The Relative Effects of Obesity and Insulin Resistance on Cardiovascular Risk Factors in Nondiabetic and Normotensive Men

Seung Ha Park, M.D., Won Young Lee, M.D., Yong Su Lee, M.D., Eun Jung Rhee, M.D. and Sun Woo Kim, M.D.

Department of Internal Medicine, Kangbuk Samsung Hospital,
Sungkyunkwan University School of Medicine, Seoul, Korea

Background : Several reports have documented that Asians have a strong tendency to develop insulin resistance. The aims of this study were to evaluate the relative effects of insulin resistance and obesity on the risk factors for coronary heart disease (CHD) and to clarify whether insulin resistance accentuates these effects in apparently healthy men.

Methods : We conducted a cross sectional survey on 4,067 apparently healthy Korean men, aged between 20 and 83 years, with body mass indices (BMI) ranging from 15.19 to 40.29 kg/m^2. The presence of insulin resistance was defined as a homeostasis model assessment (HOMA-IR) value >2.23, which is the cutoff for the highest decile in the normal BMI group (BMI <23 kg/m^2; 1,438 subjects).

Results : The prevalence of insulin resistance was 24.7% in the overweight subjects (23≤BMI<25 kg/m^2; 1,259 subjects) and 43.9% in the obese subjects (BMI≥25 kg/m^2; 1,370 subjects). The BMI was identified as the major determinant for total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C), and waist circumference (WC) as the most important for apolipoprotein B (Apo B), systolic and diastolic blood pressures and C-reactive protein (CRP), and HOMA-IR as the most important for fasting blood sugar, triglyceride (TG), low high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-I (Apo A-I) and TC/HDL ratio. The presence of insulin resistance was found to accentuate the risk factors for CHD, with the exception of LDL-C and Apo A-I in the obese.

Conclusion : WC and HOMA-IR were found to be closely associated with non-traditional markers for CHD, such as high Apo B, hypertriglyceridaemia and the TC/HDL-C ratio, which are predictors for the presence of small, dense LDL particles. The insulin resistance among obese men was more prevalent than expected, and the presence of insulin resistance accentuates the effect of obesity in terms of the risk of CHD.

Key Words : Obesity, Insulin resistance, Coronary heart disease

INTRODUCTION

The existence of an association between obesity and insulin resistance has been suggested on many occasions, and insulin resistance is considered a major risk factor of cardiovascular and metabolic diseases[1-4]. Although obesity is considered the most important cause of insulin resistance, not all obese people have this condition. According to the European Group for the study of Insulin Resistance (EGIR), only 26% of obese people show insulin resistance[5].

In general, the prevalence of type 2 diabetes and cardiovascular disease are higher in Asians than in Caucasians[6-9], which may be due to the high prevalence of insulin resistance in the Asians[10-12]. Chronic illnesses, such as type 2 diabetes and cardiovascular disease, have recently become more prevalent in Korea, but it is difficult to attribute such phenomena wholly to an increase in the prevalence of obesity.

The aims of this study were to evaluate the prevalence of insulin resistance in healthy obese males, investigate the relative effects of obesity and insulin resistance on cardiovascular risk factors, and to verity the hypothesis that obese, compared to non-obese, male subjects have more cardiovascular risk factors.

• Correspondence to : Won Young Lee, M.D., Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine 108, Pyung-Dong, Jongno-ku, Seoul, Korea Tel : 82-2-2001-2075, Fax : 82-2-2001-2049, E-mail : drlwy@hanmail.net

MATERIALS AND METHODS

1. Subjects

4,067 healthy men, 20 years or older, who underwent a medical check-up at the Kangbuk Samsung Hospital between January and November 2002 were enrolled in this study. Those with medical illnesses, such as diabetes, hypertension, coronary heart disease, or renal, hepatic or other endocrine diseases, and those with a fasting blood glucose level of higher than 126 mg/dL, a blood pressure higher than 140/80 mmHg, and those taking any medication, were excluded. The subjects were subdivided into 3 groups according to their body mass index (BMI); normal (BMI<23 kg/m^2; 1,438 subjects), overweight (23 ≤BMI<25 kg/m^2; 1,259 subjects), and obese (BMI≥25 kg/m^2; 1,370 subjects) groups. The presence of abdominal obesity was defined as a waist circumference of 90cm and over. The homeostasis model assessment (HOMA-IR) was used to assess insulin resistance[13], and the presence of insulin resistance was defined a HOMA value >2.23, which was the cutoff of the highest decile for the normal weight group.

2. Anthropometric measurements and blood chemistry

Age, gender, height, body weight, waist circumference and systolic and diastolic blood pressures were recorded. The waist circumference was measured midway between the inferior margin of the last rib and the crest of the ilium, in the hori-zontal plane, with the subject in an upright position. After 12 hours of fasting, the serum glucose, total cholesterol, triglyceride and HDL-C concentrations were determined using an autoanalyzer (747 Automatic analyzer, Hitachi, Tokyo, Japan). The LDL-C was measured by homogenous enzymatic calorimetric testing, the Apolipoprotein A-I and B by nephelo-metry (IMMAGE System, Beckman Coulter, California, USA), and the CRP levels by immunonephelometry (BNTM Systems, N High Sensitivity CRP, Dade Behring, Marburg, Germany). The fasting insulin was determined by an immunoradiometric assay (Biosource, Belgium); the inter-and intra-assay coefficients of variation (CV) were 2.1~4.5% and 4.7~12.2%.

3. Statistical Analysis

SPSS (version 10.0) for Windows was used for the statistical analysis and the data are expressed as the means±SEM. Since the values for the serum triglyceride, fasting insulin, CRP, and HOMA-IR were severely skewed, natural logarithms were used for the statistical analysis. One-way ANOVA and the Student's t-test were used to compare the mean subgroup values, and the Chi-Square test the categorical variables. In order to identify the risk factors of coronary heart disease, a multiple regression analysis was performed, with the BMI, waist circumference and HOMA-IR as independent variables. Values were considered statistically significant if the associated p values were lower than 0.05.

Table 1. Clinical and metabolic characteristics of the study population

	Lean (n=1438)	Overweight (n=1259)	Obese (n=1370)
Age (years)	43.9 (0.29)	44.7 (0.27)	43.3 (0.25)*
BMI (Kg/m^2)	21.1 (0.03)	24.0 (0.01)	27.0 (0.04)
WC (cm)	77.2 (0.14)	83.7 (0.11)	90.0 (0.14)
WHR	0.84 (0.001)	0.88 (0.001)	0.90 (0.001)
FBS (mg/dL)	88.1 (0.25)	90.5 (0.27)	93.1 (0.28)
TC (mg/dL)	198.5 (0.89)	209.1 (0.96)	214.1 (0.98)
TG (mg/dL)	129.7 (2.11)	157.48 (2.51)	189.2 (3.13)
HDL-C (mg/dL)	56.6 (0.36)	51.9 (0.33)	49.4 (0.29)
LDL-C (mg/dL)	114.7 (0.76)	123.0 (0.81)	125.5 (0.83)
Apo A-I (mg/dL)	120.3 (0.53)	117.1 (0.53)	115.5 (0.50)
Apo B (mg/dL)	95.7 (0.63)	105.9 (0.68)	110.3 (0.69)
TC/HDL-C	3.67 (0.026)	4.20 (0.030)	4.51 (0.030)
SBP (mmHg)	113.8 (0.31)	116.0 (0.32)	118.5 (0.31)
DBP (mmHg)	73.0 (0.23)	74.9 (0.25)	76.9 (0.23)
Fasting insulin (μU/mL)	6.55 (0.061)	7.87 (0.073)	9,42 (0.093)
HOMA-IR	1.44 (0.014)	1.77 (0.018)	2.19 (0.024)
CRP (mg/L)	1.01 (0.046)	1.19 (0.051)	1.38 (0.046)

Data are the means (SE).
All p values are<0.001 among the three BMI groups by ANOVA, except *p<0.05.
Lean, BMI<23 kg/m^2; Overweight, 23≤BMI<25 kg/m^2; Obese, BMI≥25 kg/m^2.
BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Apo A-I & B, apolipoprotein A-I & B; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein.

Table 2. Multiple regression analysis of the correlations between coronary heart disease risk factors with indices of obesity and HOMA-IR

	R^2	BMI		WC		HOMA-IR	
		β	p	β	p	β	p
FBS	0.236	-0.037	0.145	0.046	0.064	0.481	<0.001
TC	0.051	0.116	<0.001	0.064	0.021	0.084	<0.001
TG	0.184	0.077	0.003	0.172	<0.001	0.259	<0.001
HDL-C	0.097	-0.108	<0.001	-0.122	<0.001	-0.139	<0.001
LDL-C	0.032	0.128	<0.001	0.048	0.085	0.019	0.275
Apo A-I	0.016	-0.048	0.091	-0.049	0.083	-0.052	0.003
Apo B	0.094	0.124	<0.001	0.133	<0.001	0.101	<0.001
TC/HDL-C	0.159	0.139	<0.001	0.150	<0.001	0.184	<0.001
SBP	0.053	-0.015	0.590	0.196	<0.001	0.078	<0.001
DBP	0.057	0.011	0.682	0.187	<0.001	0.073	<0.001
CRP	0.069	0.099	<0.001	0.138	<0.001	0.063	<0.001

β, standardized coefficients.
BMI, body mass index; HOMA-IR, homeostasis model assessment; WC, waist circumference; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Apo A-I & B, apolipoprotein A-I & B; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein.

RESULTS

1. General characteristics

Table 1 shows the clinical data of the subjects. The mean age, BMI, waist circumference and HOMA-IR were 43.9 ± 0.15 years, 24.0 ± 0.04 kgm^{-2}, 83.5 ± 0.11 cm and 1.79 ± 0.012, respectively. With increasing obesity, the HOMA-IR value increased ($p < 0.05$). The overall prevalence of insulin resistance was 26.1%, and 24.7, 43.9, 20.8 and 54.3% in the overweight, obese, without and with abdominal obesity groups, respectively.

2. The relative effects of obesity and insulin resistance on the risk factors for coronary heart disease

In order to assess the relative effects of obesity and insulin resistance on the risk factors for coronary heart disease, a multiple regression analysis was performed, with the BMI, waist circumference, and HOMA-IR as independent variables (Table 2). The BMI was found to be an independent risk factor for LDL-C and the most important risk factor for total cholesterol. The waist circumference was identified an independent risk factor for high systolic and diastolic blood pressures and the most important risk factor for elevated apolipoprotein B and CRP levels. The HOMA-IR was found to be an independent risk factor for elevated fasting blood sugar level, and the apolipoprotein A-I as the most important risk factor for elevated triglyceride, HDL-C and TC/HDL-C ratio.

3. The effect of insulin resistance on the risk factors for coronary heart disease in the obese and abdominal obesity subgroups

In the obese subjects with insulin resistance, the fasting blood sugar, total cholesterol, triglyceride, apolipoprotein B,

TC/HDL-C ratio, systolic and diastolic blood pressures, and CRP were all higher, and the HDL-C levels lower than in the obese subjects without insulin resistance (Table 3). Subjects with abdominal obesity and insulin resistance had higher fasting blood sugar, total cholesterol, TC/HDL-C ratio, systolic blood pressure, and CRP levels, but lower HDL-C levels and were younger than those without insulin resistance.

To more precisely determine the effects of insulin resistance on the prevalence of CHD risk factors, the percentages of subjects within the highest or lowest deciles of the normal group and the obese subjects with and without insulin resistance (Table 4) were compared. The cutoffs for apolipoprotein A-I, apolipoprotein B, CRP and the TC/HDL-C ratio were those for the highest or lowest deciles of the normal group. The cutoffs for the other risk factors were based on the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) guidelines[14]. The prevalences of hyperglycemia, hypercholesterolemia, hypertriglyceridemia, high HDL-C, high apolipoprotein B, a high TC/HDL-C ratio and high blood pressure were significantly higher in obese subjects with, than in those without, insulin resistance ($p < 0.05$). In subjects with abdominal obesity, the prevalences of hyperglycemia, hypertriglyceridemia, hypercholesterolemia, high TC/HDL-C ratio, and high systolic blood pressure were all significantly higher in subjects with, than without, insulin resistance ($p < 0.05$).

DISCUSSION

Although diabetic or impaired glucose tolerance subjects could not be totally excluded, as no oral glucose tolerance test was performed, the results of this study show that the

Table 3. The magnitude of coronary heart disease risk factors according to insulin resistance in obese subjects.

| | Obese (BMI≥25 kg/m²) | | Abdominal obesity (WC≥90 cm) | |
	Non-IR (n=768)	IR (n=602)	Non-IR (n=291)	IR (n=346)
Age (years)	43.5 (0.33)	43.0 (0.38)	45.8 (0.62)	44.0 (0.51)*
FBS (mg/dL)	89.3 (0.32)	97.9 (0.42)†	88.7 (0.51)	97.8 (0.55)†
TC (mg/dL)	211.4 (1.29)	217.4 (1.50)*	216.2 (2.11)	219.1 (1.93)
TG (mg/dL)	161.9 (3.03)	224.4 (5.67)†	167.6 (4.70)	218.1 (6.51)†
HDL-C (mg/dL)	50.8 (0.39)	47.6 (0.43)†	50.3 (0.66)	47.5 (0.57)*
LDL-C (mg/dL)	125.5 (1.08)	125.6 (1.29)	130.0 (1.81)	127.6 (1.68)
Apo A-I (mg/dL)	115.9 (0.68)	115.0 (0.74)	116.0 (1.12)	114.3 (1.00)
Apo B (mg/dL)	107.6 (0.91)	113.6 (1.04)†	112.5 (1.51)	115.3 (1.34)
TC/HDL-C	4.32 (0.039)	4.74 (0.048)†	4.47 (0.067)	4.79 (0.062)*
SBP (mmHg)	116.9 (0.42)	120.6 (0.45)†	119.1 (0.66)	121.3 (0.58)*
DBP (mmHg)	75.8 (0.31)	78.3 (0.35)†	77.5 (0.50)	78.8 (0.45)
CRP (mg/L)	1.29 (0.062)	1.49 (0.069)†	1.41 (0.102)	1.66 (0.098)*

Data are the mean (SE).
BMI, body mass index; IR, insulin resistance; WC, waist circumference; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Apo A-I & B, apolipoprotein A-I & B; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein.
*p <0.05, †p <0.001

Table 4. Prevalence of coronary heart disease risk factors according to insulin resistance in obese subjects.

| | Obese (BMI≥25 kg/m²) | | Abdominal obesity (WC≥90 cm) | |
	Non-IR (n=768)	IR (n=602)	Non-IR (n=291)	IR (n=346)
Age≥45 years	43.9%	41.4%	55.0%	46.8%*
FBS≥110 mg/dL	2.0%	11.8%†	1.4%	11.3%†
TC≥200 mg/dL	60.2%	68.3%*	64.6%	69.1%
TG≥150 mg/dL	46.7%	70.8%†	49.8%	69.9%†
HDL-C<40 mg/dL	14.8%	21.4%*	16.5%	21.7%
LDL-C≥130 mg/dL	41.1%	43.7%	49.1%	45.4%
Apo A-I<96 mg/dL	14.2%	14.1%	12.0%	13.9%
Apo B≥128 mg/dL	19.1%	26.4%*	27.8%	29.2%
TC/HDL-C≥4.95	23.8%	36.7%†	29.2%	39.6%*
SBP≥130 mmHg	25.7%	37.0%†	28.9%	41.0%*
DBP≥85 mmHg	15.5%	21.6%*	21.0%	23.7%
CRP≥3 mg/L	9.5%	12.1%	11.0%	15.0%

The data are percentages.
BMI, body mass index; IR, insulin resistance; WC, waist circumference; FBS, fasting blood sugar; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Apo A-I & B, apolipoprotein A-I & B; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein
*p <0.05, †p <0.001

prevalence of insulin resistance in obese males with a BMI of 25 kg/m² or over and in abdominally obese males with a waist circumference of 90 cm and over were 43.9 and 54.3%, respectively. These prevalences were remarkably higher than those of an EGIR study, which showed a prevalence of 26% for insulin resistance among obese subjects[5]. Furthermore, the results of our study suggest that as the BMI increases, the risk factors of coronary heart disease also increase, and indicated that the prevalence of insulin resistance and cardiovascular risk factors were also higher in obese and abdominally obese males. Therefore, the effects of insulin resistance and obesity

on cardiovascular disease should be considered to prevent the progression of type 2 diabetes and coronary heart disease.

This study, found that the waist circumference and HOMA-IR were significant predictors of elevated apolipoprotein B, triglyceride, and TC/HDL ratio, and that the triglyceride values and TC/HDL ratios were higher in males with abdominal obesity and insulin resistance than in those with abdominal obesity only. Such results indicate that the waist circumference and HOMA-IR are closely associated with hyperinsulinemia, small dense LDL particles, and high apolipoprotein B, which are considered to be the non-traditional markers of coronary heart

disease[15]. In a prospective study by Tchernof et al, the incidence of coronary heart disease was found to increase 20-fold in middle-aged males with abdominal obesity, hyperinsulinemia, a high TC/HDL-C ratio, which reflects small dense LDL particles[16], and hyperapolipoprotein B, although they did not examine the traditional cardiovascular risk factors, i.e., type 2 diabetes, hyperlipidemia, or hypertension[17].

In this study, those with a history of diabetes and factors known to be associated with both obesity and insulin resistance, such as fasting hyperglycemia, hypertension, and hyperlipidemia, were excluded. In addition, women were also excluded in order to rule out the effect of the menopause on insulin resistance and lipid metabolism abnormalities[18-20]. A multiple regression analysis was performed in order to assess the relative effect of obesity and insulin resistance on the risk factors of coronary heart disease. The BMI, as a predictor, explained 5.1 and 3.2% of the changes in the total cholesterol and LDL-C levels, respectively. The waist circumference, as a predictor, explained 9.4, 5.7 and 6.9% of the changes in apolipoprotein B, systolic and diastolic blood pressures and CRP levels, respectively. The HOMA-IR was found to be a significant predictor of fasting blood glucose, triglyceride, HDL-C, apolipoprotein A-I, and the TC/HDL ratio, and in particular, explained 23.6%, 18.4 and 15.9% of the changes in the fasting blood glucose, triglyceride and HDL-C cholesterol, respectively. These results corresponded well with those of previous studies, which found that the BMI was the most important predictor of total cholesterol and LDL-C, and that insulin resistance was the most important predictor of impaired glucose tolerance, and the HDL-C and triglyceride levels[21].

The HOMA-IR was used as the insulin resistance index in this study, even though it is known to have a low reproducibility, due to daily fluctuations in the fasting glucose and insulin concentrations, and up to 20% of the insulin resistance index can be changed in proportion with up to a 1 μU/mL change in the insulin level. Significant correlations have been found in many studies between the HOMA and glucose clamp values[22-24]. Screening methods for, and the definition and treatment of, insulin resistance have not been widely accepted in clinical practice. Recent studies have reported that life style intervention or metformin can delay the progression of impaired glucose tolerance to type 2 diabetes[25, 26]. However, it has not been clarified how these interventions can be accepted in clinical practice. Considering the recently experienced increase in the prevalence of insulin resistance, the definition and guidelines for the screening of insulin resistant subjects in the general population should be established. Further prospective studies are needed to establish specific intervention strategies for obese, insulin resistant subjects, with careful consideration given to the cost-effectiveness and clinical usefulness.

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