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ORIGINAL ARTICLE

Relationship between Metabolic Syndrome, Metabolic Syndrome Score, Insulin Resistance and Beta Cell Function in Korean Adults with Obesity

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대한민국 비만 성인에서 대사증후군과 인슐린저항성 및 베타세포기능의 관련성

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ABSTRACT

The present study was conducted to assess the relationship between metabolic syndrome, metabolic syndrome score, homeostasis model assessment of insulin resistance (HOMA-IR), and beta-cell function (HOMA-*B*) in obese Korean adults. The study included 1,860 adults aged 20 years or older from the 2010 Korean National Health and Nutrition Examination Survey (KNHANES) data. Metabolic syndrome and metabolic syndrome score (MSS) were positively associated with HOMA-IR (both $P<0.001$). HOMA-*B* levels of elevated blood pressure ($P<0.001$) and elevated fasting blood glucose group ($P<0.001$) were significantly lower than the normal group. However, the HOMA-*B* levels of abdominal obesity ($P=0.003$) and reduced high-density lipoprotein cholesterol group ($P=0.030$) were significantly higher than the normal group. Nevertheless, metabolic syndrome ($P<0.001$) and MSS ($P<0.001$) were inversely associated with the HOMA-*B* levels. In conclusion, metabolic syndrome and MSS were positively associated with insulin resistance and inversely associated with beta-cell function in Korean adults with obesity.

INTRODUCTION

Obesity is one of the most important public health problems due to its association with many diseases, including type 2 diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome [1-4]. Metabolic syndrome is characterized by insulin resistance (IR), as studies have mainly noted IR in subjects with individual metabolic syndrome components, such as abdominal obesity, hypertension, and dyslipidemia [5-7]. The populations with obesity maintain normal glucose level since a preserved ability to secrete insulin [8]. However, if IR increases, the ability to secrete insulin decreases, as IR is one of the factors in the de-differentiation and death of beta cells [9, 10].

Recently, research on metabolic syndrome and IR is currently being conducted all over the world. However, there are few studies on the relationship between beta

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cell function and metabolic syndrome in Korea, and research findings on the association between beta cell function and metabolic syndrome components were not consistent according to countries and ethnic groups, healthy subjects and subjects with chronic disease (e.g., obesity, diabetes) [11-15]. The prevalence of metabolic syndrome and obesity in the Republic of Korea has been increasing due to the Westernized diet [16]. Therefore, the present study aimed to investigate the relationship between metabolic syndrome and the increased levels of its components and the HOMA-*B* levels in adults with obesity using the Korean National Health and Nutrition Examination Survey (KNHANES V-1, 2010) data.

MATERIALS AND METHODS

1. Study subjects

This study was based on data from the fifth KNHANES (2010), which is the most recent data that measured insulin among the KNHANES. The KNHANES is a cross-sectional survey conducted nationwide by the Division of Korean National Health and Welfare. The fifth KNHANES (2010) was performed from January 2010 to December 2010. In the fifth KNHANES (2010), 8,958 individuals over 1 year of age were sampled for the survey. Among the 6,665 subjects who participated in the fifth KNHANES (2010), we limited the analyses to adults aged over 20 years. We excluded 4,805 subjects who were in no-obesity group (3,941 subjects, body mass index [BMI] <25.0 kg/m^2) or for whom data were missing for an important analytic variables, such as the insulin, fasting blood glucose (FBG), and various blood chemistry tests (864 subjects). Finally, 1,860 subjects were included in the statistical analysis. The KNHANES study was approved by the Institutional Review Board of the Centers for Disease Control and Prevention in Korea (IRB No, 2010-02CON-21-C). All participants in the survey signed an informed written consent form.

2. General characteristics and blood chemistry

Anthropometric measurements included height, weight, waist circumference (WC), and BMI as well as final measurements of diastolic blood pressure (DBP) and systolic blood pressure (SBP). Blood chemistry included measurement of total cholesterol (TC), triglycerides (TGs), high-density lipoprotein cholesterol (HDL-C), FBG, and 25-hydroxyvitamin D [25(OH)D].

3. HOMA-IR and HOMA-*B* and obesity

The HOMA-*B* and HOMA-IR constitute a method for assessing beta cell function and IR from basal insulin concentrations and glucose [17]. HOMA-*B* and HOMA-IR are also significantly associated with diabetes risk across ethnic groups [18]. The formulas are as follows: HOMA-*B*=20×fasting insulin (μU/mL)/[FBG (mg/dL)−63]; HOMA-IR=[fasting insulin (μU/mL)×FBG (mg/dL)]/405 [17]. Obese population was defined as BMI ≥25.0 kg/m^2 [19].

4. Metabolic syndrome and metabolic syndrome score

Metabolic syndrome was defined using the diagnostic criteria of the revised National Cholesterol Education Program Adult Treatment Panel III [20], including TGs, HDL-C, BP, FBG, and WC. TGs over 150 mg/dL for dyslipidemia were set as the criteria for elevated TGs. The criteria for reduced HDL-C were HDL-C of less than 50 mg/dL and 40 mg/dL for females and males, respectively. FBG over 100 mg/dL were set as the criteria for elevated FBG. DBP over 85 mmHg or SBP over 130 mmHg were set as the criteria for elevated BP. The criteria for abdominal obesity were WC of over 80 cm and 90 cm for females and males, respectively [21]. The presence of defined abnormalities in any three of these five measures constitutes a diagnosis of metabolic syndrome. The metabolic syndrome (MSS) indicates the presence of elevated FBG, elevated TGs, and reduced HDL-C, abdominal obesity, and elevated BP. Subjects without any of the five risk factors received an MSS of 0, while those with one, two, three, or four or more of the

risk factors received an MSS of 1, 2, 3, and ≥4, respectively [22].

5. Data analysis

The collected data were statistically analyzed using SPSS statistics 20 (SPSS Inc., Chicago, IL, USA). The distributions of the subjects characteristics were converted into percentages (%), and the successive data were presented as averages with standard deviations (M±SD). Clinical characteristics grouped by men or women were analyzed using chi-square and an independent t-test. The average difference in the HOMA-IR and HOMA-*B* levels for the clinical elements of metabolic syndrome were calculated using an independent t-test. The average difference in the HOMA-IR and HOMA-*B* levels for metabolic syndrome and MSS were calculated using an analysis of variance (ANOVA) and an analysis of covariance (ANCOVA). The significance level for all of the statistical tests was set as $P<0.05$.

RESULTS

1. Clinical characteristics of research subjects

The clinical characteristics of the research participants are shown in Table 1. In the males, the HOMA-IR and HOMA-*B* levels of participants were 3.20±1.86 and 129.55±69.85, respectively. According to the classification of the MSS guidelines, 80 (8.6%), 172 (18.4%), 260 (27.8%), 248 (26.6%), and 174 (18.6%) participants were classified as MSS 0, MSS 1, MSS 2, MSS 3, and MSS ≥4, respectively, while the prevalence rate of metabolic syndrome was 422 of the 934 patients (45.2%). In the females, the HOMA-IR and HOMA-*B* levels of subjects were 3.23±1.99 and 139.65±79.13, respectively. According to the classification of the MSS guidelines, 27 (2.9%), 176 (19.0%), 273 (29.5%), 250 (27.0%), and 200 (21.6%) participants were classified as MSS 0, MSS 1,

Table 1. General characteristics of research subjects N (%), Mean±SD (N=1,860)

Variables	Category	Males (N=934)	Females (N=926)	*P*
Age	20~29	79 (8.5)	59 (6.2)	<0.001
	30~39	214 (22.9)	125 (13.5)	
	40~49	227 (24.3)	151 (16.3)	
	50~59	173 (18.5)	226 (24.4)	
	≥60	241 (25.8)	367 (39.6)	
Metabolic syndrome	MSS <3	512 (54.8)	476 (51.4)	0.150
	MSS ≥3	422 (45.2)	450 (48.6)	
Metabolic syndrome score	0	80 (8.6)	27 (2.9)	<0.001
	1	172 (18.4)	176 (19.0)	
	2	260 (27.8)	273 (29.5)	
	3	248 (26.6)	250 (27.0)	
	≥4	174 (18.6)	200 (21.6)	
WC (cm)		91.86±6.68	88.57±7.64	<0.001
BMI (kg/m^2)		27.15±2.11	27.59±2.41	<0.001
SBP (mmHg)		122.83±15.43	124.47±17.70	0.033
DBP (mmHg)		79.96±10.39	76.88±10.19	<0.001
HOMA-IR		3.20±1.86	3.23±1.99	0.750
HOMA-*B*		129.55±69.85	139.65±79.13	0.004
TC (mg/dL)		195.19±37.18	200.20±39.48	0.005
TG (mg/dL)		190.30±152.14	142.55±84.56	<0.001
HDL-C (mg/dL)		42.57±8.78	47.34±10.16	<0.001
25(OH)D (ng/dL)		19.25±6.27	17.00±6.29	<0.001
FBG (mg/dL)		104.06±26.96	100.65±20.94	0.002

Abbreviations: WC, waist circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-*B*, homeostasis model assessment of beta-cell function; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, LDL-cholesterol; 25(OH)D, 25-hydroxyvitamin D; FBG, fasting blood glucose.

MSS 2, MSS 3, and MSS ≥4, respectively, while the prevalence rate of metabolic syndrome was 450 of the 926 patients (48.6%).

2. Comparisons of the HOMA-IR and HOMA-*B* according to metabolic syndrome characteristics in subjects with obesity

Comparisons of the HOMA-IR and HOMA-*B* levels according to metabolic syndrome characteristics are shown in Table 2. In terms of components of metabolic syndrome, the HOMA-IR were significantly higher ($P<0.001$) than the normal groups in all metabolic syndrome components [except elevated BP ($P=0.054$)]. The HOMA-*B* levels were significantly lower in the elevated BP ($P<0.001$) and elevated FBG group ($P<0.001$) than in the normal groups. However, the HOMA-*B* were significantly higher in the abdominal obesity ($P=0.003$) and reduced HDL-C group ($P=0.030$) than the normal group.

3. Comparisons of the HOMA-IR and HOMA-*B* according to metabolic syndrome and MSS in subjects with obesity

Comparisons of the HOMA-IR and HOMA-*B* levels according to metabolic syndrome and MSS in subjects with obesity are shown in Tables 3, 4. In terms of the HOMA-IR by MSS values after adjusting for age, gender, BMI, TC, and 25(OH)D, the HOMA-IR [M±SE, 95% confidence interval (CI)] were 2.41±0.17 (95% CI, 2.06~

Table 2. Comparisons of the HOMA-IR and HOMA-*B* levels according to metabolic syndrome characteristics in obesity subjects
Mean±SD (N=1,860)

Variable	Category	Obesity subjects [BMI ≥25.0 kg/m^2]			
		HOMA-IR	*P*	HOMA-B	*P*
WC (cm)	Reference[a]	2.66±1.17	<0.001	126.72±62.83	0.003
	Abdominal obesity[b]	3.41±2.10		137.35±78.38	
BP (mmHg)	Reference[c]	3.13±2.12	0.054	141.20±73.21	<0.001
	Elevated blood pressure[d]	3.30±1.72		127.91±75.43	
TGs (mg/dL)	Reference[e]	2.97±1.77	<0.001	132.36±65.51	0.169
	Elevated triglycerides[f]	3.60±2.08		137.45±86.19	
HDL-C (mg/dL)	Reference[g]	3.01±1.71	<0.001	131.32±66.84	0.030
	Reduced HDL-C[h]	3.56±2.20		139.53±85.70	
FBG (mg/dL)	Reference[i]	2.62±1.16	<0.001	158.04±77.92	<0.001
	Elevated FPG[j]	4.13±2.45		97.86±50.92	

Abbreviations: [a]Reference is defined as WC <90 cm in males or <80 cm in females, [b]Abdominal obesity is defined as WC >90 cm in males or >80 cm in females, [c]Reference is defined as SBP <130 mmHg or DBP <85 mmHg, [d]Elevated blood pressure is defined as SBP >130 mmHg or DBP >85 mmHg, [e]Reference is defined as TGs <150 mg/dL, [f]Elevated triglycerides is defined as TGs >150 mg/dL, [g]Reference is defined as HDL-C >40 mg/dL in males or >50 mg/dL in females, [h]Reduced HDL-C is defined as HDL-C <40 mg/dL in males or <50 mg/dL in females, [i]Reference is defined as FBG <100 mg/dL, [j]Elevated FBG is defined as FBG >100 mg/dL.

Table 3. Comparisons of the HOMA-IR levels according to metabolic syndrome and metabolic syndrome scores in obesity subjects
(N=1,860)

	HOMA-IR (M±SD) non-adjusted (95%, CI)	*P*	HOMA-IR (M±SE) adjusted* (95%, CI)	*P*
MSS 0	2.14±0.81 (1.99~2.30)	<0.001	2.41±0.17 (2.06~2.75)	<0.001
1	2.40±0.95 (2.30~2.50)		2.55±0.01 (2.36~2.74)	
2	3.00±1.81 (2.85~3.15)		2.99±0.08 (2.84~3.14)	
3	3.48±1.80 (3.32~3.64)		3.41±0.08 (3.26~3.57)	
≥4	4.24±2.53 (3.98~4.49)		4.12±0.09 (3.93~4.29)	
Non-mets	2.69±1.50 (2.61~2.79)	<0.001	2.65±0.07 (2.51~2.79)	<0.001
Mets	3.80±2.17 (3.66~3.94)		3.76±0.06 (3.64~3.88)	

Abbreviations: MSS, metabolic syndrome score; Non-Mets, non-metabolic syndrome; Mets, metabolic syndrome.
*Adjusted for age, gender, BMI, TC, and 25(OH)D.

Table 4. Comparisons of the HOMA-*B* levels according to metabolic syndrome and metabolic syndrome scores in obesity subjects (N=1,860)

	HOMA-*B* (M±SD) non-adjusted (95%, CI)	*P*	HOMA-*B* (M±SE) adjusted* (95%, CI)	*P*
MSS 0	145.82±54.39 (135.39~156.24)	<0.001	146.19±7.12 (132.22~160.16)	<0.001
1	142.82±70.55 (135.38~150.26)		141.83±3.92 (134.14~149.51)	
2	142.66±66.44 (137.01~148.32)		141.09±3.09 (135.02~147.15)	
3	129.33±70.99 (122.46~136.19)		130.44±3.22 (124.12~136.76)	
≥4	119.15±86.69 (110.34~127.97)		120.73±3.79 (113.30~128.16)	
Non-mets	143.06±66.69 (139.09~147.25)	<0.001	143.03±2.96 (137.23~148.83)	<0.001
Mets	124.96±81.94 (119.35~130.27)		125.59±2.52 (120.64~130.53)	

Abbreviation: See Table 3.
*Adjusted for age, gender, BMI, TC, and 25(OH)D.

2.75) for MSS 0, 2.55±0.01 (95% CI, 2.36~2.74) for MSS 1, 2.99±0.08 (95% CI, 2.84~3.14) for MSS 2, 3.41±0.08 (3.26~3.57) for MSS 3, and 4.12±0.09 (95% CI, 3.93~4.29) for MSS ≥ 4. The HOMA-IR increased as increases of metabolic syndrome components (P<0.001). In addition, the HOMA-IR of metabolic syndrome group [3.76±0.06 (95% CI, 3.64~3.88)] was significantly higher (P<0.001) than the non-metabolic syndrome group [2.65±0.07 (95% CI, 2.51~2.79)]. In terms of the HOMA-*B* by MSS values after adjusting for age, gender, BMI, TC, and 25(OH)D, the HOMA-*B* [M±SE (95% CI)] were 146.19±7.12 (95% CI, 132.22-160.16) for MSS 0, 141.83±3.92 (95% CI, 134.14~149.51) for MSS 1, 141.09±3.09 (95% CI, 135.02~147.15) for MSS 2, 130.44±3.22 (95% CI, 124.12~136.76) for MSS 3, and 120.73±3.79 (95% CI, 113.30~128.16) for MSS ≥4. The HOMA-*B* decreased as increases of metabolic syndrome components (P<0.001). In addition, the HOMA-*B* of metabolic syndrome group [125.59±2.52 (120.64~130.53)] was significantly lower (P<0.001) than the non-metabolic syndrome group [143.03±2.96 (95% CI, 137.23~148.83)].

DISCUSSION

The present study investigated the association between metabolic syndrome and its components and HOMA-*B* levels using data from the KNHANES V-I. Although individually, its components may not be associated with the HOMA-IR and HOMA-*B* levels, metabolic syndrome and MSS were positively associated with the HOMA-IR levels and inversely associated with the HOMA-*B* levels (Tables 3, 4).

Many previous studies have shown that IR is associated with metabolic syndrome and its components. Yin et al [23] reported that all of the metabolic syndrome components were associated with the HOMA-IR of Chinese children and teenagers (P<0.001). Ying et al [24] reported that all of the metabolic syndrome components were associated with the HOMA-IR in young Chinese men (P< 0.001). In addition, Yamada et al [25] reported that all of the metabolic syndrome components were associated with the HOMA-IR in Japanese adults (P<0.001). In populations with obesity, the association between metabolic syndrome components and the HOMA-IR vary across the ethnic groups and countries. Gobato et al [26] evaluated the association between the HOMA-IR and metabolic syndrome in adolescent with obesity. SBP (P =0.352), DBP (P=0.182), and TGs (P=0.051) are not significantly associated with insulin resistance. On the other hand, Margoth et al [27] evaluated the association between IR and metabolic syndrome in Bolivian children and adolescents with obesity. High TGs (P=0.0025) and high blood pressure (P= 0.0148) are significantly associated with insulin resistance. In the present study, abdominal obesity (P<0.001), reduced HDL-C (P<0.001), elevated FBG (P<0.001), and elevated TGs (P<0.001) are significantly associated with the HOMA-IR levels, but the elevated BP (P=0.054) was not significantly

associated with the HOMA-IR, and metabolic syndrome and increases of its components were positively associated with IR.

Studies on the association between beta cell function and metabolic syndrome components are not so much, and previous results were not consistent according to healthy subjects and subjects with disease, country and ethnicity [13, 28, 29]. Imamura et al [28] conducted the association between the risk factors of type 2 diabetes mellitus (T2DM) and IR and beta cell function in the Cardiovascular Health Study and they suggested that HOMA-*B* was positively associated with the elevated TGs and FBG, but was not associated with the elevated BP and reduced HDL-C. Garg et al [29] evaluated the association between beta cell function and metabolic syndrome in the USA adults and they suggested that beta cell function was positively associated with fasting plasma glucose and waist hip ratio, but was not associated with hypertension, TGs and HDL-C. On the other hand, Haffner et al [13] reported that all of the metabolic syndrome components were not associated with beta cell function in Mexican Americans and non-Hispanic Whites. In the present study, the HOMA-*B* levels were significantly lower in the elevated BP ($P<0.001$) and elevated FBG groups ($P<0.001$) than the normal group, but they were not associated with the elevated TGs group ($P=0.169$). Whereas, the HOMA-*B* levels of the abdominal obesity ($P=0.003$) and reduced HDL-C groups ($P=0.030$) were significantly higher than those of the normal group. However, if the metabolic syndrome components occur simultaneously, they decrease the HOMA-*B* levels. Currently, research on the association between beta cell function and the metabolic syndrome components is lacking. Baez-Duarte et al [11] reported that the progressive deterioration of insulin sensitivity and beta cell function in subjects with metabolic syndrome as the number of features of metabolic syndrome increases in Mexican subjects. Cubeddu and Hoffmann [12] reported that beta cell function and insulin sensitivity were inversely associated with a number of metabolic syndrome components in apparently healthy Latin-American subjects. In addition, Garg et al [29] reported that increasing number of metabolic abnormalities was inversely associated with the HOMA-*B* levels in USA adults. In the present study is performed for obese population, although individual components may not be associated with the HOMA-*B* levels, increases of metabolic syndrome components were inversely associated with the HOMA-*B* levels ($P<0.001$).

Obesity is the one of the factors responsible for T2DM. However, in order to develop into hyperglycemia, the human body must fail to produce sufficient insulin, and this is associated with the beta cells that secrete insulin. Even in the populations with obesity, in the absence of IR, beta cells are activated for insulin secretion when blood glucose increases [30, 31]. However, the beta cell function or mass is significantly reduced in subjects with IR, such as T2DM and metabolic syndrome [32, 33]. In previous studies [34, 35], decreases in pancreatic beta cell mass were mainly seen in subjects with IR, implying that it is caused by an increase in beta cell apoptosis or necrosis or autophagy in the state of IR. Metabolic syndrome is characterized by IR [5], and the risk factors of metabolic syndrome are the strongly associated with oxidative stress or the elevated circulating concentration of free fatty acids [36], Oxidative stress increases in response to the increased production of reactive oxygen species, which is increased by the decrease of antioxidant enzymes. In particular, endoplasmic reticulum stress is caused by prolonged high lipid molecules or insulin production, such as free fatty acids [9]. The de-differentiation and death of pancreatic beta cells are caused by IR [11], oxidative stress [37], and increased endoplasmic reticulum stress [38].

In conclusions, the relationship between the HOMA-*B* levels and individual metabolic syndrome components varies between countries and races. In the present study, although individual components of metabolic syndrome may not be associated with HOMA-IR and HOMA-*B* levels, metabolic syndrome component increases were positively associated with

insulin resistance and inversely associated with beta cell function in Korean adults with obesity. The present study has a limitation. Because this study was a cross-sectional study, the ability to establish a causal relationship between metabolic syndrome and the increased its components and pancreatic beta cell dysfunction was limited. Therefore, the more accurate results might be obtained by performing a cohort study.

요 약

본 연구는 대한민국 비만 성인에서 대사증후군과 대사증후군 구성요소의 증가와 인슐린저항성(homeostasis model assessment of insulin resistance, HOMA-IR) 및 베타세포 기능(homeostasis model assessment of beta cell function, HOMA-*B*)의 관련성을 조사하였다. 본 연구는 2010년 국민건강영양조사 자료(2010 Korean National Health and Nutrition Examination Survey, KNHANES V-1)의 20세 이상 성인 1,860명을 대상으로 실시하였다. 본 연구의 주요한 결과는 다음과 같다. 첫째, 대사증후군(P<0.001) 및 대사증후군 구성요소의 증가(P<0.001)는 HOMA-IR의 증가와 관련이 있었다. 둘째, 증가된 혈압군(P<0.001)과 증가된 혈당군(P<0.001)의 HOMA-*B*는 정상군보다 낮았고, 복부비만군(P=0.003)과 감소된 저밀도 콜레스테롤군(P=0.030)의 HOMA-*B*는 정상군보다 높았다. 그럼에도 불구하고 대사증후군 및 대사증후군 구성요소의 증가에 따라 HOMA-*B*은 감소하였다. 결론적으로, 대한민국 비만 성인에서 대사증후군 및 대사증후군 구성요소의 증가에 따라 인슐린저항성은 증가하였고 베타세포기능은 감소하였다.

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