

Relationship between Metabolic Syndrome Categorized by Newly Recommended by International Diabetes Federation Criteria with Plasma Homocysteine Concentration

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Abstract. Plasma total homocysteine (tHcy) is an independent risk factor for cardiovascular disease and increased tHcy levels have been reported to be a novel risk factor of atherosclerotic disease. The aim of this study was to assess the association of the metabolic syndrome components with plasma (tHcy) level. Total 722 participants (284 men, 438 women) from the medical checkup program were enrolled in this study. The clinical characteristics and biochemical parameters of the subjects were assessed and the tHcy levels were compared according to the components of metabolic syndrome diagnosed by Adult Treatment Panel (ATP) III guideline and International Diabetes Federation (IDF) criteria. Among the components, groups with larger waist circumference and higher fasting blood glucose levels showed significantly higher tHcy level than the counterparts. Although statistically insignificant, mean concentrations of tHcy was higher in subjects with metabolic syndrome defined by both criteria. In multiple regression analysis, age, sex and systolic blood pressure were the independent determinants of tHcy level. In conclusion, tHcy level was not associated with metabolic syndrome defined by either criteria in Korean subjects.

Key words: Homocysteine, Metabolic syndrome, Insulin resistance, International Diabetes Federation criteria

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PLASMA total homocysteine is an amino acid with a sulfa group that is generated during methionine metabolism and since, homocysteine is produced from methionine, intake of large amounts of methionine would presumably increase serum homocysteine levels [1]. Increased tHcy levels have been reported to be a new risk factor of atherosclerotic disease [2–5]. Plasma homocysteine induces the functional impairment of vascular endothelial cells, oxidation of low density lipoprotein cholesterol, proliferation of vascular smooth muscles and other various actions on vascular cells and it activates blood coagulation factors and so induces

thrombosis [6–9].

The plasma insulin concentration has an effect on the metabolism of tHcy by influencing the glomerular filtration rate or the activity of 5,10-methylenetetrahydrofolate reductase [10–11]. Research in rat models has proposed that insulin alters the activity of metabolic enzymes involved in the turnover of Hcy [12], suggesting the pathogenetic involvement of insulin resistance with Hcy levels. According to recent studies, the tHcy levels correlates well with the plasma insulin concentration, and increased tHcy levels in insulin resistant subjects, such as patients with polycystic ovarian syndrome, have been reported [13]. However, in most studies, the concentration tHcy in type 2 diabetes patients and the control group has been reported to be comparable [14–16].

Metabolic syndrome is a cluster of various diseases, such as hypertension, obesity, dyslipidemia and hyperglycemia, in which insulin resistance plays a key role

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as the pathogenesis [17, 18]. It has been proposed that this syndrome is a powerful determinant of diabetes and cardiovascular disease [19]. Among the various diagnostic criteria published up to date, the National Cholesterol Education Program's 3rd Adult Treatment Panel (ATP III) definition is overwhelmingly the most common definition used in research studies, although numerous limitations have been proposed in multiple studies [20–22]. Recently, the International Diabetes Federation (IDF) published a new world-wide definition of metabolic syndrome that is intended to be applicable to various ethnic groups [23]. This new definition basically agrees with ATP III definition but introduces some important changes in that the presence of central obesity is mandatory in the diagnosis of metabolic syndrome and specified cutoffs of waist circumference for different ethnic groups emphasizing abdominal obesity as the core feature of metabolic syndrome. These two criteria for metabolic syndrome confers somewhat different aspects in the prediction of cardiovascular diseases and diabetes, but not much comparable data are available concerning the internal features of the criteria.

This study was performed to analyze the association of tHcy level with metabolic syndrome, diagnosed according to either ATP III guideline or newly recommended guideline by IDF, and with its individual components in Korean adults.

Subjects and Methods

Study population

Among the individuals who underwent physical examinations at Kangbuk Samsung Hospital, Sungkyunkwan University, from January 2004 to March 2004, this study was performed on 722 individuals (284 males and 438 females) whose plasma homocysteine levels were measured. The patients who were suspected of having malignant tumor, acute infectious diseases, acute inflammatory diseases, thyroid diseases, renal diseases and etc. were excluded from the study.

Anthropometric measurement and blood chemistry

Height, weight, the waist-hip circumference and the systolic and diastolic blood pressure were measured;

blood pressure was measured according to the Hypertension Detection and Follow-up Program protocol by using a mercury blood pressure device after the subjects had rested longer than 5 minutes [24]. For the cases with a systolic pressure higher than 140 mmHg and a diastolic blood pressure higher than 90 mmHg, the BP was measured two more times after resting, and the average value was used. The height and weight were measured by an automatic scale, and body mass index was obtained by the calculation applying the measured height and weight (kg/m^2). The waist circumference was measured at the umbilical level with the subject standing straight up, and the hip circumference was measured in the trochanter area of the pelvis. As for the body components, the amount of body fat, the body fat ratio and the ratio of abdominal fat were measured using a bioelectric impedance analyzer (Inbody720, Biospace CO. Ltd, Korea).

Venous blood was collected after confirming a 12 hour or longer fasting state by the subjects; the serum uric acid concentration, fasting serum glucose concentration, total cholesterol concentration, serum triglyceride concentration, high density lipoprotein cholesterol (HDL-C) concentration and low density lipoprotein cholesterol (LDL-C) concentration were measured by an automated analyzer (Advia 1650, Bayer, Germany). The serum uric acid concentration was measured by applying the Uricase EMST method, and the fasting glucose concentration was measured by using the Hexokinase method (Hitachi 747 automatic analyzer, Hitachi, Japan). The fasting insulin concentration was measured by immunoradiometric assay (Biosource, Belgium); the intra-assay coefficient of variance was 2.1–4.5%, and the inter-assay coefficient of variance was 4.7–12.2%. The total cholesterol concentration and serum triglyceride concentration were measured by an enzymatic calorimetric test, the concentration of HDL-C was measured by a selective inhibition method, and the concentration of LDL-C was measured by the homogenous enzymatic calorimetric test.

Plasma total Hcy was assayed by fluorescence polarization immunoassay (FPIA) by the IMx Analyzer[®] (AxSYM Abbott Inc, USA) in an identical manner in both laboratories; with intra-assay coefficient of variance of 4% and 2.6%, respectively, for a level of 7 $\mu\text{mol}/\text{l}$ and 2% and 3.4%, respectively, at a level of 12 $\mu\text{mol}/\text{l}$, and interlaboratory correlation of $r = 0.63$.

As a marker of insulin resistance, homeostasis model assessment (HOMA)-insulin resistance (IR) was used,

and the calculation formula was as follows [25]:

HOMA-IR: $[\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glycemia } (\text{mmol/L})]/22.5$

The diagnosis of metabolic syndrome

Based on the modified ATP III standard and , the diagnosis of metabolic syndrome was made when the subject satisfied more than 3 categories among the 5 categories described below [21]:

- Abdominal obesity: a waist circumference >90 cm in males and a waist circumference >88 cm in females [26]
- Hypertriglyceridemia: ≥ 150 mg/dL
- HDL-C: <40 mg/dL in males and <50 mg/dL in females
- Hypertension: $\geq 130/85$ mmHg
- Fasting hyperglycemia: ≥ 100 mg/dL

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have [23]:

Central obesity: defined with ethnicity specific values (≥ 90 cm in men, ≥ 80 cm in women in this study)

Plus any two of the following four factors:

1. Hypertriglyceridemia: ≥ 1.7 mmol/L (150 mg/dL), or specific treatment for this lipid abnormality
2. Low HDL-C : <1.0 mmol/L (40 mg/dL) in males and <1.3 mmol/L (50 mg/dL) in females, or specific treatment for this lipid abnormality
3. Hypertension: $\geq 130/85$ mmHg, or treatment of previously diagnosed hypertension
4. Fasting hyperglycemia: ≥ 5.6 mmol/L (≥ 100 mg/dL)

The diagnoses of hypertension and diabetes

Hypertension was defined as the cases with a systolic blood pressure higher than 140 mmHg and a diastolic blood pressure higher than 90 mmHg, which was determined according to the JNC 7, 2003 [27]. Diabetes was determined by applying the standard selected by the 57th American Diabetes Society in 1997, among the following three categories: (1) patients with diabetic symptoms and a random serum glucose ≥ 200 mg/dL, (2) after longer than 8 hours fasting, the patients with ≥ 126 mg/dL fasting serum glucose, and (3) 2 hours after a oral glucose tolerance test, the patient with ≥ 200 mg/dL serum glucose etc. The cases showing more than 1 of these categories as detected more than twice

on different days were defined as being diabetic [28].

Statistical analysis

Statistical analysis was performed by applying the Windows SPSS program (version 13.0; Chicago, Ill, USA). The statistic results were presented as the mean \pm standard deviation or as the 95% confidence level. For the comparison of mean values between two groups of subjects divided according to the presence or absence of the components of or the metabolic syndrome itself, Student *t*-test was used, and the comparison of the values among the groups categorized by the numbers of the metabolic components and the tHcy quartile groups were analyzed by ANOVA test. Correlation analyses were performed with Pearson's correlation analysis, and partial correlation analyses were done with the adjustment for age, sex and serum creatinine. Backward multiple regression analysis was performed to analyze the significant determinants of tHcy. *P* values less than 0.05 were considered to be statistically significant.

Results

Baseline characteristics of the subjects

For total of 722 individuals (284 males and 438 females), their mean age was 58.6 ± 6.5 years and the mean tHcy was 9.51 ± 4.06 $\mu\text{mol/L}$. Mean value for tHcy was higher in males than females (11.4 ± 5.3 vs. 8.3 ± 2.3 $\mu\text{mol/L}$, $p < 0.01$).

The fasting glucose level, serum triglyceride concentration, serum HDL-C and serum LDL-C was 100.3 ± 26.6 mg/dL, 140.4 ± 70.8 mg/dL, 57.8 ± 12.5 mg/dL and 123.6 ± 32.0 mg/dL, respectively, and the body mass index, the waist circumference, and HOMA index were 24.5 ± 2.9 kg/m², 81.6 ± 7.8 cm and 2.15 ± 1.0 , respectively (Table 1).

The differences in homocysteine values according to the presence or absence of metabolic syndrome components

Mean homocysteine levels were compared between two groups divided by each components of metabolic syndrome (Table 2). Subjects with larger waist circumference and higher fasting blood glucose levels

Table 1. Baseline Characteristics of Study Population

	Total (n = 722)
Age (years)	58.6 ± 6.5
Sex (Male)	284 (39.3%)
Waist circumference (cm)	81.6 ± 7.8
BMI (kg/m ²)	24.5 ± 2.9
Fat mass	17.8 ± 5.4
Fat mass ratio	28.2 ± 6.9
Abdominal Fat ratio	0.91 ± 0.04
Systolic blood pressure (mmHg)	127.3 ± 19.1
Diastolic blood pressure (mmHg)	78.0 ± 9.8
Total cholesterol (mg/dL)	204.3 ± 36.4
Triglyceride (mg/dL)	140.4 ± 70.8
HDL-cholesterol (mg/dL)	57.8 ± 12.5
LDL-cholesterol (mg/dL)	123.6 ± 32.0
Fasting Glucose (mg/dL)	100.3 ± 26.6
Fasting Insulin (IU/L)	8.7 ± 3.2
HOMA-IR	2.15 ± 1.0
Uric acid (mg/dL)	4.82 ± 1.24
Homocysteine (μmol/L)	9.51 ± 4.06
Diabetes mellitus (%)	59 (8.2%)
Hypertension (%)	274 (38.0%)
Metabolic syndrome (%)	
Modified ATPIII	215 (29.8)
IDF	201 (27.8)

Values are mean ± SD

BMI, body mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance

Table 2. The differences in homocysteine values according to the presence or absence of metabolic syndrome components

	N = 722	Homocysteine (μmol/L)	p value
Waist circumference (cm)			
≥90 for men/≥80 for women	285	9.83 ± 4.37	0.008
<90 for men/<80 for women	437	9.01 ± 3.48	
Triglyceride (mg/dL)			
≥150	265	9.45 ± 2.49	0.786
<150	457	9.54 ± 4.74	
HDL cholesterol (mg/dL)			
<40 for men/<50 for women	195	9.61 ± 3.19	0.691
≥40 for men/≥50 for women	527	9.47 ± 4.34	
Blood pressure (mmHg)			
≥130/85	146	9.65 ± 2.65	0.619
<130/85	576	9.46 ± 4.34	
Fasting glucose (mg/dL)			
≥100	226	9.96 ± 5.25	0.042
<100	496	9.30 ± 3.37	

Difference of the means, HDL: high density lipoprotein cholesterol

Table 3. Comparisons of mean homocysteine values according to the clustered features and the presence or absence of metabolic syndrome

Numbers of the features*	N = 722 (%)	Homocysteine (μmol/L)	<i>p</i> value
0	137 (19.0)	9.01 ± 4.29	0.137
1	175 (24.2)	9.06 ± 3.11	
2	195 (27.0)	10.05 ± 5.33	
3	163 (22.6)	9.71 ± 3.32	
4	45 (6.2)	9.57 ± 2.24	
5	7 (1)	10.35	
Modified ATP III guideline			
With metabolic syndrome	215 (29.8)	9.70 ± 3.08	0.41
Without metabolic syndrome	507 (70.2)	9.43 ± 4.41	
IDF guideline			
With metabolic syndrome	201 (27.8)	9.65 ± 3.00	0.565
Without metabolic syndrome	521 (72.2)	9.45 ± 4.40	

* Features of the MS: high waist circumference, high triglyceride, low HDL cholesterol, high blood pressure and high fasting glucose levels

Table 4. Mean HOMA-IR values according to homocysteine quartile groups

Groups	N (=722)	HOMA-IR (95% CI)
I	179	2.07 (1.93~2.21)
II	179	2.19 (2.04~2.33)
III	185	2.24 (2.10~2.40)
IV	169	2.12 (1.95~2.28)

No significant differences were observed among the groups based on One-way ANOVA test.

Groups I: 0–7.48

Group II: 7.49–8.84

Group III: 8.85–10.80

Group IV: 10.81–

showed significantly higher tHcy levels ($p < 0.05$), and subjects with higher triglycerides, lower HDL-C and higher blood pressure showed higher tHcy levels, but without significance (Table 2).

Differences in homocysteine values for clustered features of metabolic syndrome and HOMA-IR

No significant differences in the serum tHcy levels were detected according to the number of satisfied risk factors of metabolic syndrome (Table 3). tHcy levels were higher in subjects with metabolic syndrome defined by both the criteria, although not statistically significant (Table 3).

There were no significant differences in mean

Table 5. Correlation coefficients of homocysteine with multiple characteristic variables before and after adjustment for sex, age and serum creatinine

	Bivariate correlation		Partial correlation	
	coefficient	<i>p</i> value	coefficient*	<i>p</i> value
Age (years)	0.213	<0.01	—	—
Waist circumference (cm)	0.101	0.007	−0.032	0.398
BMI (kg/m ²)	−0.054	0.144	−0.009	0.812
Fat mass	−0.135	<0.01	0.001	0.980
Fat mass ratio	−0.223	<0.01	0.032	0.394
Abdominal Fat ratio	0.047	0.209	0.011	0.762
Systolic blood pressure (mmHg)	0.109	0.003	0.049	0.196
Diastolic blood pressure (mmHg)	0.109	0.003	0.041	0.271
Total cholesterol (mg/dL)	−0.052	0.161	−0.023	0.540
Triglyceride (mg/dL)	0.020	0.597	−0.057	0.126
HDL-cholesterol (mg/dL)	−0.087	0.252	−0.009	0.821
LDL-cholesterol (mg/dL)	−0.023	0.539	0.005	0.901
Fasting Glucose (mg/dL)	0.007	0.848	−0.031	0.415
Fasting Insulin (IU/L)	0.011	0.776	0.040	0.290
HOMA-IR	0.016	0.672	0.020	0.603
Uric acid (mg/dL)	0.337	<0.01	0.140	<0.001

BMI, body mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance

* Partial correlation analyses were performed with adjustment for age, sex and serum creatinine

HOMA-IR values among the 4 groups divided according to their concentration of the tHcy (Table 4).

Association of homocysteine with insulin resistance and the cardiovascular risk factors

In the simple correlation analyses of tHcy levels with cardiovascular risk factors, positive correlations were seen with age, waist circumference, blood pressure and uric acid, and inverse correlations were seen with fat mass, and these correlations were statistically insignificant after adjustment for age, sex and serum creatinine levels except uric acid (Table 5).

In multiple regression analysis, age, gender and uric acid were found to be the independent risk factors for serum homocysteine level (Table 6).

Discussion

In this study, tHcy levels failed to show statistically significant association with metabolic syndrome defined by either the modified NCEP-ATP III or newly recommended IDF criteria, although subjects with positive components of or metabolic syndrome itself showed higher levels of tHcy and positive components

Table 6. Multiple linear regression analysis showing association between homocysteine and characteristic variables of study population

Predictor variable	Regression coefficient	<i>p</i> value
Age	0.132	<0.01
Sex	0.237	<0.01
Waist circumference	−0.051	0.159
Systolic BP	0.037	0.288
Total Cholesterol	−0.026	0.456
Triglyceride	−0.029	0.392
Fat mass	−0.024	0.518
HOMA-IR	0.006	0.172
Uric acid	0.207	<0.01
$R^2 = 0.185$		

than those without the components or metabolic syndrome by either criteria, in the individuals undergoing medical checkups in a university hospital in Korea. In addition, the degree of insulin resistance, calculated by HOMA-IR also failed to show significant association with tHcy levels. In multiple regression analysis, age, sex and uric acid levels were the independent determinants for tHcy. Since male subjects showed significantly higher tHcy levels than females, all the analyses were repeated separately in each gender

groups; however, no significant associations were observed between tHcy and metabolic syndrome in either group (data not shown).

Homocysteine is an amino acid that contains sulfa groups, and an intermediate metabolite of methionine metabolism, an essential amino acid. In 1969, McCully *et al.* [29] reported several cases systemic arterial thrombosis and atherosclerosis in homocystinuria pediatric patients, and they suggested that hyperhomocysteinemia might induce atherosclerosis. The increased tHcy concentration is known to be caused by genetic causes, aging, menopause, hypothyroidism, deficiency of vitamin cofactors (B₆, B₁₂, folate), chronic renal diseases, and since homocysteine is produced from methionine, intake of large amounts of methionine would presumably increase serum homocysteine levels [1]. Meat, fish and dairy are all good sources of methionine and vegetables containing folic acid, beta-carotene and vitamin C effectively lowered homocysteine levels [30–35]. The results of this study have limitation in that the pattern of food intake of the participants were not considered in the analyses, since the amount of foods taken that could affect the serum homocysteine levels could have affected the tHcy levels.

The studies on the relationship between tHcy levels and metabolic syndrome or insulin resistance shows conflicting results. Godsland *et al.* [36] examined the association of homocysteine concentrations with insulin sensitivity, as measured by a glucose tolerance test, and with the components of metabolic syndrome in healthy males, and showed that homocysteine metabolism was not affected by insulin action. In addition, Abbasi *et al.* and Pouwels *et al.* [37, 38] have reported that tHcy was unrelated with insulin resistance in healthy volunteers and diabetic subjects, even after the improvement of insulin sensitivity. In contrast, in a recent work by Bjorck *et al.* analysed in a population-based sample of Swedish subjects, positive association between serum insulin and serum Hcy independent of age and sex were observed [39], suggesting the possible link between the metabolic syndrome and Hcy. They suggested two plausible theories to explain their results. Increased insulin levels in insulin resistant subjects affect the activity of enzymes that are critical in the metabolism of Hcy leading to its accumulation in human body. In an alternative theory, elevated Hcy

levels damage the endothelium through the generation of reactive oxidative chemicals, hampering the vasodilating function of nitric oxide and thus will aggravate insulin resistance. In both cases, insulin resistance seems to be an important factor, with strong possibility that the presence of metabolic syndrome, in which insulin resistance is the most important pathogenic mechanism, would lead to elevated Hcy concentrations and vice versa. In another study performed in a small group of Turkish subjects, tHcy level was higher in subjects with metabolic syndrome defined by NCEP-ATP III guideline [40, 41]. There are several other studies from various ethnic groups and population size, reporting the relationship between metabolic syndrome or insulin resistance and tHcy levels, but the results are too diverse to draw a conclusion [42–44].

In this study, neither insulin resistance assessed by HOMA-IR nor the presence of metabolic syndrome defined by the two mostly popular criteria, showed significant association with tHcy levels in 772 Korean subjects. The discrepancies seen between the results of ours and the previous study results performed in various ethnic and age groups, cannot be easily explained. However, since homocysteine is affected by diverse factors, such as genetic, cultural, and socioeconomic backgrounds, and the food intake patterns, the discrepancies could be due to the effects of these different factors. Therefore, if the precise conclusion is to be drawn out, all these confounding factors have to be considered and adjusted in the course of analyses, which could be a very difficult process.

Diverse results are reported from studies on tHcy, insulin resistance and metabolic syndrome factors in the literature. Our study result failed to show any significant association between tHcy levels and metabolic syndrome defined by two different criteria or insulin resistance in Korean population. Since this was a cross section study, it was not sufficient to prove any cause-effect relation of tHcy with insulin resistance or metabolic syndrome. However, our study was meaningful as the first study performed in this far east Asian population. To clarify whether hyperhomocysteinemia is the independent marker for metabolic syndrome or not, better designed and larger scaled prospective studies have to be preformed in diverse ethnic and age groups in the future.

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