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Overweight of Korean Male Workers and Genetic Polymorphism of Insulin Receptor Substrate 1 (IRS1) Gene

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Abstract: We have examined the hypothesis that the Gly972Arg variant of the insulin receptor substrate 1 (IRS1) gene is associated with the components contributing to overweight (obesity) and metabolic syndrome. We describe IRS1 genotype frequencies in 274 Korean men. The frequencies of Gly972Gly (G/G) and Gly972Arg (G/A variant) of the IRS1 gene were 88.3% and 11.7%, respectively, and the differences in frequencies between the overweight (BMI≥25 kg/m^2) group and non-overweight (BMI<25 kg/m^2) group were statistically significant. The subjects with G/A variant of IRS1 gene in non-overweight had significantly higher level of visceral fat thickness and adiponectin/leptin ratio than those with G/G alleles. In overweight group, the subjects with G/A variant of IRS1 gene also showed significantly higher level of insulin than those with G/G alleles. These results suggest that the IRS1 genetic polymorphism is involved in the occurrence of overweight, as well as metabolic syndrome.

Key words: obese (overweight), IRS1 genetic polymorphism, Korean men

INTRODUCTION

Modern society requires more and more mental activity rather than physical one due to the change in daily life and working environment in the course of progress of science and technology. One of the most prominent features of the society of this kind is the increase of chronic diseases including overweight (obesity) and circulatory, endocrine, nutritional and metabolic diseases from under- or over-nutrition caused by energy imbalance due to the decreased physical activity (Prentice and Jebb, 2003; Redman et al., 2008). Obesity and insulin resistance have been known to be major factors for metabolic syndrome (Despres and Lemieux, 2006). Type 2 diabetes, hypertension, and cardiovascular disease are also associated with obesity (Reaven, 1988; Pyorala et al., 2000).

Overweight is on the increase in most countries including Korea (Korea Ministry of Health and Welfare, 2007), Mediterranean and European countries (Aranceta, 2003), and Africa and the Unites States (Ogden et al., 2007), and therefore is recognized as a worldwide issue not limited to specific regions and populations. In Korea, in the year 2005, overweight was observed in 35.2% of adults 20 years old and over, and the prevalence of the metabolic syndrome was 35.2% and 28.3% in male and female, respectively (Korea Ministry of Health and Welfare, 2007). Epidemiological survey in 2003 revealed overweight or obesity in 56.2% of the adults in West Africa (Demographic and Health Survey, 2003), and Centre for Disease Control and Prevention (CDC) reported overweight or obesity in 87.4% of the adults in the United States in 2005 (CDC, 2006).

Obesity is well known to be brought about by life habit and food choice. Risk of obesity rises when bodies are not in energy balance by balanced food intake and energy consumption through physical activity (De Boer et al., 2007). Obesity is caused synthetically by various factors including life habit (excessive food intake, inactive activity, drinking, or smoking), socioeconomic status, and biological factors including genetics (Hill and Peters, 1998). Therefore etiology of obesity is studied in relation to interaction of environmental factors and genetic factors.

Obesity is associated with numerous genetic symptoms

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(Chung and Leibel, 2005), and various genes are involved in the progress of obesity (Clément, 2006). By genetic polymorphism, insulin receptor substrate 1 (IRS1) gene and β_3-adrenergic receptor (β_3-AR) gene can show diverse susceptibility to obesity and insulin-resistant Type 2 diabetes (Yamada et al., 2007). Peroxisome proliferator-activated receptor gamma (PPARγ) (Boon et al., 2008), fat mass and obesity associated (FTO) (Peeters et al., 2008), β_2-adrenergic receptor (Ikarashi et al., 2004), and ATP-binding cassette subfamily B member 1 (ABCB1) (Ichihara et al., 2008) genes also have been reported to be related to the occurrence of obesity, among others. Glycine-to-arginine substitution at codon 972 (Gly972Arg) variant of IRS1 are present in considerable heterogeneity (about 10%) of the population and carriers of the variant are at high risk of insulin-resistant Type 2 diabetes and lipid disorder due to the frequent IRS1 functional impairment (Jellema et al., 2003a, b).

In this study, we sought to understand the occurrence of overweight on the molecular level through analyzing the genetic polymorphism of IRS1 using polymerase chain reaction (PCR) to examine the relevance between factors affecting overweight and IRS1 polymorphism.

MATERIALS AND METHODS

Subjects

Study subjects were 274 male workers who worked in metal machinery manufacturing and assembling industry and had not been exposed to harmful chemicals. The study was approved by the Institutional Review Board of Occupational Safety and Health Research Institute, Korea Occupational Safety and Health Agency. The authors visited the selected workplace and explained carefully the object and method of the study, privacy policy, directions and other related matters to the workers, and each volunteer provided informed consent.

Questionnaire

Life habit and general characteristics of the subjects were surveyed using self-reported questionnaire and interview. Dietary habit was investigated with the questionnaire composed of 6 items (Yoon and Lee, 2006).

Metabolic syndrome components and measurement of visceral fat thickness (VFT)

Metabolic syndrome was identified by the presence of three or more of the five components listed in the "Third report of the National Cholesterol Education Program's Adult Treatment Panel III Report (NCEP-ATP III, 2002)", that is, i) Abdominal Obesity: Body mass index (BMI) ≥25 kg/m^2) or waist circumference >102 cm for men, >88 cm for women (Asia-Pacific standard: ≥90 cm for men, ≥80 cm for women), ii) Triglycerides ≥150 mg/dL, iii) High-density lipoprotein (HDL) cholesterol: <40 mg/dL for men, <50 mg/dL for women, iv) Blood pressure ≥130/85 mmHg, and v) Fasting glucose ≥110 mg/dL.

BMI was measured using body composition analyzer (X-SCAN plus II, Jawon Medical, Seoul, Korea). Systolic and diastolic blood pressures were measured using mercury manometer after 10-minute rest. Visceral fat thickness (VFT) and subcutaneous fat thickness (SFT) were measured with ultrasonic diagnostic equipment (SonoAce 8800, Madison, Seoul, Korea) using B-mode ultrasound 3.5 MHz oval probe. To minimize measurement error, subjects were asked to suspend breathing at end inspiration when VFT was measured. VFT was presented as the mean value of 3 measurements for each subject. Serum biochemistry including fasting glucose, triglycerides, total cholesterol, HDL-cholesterol was performed by automatic biochemistry analyzer (COBAS Integra 400, Roche Diagnostics Ltd., Rotkreuz, Switzerland). Serum insulin was measured by automatic chemiluminescence immune analyzer (Sanofi Diagnostics Pasteur, Inc., Minn, USA), and then homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the equation [HOMA-IR=(fasting insulin (μU/mL)×fasting glucose (mmol/L)/22.5]. Serum brain-derived neurotrophic factor (BDNF), adiponectin, and leptin were measured with ELISA kit (LINCO Research Inc., Mo, USA) and Ultra Microplate Reader (Bio-Tek instruments Inc., Highland Park, USA) at 450 nm.

IRS1 genetic polymorphism analysis

Genomic DNA was extracted from collected blood with QIAamp®DNA Mini Kit (QIAGEN, Germany) according to standard procedures recommended in the QIAamp DNA blood mini kit handbook. A 263 base pair (bp) fragment of Gly972Arg polymorphism of IRS1 gene was amplified by polymerase chain reaction (PCR) with sense primer (5'-CTTCTGTCAGGTGTCCATCC-3') and anti-sense primer (5'-TGGCGAGGTGTCCACGTAGC-3') as described previously (Almind et al., 1993, Fallucca et al., 2006). The PCR products were digested with 3 U of *Bst*NI (Roche Diagnostics, Mannheim, Germany) for 2 hours at 60°C. All the digested fragments were analyzed by 4.5% agarose gel electrophoresis (FMC, Rockland, ME, USA) in presence of ethidium bromide (Sigma-Aldrich Chemical Co, St. Louis, MO, USA), and visualized under ultraviolet light. The sizes of 159, 81, and 23 bp in Gly972 homozygotes (Gly/Gly) and 159, 108, 81, 51, and 23 bp in Gly972/Arg972 heterozygotes (Gly/Arg) (Fig. 1). We could not identify the Arg972 homozygotes (Arg/Arg, 108, 81, 51, and 23 bp) in this study.

Statistical analysis

Statistical analysis was performed using SPSS software

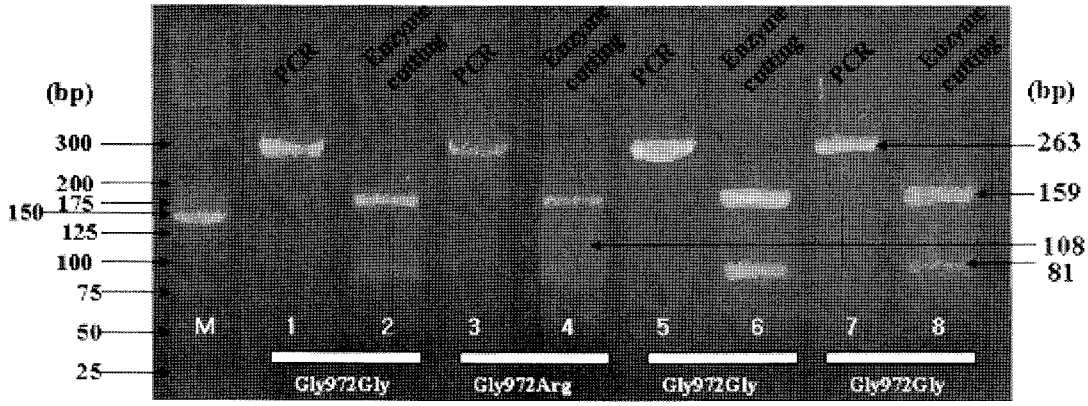

Fig. 1. Agarose gel electrophoresis for identification of the polymorphism of *IRS1* gene. For genotyping analysis, the PCR amplified fragment of 263 bp containing the polymorphic site at codon 972 (glycine-to-arginine substitution) was digested with *Bst*NI. Individuals were divided into genotypes, namely, Gly/Gly and Gly/Arg. Arg/Arg was not found in this study. M is size marker. Lanes 1, 3, 5, and 7 are PCR amplified products of IRS1 gene. And lanes 2, 6, and 8 are showing the Gly/Gly genotype and lane 4 is showing the Gly/Arg genotype.

(version 12.0, SPSS Inc., Chicago, USA). Independent t-test or χ^2 test was done for comparing the metabolic syndrome components and adiponectin between genotypic groups, and multiple logistic regression analysis was done for estimating the odds ratios of metabolic syndrome and adipose derived hormone.

RESULTS

Genetic polymorphism study of Gly972Arg of IRS1

Genetic polymorphism analysis of IRS1 revealed that the frequency of the Arg allele was 0.06, and the genotype distribution (242 workers Gly/Gly, 32 workers Gly/Arg) was in Hardy-Weinberg equilibrium (Table 1). The frequency of the Arg allele was significantly higher in obese group than in non-obese group (0.088 vs 0.076, $P<0.05$). The allele frequency of overweight group was, however, not in Hardy-Weinberg equilibrium.

Anthropometric and clinical characteristics study of non-overweight and overweight subjects

Subjects were subdivided into obese (overweight) group and non-obese (non-overweight) group by BMI criteria suggested in NCEP-ATP III (2002), and obesity risk factor, metabolic syndrome components and adipose derived hormones levels were compared between carriers (Gly/Arg) and non-carriers (Gly/Gly) of Gly972Arg variant IRS1 gene (Table 2).

Table 1. Genotypes of the IRS1 gene in Korean male subjects

	IRS 1 genotypes		Allele frequency
	Gly/Gly, *n* (%)	Gly/Arg, *n* (%)	Arg
Non-overweight (BMI<25 kg/m^2)	158 (85.4)	27 (14.6)	0.076
Overweight (BMI≥25 kg/m^2)*	84 (94.4)	5 (5.6)	0.088
Total (*n*=274)	242 (88.3)	32 (11.7)	0.060

*$P<0.05$, compared to the non obese group (by independent t-test).

In non-overweight group (BMI<25 kg/m^2), carriers of Gly/Arg variant showed statistically significant higher in visceral fat thickness ($P<0.003$) and adiponectin/leptin ratio ($P<0.028$) than Gly/Gly homozygotes. On the other hand, in overweight group (BMI≥25 kg/m^2), carriers of Gly/Arg variant showed statistically significant higher in insulin level ($P<0.001$) than Gly/Gly homozygotes (Fig. 2). The systolic blood pressure was also higher in Gly/Arg variant carriers ($P<0.090$) while LDL-cholesterol was higher in Gly/Gly homozygotes ($P<0.058$), although the differences were not statistically significant.

Associations between overweight, metabolic syndrome components and adipose derived hormone were evaluated by Pearson's correlation analysis, and overweight and metabolic syndrome components showed high correlation with diagnostic criteria items in NCEP-ATP III as expected (data not shown).

Accordingly multiple logistic regression analysis was performed with BMI<25 kg/m^2 group and BMI≥25 kg/m^2 group as independent variables and overweight, metabolic syndrome components and adipose derived hormone as covariates (Table 3). In BMI≥25 kg/m^2 group, odds ratios (OR) of SFT and VFT were 7.436 (95% confidence interval (C.I): 4.135-13.373, $P<0.001$) and 2.596 (95% C.I: 2.033-3.316, $P<0.001$), respectively. In BMI<25 kg/m^2 group, odds ratios of LDL-cholesterol and adiponectin were 0.750 (95% C.I: 1.038-1.112, $P<0.001$) and 0.755 (95% C.I: 0.698-0.817, $P<0.001$), respectively. Odds ratio by overweight was not great, but waist circumference, total cholesterol, HDL-cholesterol, triglycerides, insulin and leptin showed statistically significant odds ratio with overweight (BMI≥25 kg/m^2).

Table 2. Anthropometric and clinical characteristics of non-obese (BMI<25 kg/m^2) and obese (BMI≥25 kg/m^2) subjects according to the presence or absence of the Gly/Arg variant of IRS1 gene in Korean men

	BMI<25 kg/m^2			BMI≥25 kg/m^2		
	Gly/Gly	Gly/Arg	*p*	Gly/Gly	Gly/Arg	*p*
Age (year)	36.4±10.1	38.2±8.4	0.399	39.2±11.5	39.3±9.8	0.988
SBP (mm/Hg)	124.5±15.0	124.9±13.1	0.898	131.2±15.6	145.0±16.7	0.090
DBP (mm/Hg)	75.0±10.4	74.0±11.1	0.664	79.6±11.2	87.3±13.4	0.193
WC (cm)	79.1±8.8	80.3±7.1	0.478	90.9±5.5	89.8±7.6	0.699
BMI (kg/m^2)	22.0±1.8	22.6±1.6	0.116	27.4±1.9	26.7±1.5	0.494
SFT (cm)	1.4±0.5	1.3±0.4	0.166	1.9±0.5	2.1±0.6	0.652
VFT (cm)	2.9±1.2	3.7±1.0	0.003	4.8±1.4	3.8±1.1	0.147
T-Chol (mg/dL)	187.1±32.6	193.7±40.0	0.347	195.6±33.5	172.8±34.8	0.189
HDL-Chol (mg/dL)	54.2±13.6	54.1±11.0	0.971	45.5±11.6	44.7±15.8	0.891
LDL-Chol (mg/dL)	105.4±27.1	110.2±32.0	0.405	114.0±28.7	85.5±30.9	0.058
TG (mg/dL)	120.5±77.2	126.9±73.4	0.689	173.8±122.3	225.3±172.1	0.423
FG (mg/dL)	93.8±19.1	91.1±11.0	0.478	93.4±12.5	96.5±14.0	0.631
Insulin (μIU/L)	4.8±4.1	5.4±5.8	0.553	6.6±3.7	14.5±12.6	0.001
HOMA-IR	2.8±6.8	2.2±2.6	0.686	4.8±13.3	6.5±6.0	0.793
BDNF (pg/mL)	25.6±6.3	25.8±5.3	0.859	28.0±7.3	22.3±4.6	0.128
A (ng/mL)	6.9±3.7	7.2±3.6	0.697	4.6±2.5	3.8±2.7	0.525
L (ng/mL)	3.1±3.5	4.3±12.7	0.334	6.6±6.5	6.0±5.3	0.864
A/L ratio	5.9±7.1	9.3±9.4	0.028	1.8±2.2	0.8±0.7	0.363

SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; SFT, subcutaneous fat thickness; VFT, visceral fat thickness; T-Chol, total cholesterol; HDL-Chol, HDL-cholesterol; LDL-Chol, LDL-cholesterol; TG, triglyceride; FG, fasting glucose; HOMA-IR, homeostasis model assessment of insulin resistance; BDNF, brain-derived neurotrophic factor; A, Adiponectin; L, Leptin.

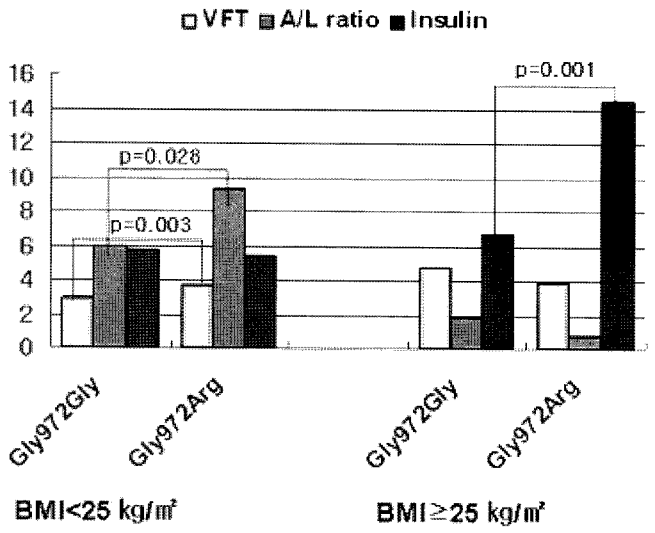

Fig. 2. Comparisons of VFT, A/L ratio and insulin levels in non-obese and obese by Gly/Arg variant of IRS1 gene. VFT, visceral fat thickness (cm); A/L ratio, adiponectin (ng/mL)/leptin (ng/mL) ratio; insulin, μIU/L.

Table 3. Multiple logistic regression analysis for association between obesity, anthropometric and biochemical parameters

	Obesity				
	β	S.E.	OR	95% C.I.	*P* value
WC	0.070	0.016	1.073	1.040-1.107	0.000
SFT	2.006	0.299	7.436	4.135-13.373	0.000
VFT	0.954	0.125	2.596	2.033-3.316	0.000
T-Chol	-0.063	0.016	0.939	0.910-0.970	0.000
HDL-Chol	0.001	0.018	1.001	0.967-1.036	0.957
LDL-Chol	0.072	0.018	0.075	1.038-1.112	0.000
TG	0.014	0.003	1.014	1.008-1.021	0.000
FG	-0.006	0.007	0.994	0.980-1.007	0.364
Insulin	0.057	0.020	1.058	1.018-1.100	0.005
BDNF	0.006	0.016	1.006	0.974-1.039	0.716
A	-0.281	0.040	0.755	0.698-0.817	0.000
L	0.160	0.026	1.173	1.116-1.233	0.000

WC, waist circumference; SFT, subcutaneous fat thickness; VFT, visceral fat thickness; T-Chol, total cholesterol; HDL-Chol, HDL-cholesterol; LDL-Chol, LDL-cholesterol; TG, triglyceride; FG, fasting glucose; BDNF, brain-derived neurotrophic factor; A, Adiponectin; L, Leptin.

DISCUSSION

IRS1 is a protein composed of 1,242 amino acids with molecular weight of 131.6 kDa, and locates on chromosome 2q36. It is expressed mainly in insulin-sensitive tissues and plays an important role in insulin signal transduction and regulating the insulin effect in cells (Sun et al., 1991; White

and Kahn, 1994; Sesti et al., 2001). Genotypic variation of IRS1 usually happens at codon 972 with glycine-to-arginine substitution. Gly972Arg variant of IRS1 gene is reported to be highly associated with insulin-resistant Type 2 diabetes (Fallucca et al., 2006), and genotype frequencies varied by ethnic groups (Hitman et al., 1995; Jellema et al., 2003a).

In this study, 11.7% of total subjects had Gly972Arg variant (Gly/Arg carrier) of IRS1 gene. The frequencies of Gly/Arg were 14.6% in non-overweight (BMI<25 kg/m^2) group and 5.6% in overweight (BMI≥25 kg/m^2) group, respectively, and the difference between the groups was statistically significant. However, because of the present study has a limitation of small number of subjects with Gly/Arg, the study with a greater number of subjects with Gly/Arg should therefore be performed in the future.

Jellema et al. (2003a, b) reported that Gly972Arg variant of IRS1 gene was present in about 6 % of the general population, and 14.1% of the Dutch subjects were shown to have Gly972Arg variant, and Baba et al. (2007) reported that 4.5% of 362 healthy Japanese had Gly972Arg variant. IRS1 genotype frequencies vary with study subjects, and it is thought to be affected by race and the environment of habitation (Hitman et al., 1995; Jellema et al., 2003a).

IRS1 gene is involved in expression and regulation of IRS1. It was reported that heterozygous IRS1 knockout mice showed less insulin expression than normal mice and the consequent glucose tolerance decrease led to obesity (Shirakami et al., 2002). IRS1 Gly972Arg variant gene is also reported to be closely related with gestational diabetes and glucose tolerance damage (Fallucca et al., 2006).

Adiponectin is negatively, while leptin is positively, correlated with obesity and insulin resistance, and therefore it has been suggested that adiponectin/leptin ratio may serve as a biomarker of obesity and metabolic syndrome (Xita et al., 2007). It was reported that the group with higher BMI (27-39 kg/m^2) showed higher insulin level and HOMA-IR than the group with lower BMI (19-23 kg/m^2), and suggested susceptibility of IRS1 gene (Jellema et al., 2003b). In Table 2, we found that Gly972Arg variant carriers showed higher VFT and adiponectin/leptin ratio in non-overweight group, indicating that Gly972Arg variant carriers are more likely to become an overweight. And also we found that variant carriers showed higher insulin level in overweight group, implying that possibility of metabolic syndrome and diabetes is higher in obese persons. Higher systolic blood pressure, glucose and triglycerides in Gly972Arg variant carriers, though not statistically significant, also support this speculation.

This study demonstrates that VFT, adiponectin/leptin ratio, insulin and systolic blood pressure which are related with Type 2 diabetes as well as obesity and metabolic syndrome were observed higher in carriers of Gly972Arg variant IRS1 gene, indicating the association between IRS1 genetic polymorphism and metabolic syndrome as well as obesity.

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