0.521$; $P = 0.428$).

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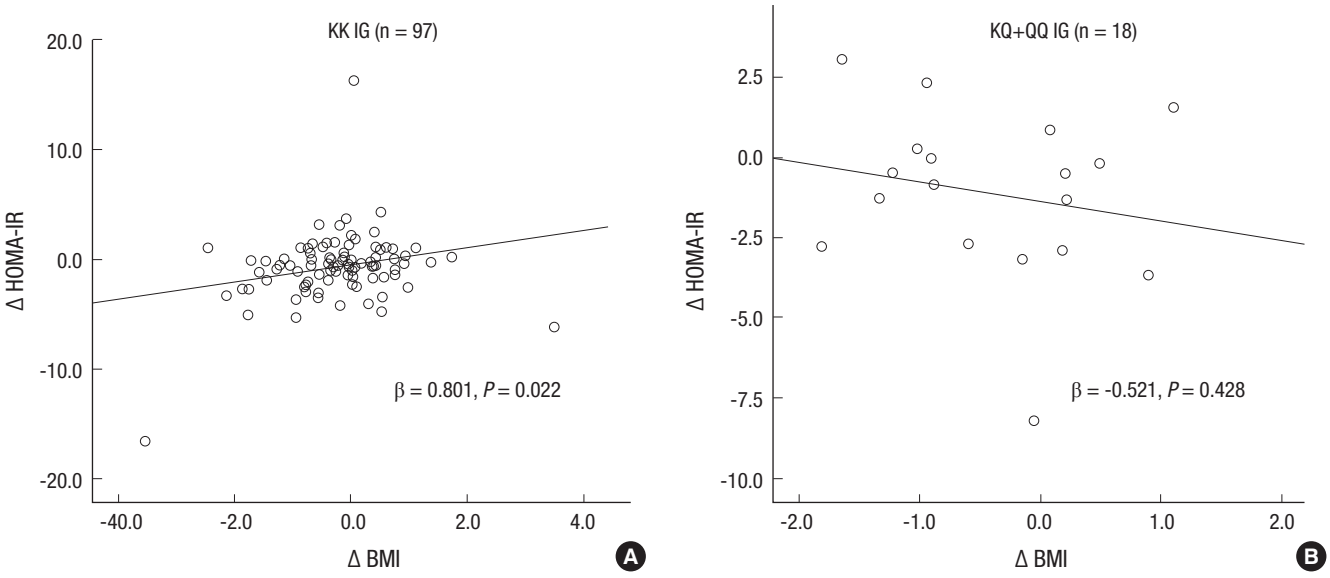

Fig. 2. Association of the change in HOMA-IR and BMI in intervention group with T2DM according to the (**A**) K allele subjects, (**B**) Q allele subjects. Δ, Post-Pre; BMI, body mass index; WC, waist circumference; HOMA-IR, homeostasis model of insulin resistance.

DISCUSSION

In the present study, we demonstrated that web-based lifestyle intervention is effective in improving IR without reference to *ENPP1* K121Q polymorphism. Additionally, the K allele has a beneficial effect of weight loss on IR decrease in subjects with T2DM.

IR is one of the main mechanisms implicated in the pathogenesis of both T2DM and metabolic syndrome (20). The HOMA-IR is widely used to estimate IR in large epidemiological studies and in clinical practice (21). Also, the HOMA-IR index correlates fairly well with invasive test of insulin sensitivity and has an acceptable degree of reproducibility (22). Therefore, it has been suggested that HOMA-IR must be assessed as an index of improvement in insulin sensitivity after lifestyle changes (23).

Several studies have reported dichotomous findings concerning the ability of the *ENPP1* K121Q polymorphism during lifestyle intervention (13, 14, 24). Recent studies reported that individuals with Q allele benefited more with intervention efficacy (14, 24). However, while the levels of HbA1c and HOMA-IR were significantly reduced in IG, there was no significant difference according to polymorphism in this study. As several previous studies had suggested, different ethnicity may affect environmental and functional genetic factors on other genes (13, 25). Moreover, the Q (risk) allele frequency varies greatly according with the ethnic group (26). Therefore, we suggest that it is important to clarify gene effect in a homogenous racial population.

Energy over-consumption was key to the development of IR and T2DM (27). Macronutrients (calorie nutrients) including carbohydrate, protein and fat have varying effects on blood glucose level (28). Intakes of total energy and fat are closely related with glycemic control (29, 30). Also, effects of dietary change on blood biomarker concentrations differ significantly between individuals. Genetic polymorphisms lead to alteration of the response to dietary components by influencing absorption and metabolism (31). For example, genetic background can interact with habitual dietary fat composition, affecting predisposition to IR syndrome and individual responsiveness to change in dietary fat intake (32). Recently, nutrigenomics raises ethical, legal and social issues particularly with respect to how the public may access nutrigenetic tests and associated nutritional and lifestyle advice (9).

Obesity increases the concentration of insulin in plasma and is the major contributor to IR (33). Increased visceral fat mass may lead to IR in Chinese type 2 diabetic and normorglycemic subjects (34). Moreover, it was recently demonstrated that individuals with elevated body fat percentage have an increased risk of developing cardiometabolic disease despite having a normal BMI (35). In Korean non-obese men, high BMI and waist circumference (abdominal obesity) have been associated with IR (36). Gillies et al. (37) demonstrated that lifestyle modification with weight loss can reduce the incidence of T2DM by up to 58% in populations at risk for T2DM. However, Vogeser et al. (23) showed no correlation between individual change in BMI and change in HOMA-IR during 1 yr of the MOBILIS lifestyle intervention program in obese persons (BMI ≥ 30.0 kg/m^2). Maranghi et al. (24) showed that after 6 weeks lifestyle intervention, significant relationship between BMI and HOMA-IR changes according to *ENPP1* genotype (β values were 0.34 in 145 KK individuals and 0.85 in 47 KQ+QQ individuals) in Italian men and women. In this study, this correlation was strongly significant among the 97 KK IG with T2DM (adjusted β = 0.801). The rea-

sons for this discrepancy may be due to the following differences: 1) intervention type and period (6 weeks, man to man intervention, vs. 10 months, web-based intervention); 2) ethnicity; 3) characteristic of subjects (non-diabetic overweight-obese adults, vs. men with IFG and T2DM); 4) confounding factors (not include dietary change, vs. include dietary change). Intervention type and contact frequency reportedly influence the response to a lifestyle intervention (38, 39). Although data are not shown, BMI were more decreased in the intervention group subjects with T2DM (-0.28 kg/m^2) when compared to intervention group subjects with IFG (-0.06 kg/m^2) (P = 0.039). It is expected that subjects with T2DM would benefit more from HOMA-IR reduction than subjects with IFG.

There were some limitations that need to be addressed. The first is the lack of Q allele subjects. A low proportion of QQ homozygous type is observed in most studies (approximately 2%-3% of the general population) (40). The frequency of the QQ type was very low (1.1%) in our data, so, it prevented appropriately testing of different genetic models (dominant, additive or recessive). Secondly, we did not measure the energy expenditure according to physical activity and exercise, and so were unable to distinguish the additive effects of change in energy expenditure on glycemic control and IR. Nevertheless, this study had the strength in that we tested the ability of *ENPP1* to predict intervention efficacy on IR after adjustment for confounding factors such as weight loss and dietary intake. Also, our results provided an interesting concept that is amenable to further study, in terms of a clear effect of genotype.

In conclusion, the *ENPP1* K121Q polymorphism is associated with IR during web-based lifestyle intervention, and the K121 allele has a beneficial effect of weight loss on IR. More comprehensive analyses in larger studies are needed to understand the full impact of *ENPP1* in Koreans on lifestyle intervention to prevent and delay T2DM.

DISCLOSURE

The authors have no conflict of interest to disclose.

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