

## Cardio-Metabolic Features of Type 2 Diabetes Subjects Discordant in the Diagnosis of Metabolic Syndrome

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**Background:** The aim of this study is to investigate the cardio-metabolic parameters and surrogate markers of insulin resistance in a discordant group of type 2 diabetes (T2DM) subjects who satisfy the Adults Treatment Panel (ATP) III criteria, but not the International Diabetes Federation (IDF) criteria, for metabolic syndrome (MetS).

**Methods:** We assessed the prevalence of MetS in T2DM subjects ( $n = 167$ ) who were selected from subjects registered at the diabetes center of Dong-A University Medical Center. We used the ATP III criteria and the IDF criteria for the diagnosis of MetS and sorted the subjects into 2 MetS groups: one group diagnosed per ATP III criteria (MetS<sub>a</sub>) and one diagnosed per IDF criteria (MetS<sub>i</sub>). We then compared the clinical characteristics, metabolic parameters (homeostasis model assessment of insulin resistance, aspartate aminotransferase, alanine aminotransferase, and uric acid values) and co-morbidities (prevalence of microalbuminuria, fatty liver, and cardiovascular disease) between the MetS<sub>a</sub>, MetS<sub>i</sub>, and discordant MetS groups.

**Results:** The prevalence of MetS in the MetS<sub>a</sub> group (73.6%) was higher than in the MetS<sub>i</sub> group (62.2%). The MetS prevalence in the discordant group was 11.4%. The discordant group showed no significant differences in clinical characteristics (except waist circumference and body mass index), metabolic parameters, or prevalence of co-morbidities, as compared with subjects with MetS by both criteria.

**Conclusion:** In this study, cardio-metabolic features of the subjects diagnosed with MetS using ATP III criteria, but not IDF criteria, are not significantly different from those of subjects diagnosed with MetS using both criteria.

**Keywords:** Diabetes mellitus; Discordant group; Metabolic syndrome; Waist circumference

### INTRODUCTION

Metabolic syndrome (MetS) is described as a cluster of cardiovascular risk factors associated with insulin resistance [1]. The identification of MetS among subjects with type 2 diabetes (T2DM) is important because of the higher cardiovascular

risk [2-5]. During the past decade, there have been various attempts to standardize the definition of MetS as a diagnostic category, with several institutions proposing various criteria [6-8]. Also, there have been reports comparing each criteria with respect to the prediction of cardiovascular risk [9-12].

Ethnicity-specific waist circumference (WC) cut-off points

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were incorporated into the International Diabetes Federation (IDF) new definition of MetS in 2005 [8]. For the first time, the IDF provided different obesity cut-off points for different ethnic groups. The IDF suggested WC cut-off points for South Asians including Chinese, of 90 cm (male) and 80 cm (female). Nevertheless, there are different opinions in Asia [8,13]. The Korean Society for the Study of Obesity (KSSO) [14] has provided a WC cut-off point for obesity of 90 cm (male) and 85 cm (female).

The updated Adults Treatment Panel (ATP) III criteria [15] from the American Heart Association/ National Heart, Lung, and Blood Institute maintain the ATP III criteria [6], with minor modifications. The threshold for impaired fasting glucose was reduced from 110 to 100 mg/dL, and lower WC were applied to Asians, as with the IDF criteria. In this study, the term the 'ATP III criteria' refers to the updated ATP III criteria for MetS.

Discordant cases that satisfy the ATP III criteria, but not the IDF criteria, may exist because the IDF criteria require central obesity as a prerequisite for the diagnosis of MetS.

A previous report on a discordant group of general population Koreans showed paradoxically more adverse metabolic profiles and unfavorable lifestyles than those diagnosed with MetS by both the IDF and ATP III criteria [16].

From this report we have come to wonder if such a finding also would be found in T2DM subjects. Thus, we hypothesized that a discordant group of T2DM subjects would also have similar clinical features as T2DM patients with MetS by both criteria. To prove this hypothesis we compared the clinical characteristics and cardio-metabolic parameters, including surrogate markers for insulin resistance, between a discordant group and subjects with MetS defined by both ATP III and IDF criteria.

## METHODS

### Subjects

This was a cross-sectional study of 167 subjects with T2DM, between 20 and 70 years of age, who were recruited from ambulatory patients presenting at the Diabetes Center, Dong-A Medical Center between September 2005 and July 2007. Subjects were eligible if they had been diagnosed with clearly documented T2DM and without secondary causes of diabetes (chronic renal failure, active hepatic disease). Subjects were excluded if they had been receiving insulin or had a history of

type 1 diabetes. Those who had malignancy, autoimmune thyroid disease, chronic hepatitis B, chronic hepatitis C, renal disease, or other acute illness were excluded. Those who consumed more than 40 g alcohol per day were also excluded.

### Definition of MetS

We applied the ATP III criteria and the IDF criteria for the diagnosis of MetS. The ATP III defines MetS as the presence of any three of the following five abnormalities: 1) abdominal obesity (WC  $\geq$ 90 cm for Asian men and  $\geq$ 80 cm for Asian women); 2) triglycerides levels  $\geq$ 150 mg/dL; 3) high density lipoprotein cholesterol (HDL-C) levels  $<$ 40 mg/dL in men and  $<$ 50 mg/dL in women; 4) blood pressure  $\geq$ 130/85 mm Hg or drug treatment for hypertension; and 5) fasting plasma glucose  $\geq$ 100 mg/dL or drug treatment for elevated glucose. The updated ATP III criteria recommend a lower WC cut-off for Asian Americans (i.e.,  $\geq$ 90 cm for men and  $\geq$ 80 cm for women) because Asians are predisposed to insulin resistance, MetS, and T2DM at lower WC than Caucasians. Therefore, we applied the WC  $\geq$ 90 cm for men and  $\geq$ 80 cm for women criteria as cut-off values for central obesity. According to the IDF criteria, MetS is diagnosed in those with a high WC ( $\geq$ 90 cm for South Asian men and  $\geq$ 80 cm for South Asian women) plus any two of the following: triglycerides levels  $\geq$ 150 mg/dL or specific treatment for this lipid abnormality; HDL-C levels  $<$ 40 mg/dL in men and  $<$ 50 mg/dL in women or specific treatment of this lipid abnormality; systolic blood pressure  $\geq$ 130 mm Hg or diastolic blood pressure  $\geq$ 85 mm Hg or treatment of previously diagnosed hypertension; and fasting plasma glucose levels  $\geq$ 100 mg/dL or previously diagnosed T2DM.

We also measured the prevalence of using WC cut-off value  $>$ 90 cm for men and  $>$ 85 cm for women, as recommended by KSSO.

Subjects diagnosed with MetS per the ATP III criteria, but not the IDF criteria, were called the discordant group.

### Collection of data

Information on baseline characteristics (sex, age, duration of diabetes, and presence of hypertension or dyslipidemia) and presence of cardiovascular disease (CVD) and fatty liver were collected from medical records. CVD included cerebral vascular disease, coronary heart disease, and peripheral vascular disease. The diagnosis of fatty liver was based on the results of abdominal ultrasonography, which was done by trained tech-

nicians using a Siemens-Acuson SEQUOIA 512 (Siemens, Erlangen, Germany). The diagnosis of fatty liver was made according to four known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring). We collected data on the presence of fatty liver regardless of the degree of fatty liver.

WC was measured in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest. Experienced nurses measured systolic and diastolic pressure with the subjects in the sitting position after a 15-minute rest. Body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) was calculated by dividing weight (in kilograms) by the square of height (in meters), as a measure of total adiposity. Blood samples were drawn after 8 to 12 hours overnight fasting for the measurement of the lipid profile and fasting plasma glucose levels. Twenty-four-hour urine was collected for the measurement of microalbuminuria. Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR). The following equations were used to calculate HOMA-IR: fasting plasma glucose ( $\text{mmol}/\text{L}$ )  $\times$  fasting insulin ( $\mu\text{U}/\text{mL}$ )/22.5. The amount of albumin in the urine was measured by immunoradiometric assay. The definition of microalbuminuria was 30 to 300 mg per day.

### Statistical analysis

Categorical variables were summarized by counts and relative frequencies; numeric variables, by their mean and standard deviation with range. Differences in characteristics between the discordant group and the MetSa and MetSi groups were tested with *t*-tests for normally distributed variables and with the Wilcoxon-Mann-Whitney test for skewed variables. Fisher's exact test was used for categorical variables.

Odds ratio (OR) for comparison of two groups was summarized with its 95% confidence interval and *P* value using logistic regression.

**Table 1.** Prevalence of metabolic syndrome

	WC 90 cm/80 cm, %	WC 90 cm/85 cm <sup>a</sup> , %
MetS by ATP III criteria	73.6	68.2
MetS by IDF criteria	62.2	54.5
Discordant <sup>b</sup>	11.4	11.7

WC, waist circumference (male/female); MetS, metabolic syndrome; ATP, Adults Treatment Panel; IDF, International Diabetes Federation. <sup>a</sup>By the Korean Society for the Study of Obesity; <sup>b</sup>A group of patients who were satisfying the ATP III but not the IDF criteria.

*P* values lower than 0.05 were considered statistically significant. By its nature, the study was explorative and therefore no adjustment for multiple testing was applied. All statistical analyses were carried out using SAS statistical software (SAS Institute, Cary, NC, USA).

**Table 2.** Clinical and laboratory characteristics of subjects, comparing MetS by IDF criteria with the discordant group

Characteristic	WC 90 cm/80 cm ( <i>n</i> =123)		WC 90 cm/85 cm <sup>a</sup> ( <i>n</i> =114)	
	MetSi	Discor- dant <sup>b</sup>	MetSi	Discor- dant <sup>b</sup>
Total no.	104	19	91	23
Sex				
Male	40	17	40	17
Female	64	2 <sup>d</sup>	51	6 <sup>d</sup>
Age, yr	59±10	61±12	59±11	61±12
Diabetes duration, yr	8±7	8±6	8±7	8±6
WC, cm	119.9±43.1	82.7±5.3 <sup>c</sup>	125.3±43.5	82.8±4.8 <sup>c</sup>
BMI, $\text{kg}/\text{m}^2$	25.6±2.9	22.7±2.8 <sup>c</sup>	25.9±2.9	22.9±2.9 <sup>c</sup>
HbA1c, %	8.4±3.4	8.3±3.1	8.4±3.8	8.6±3.2
C-peptide, ng/mL	2.7±2.5	2.5±2.3	2.8±2.4	2.2±2.0
Total cholesterol, mg/dL	185±35	180±30	187±35	181±31
Triglycerides, mg/dL	167±35	165±33	173±38	163±32
<150	58	9	47	11
≥150	46	10	44	12
HDL, mg/dL	43±19	39±15	42±18	40±16
M: ≥40; F: ≥50	27	5	24	5
M: <40; F: <50	77	14	67	18
LDL, mg/dL	108±28	109±31	110±30	108±29
Hypertension				
No	40	2 <sup>d</sup>	32	4
Yes	64	17	59	19

Values are presented as mean ± standard deviation or number of subjects.

MetS, metabolic syndrome; WC, waist circumference (male/female); BMI, body mass index; HbA1c, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein; ATP, Adults Treatment Panel; IDF, International Diabetes Federation; MetSi, metabolic syndrome by the IDF criteria.

<sup>a</sup>By the Korean Society for the Study of Obesity; <sup>b</sup>A group of patients who were satisfying the ATP III but not the IDF criteria; <sup>c</sup>*P* value <0.05; <sup>d</sup>*P* value <0.05, but not significant due to small sample size.

## RESULTS

### Prevalence of MetS and the discordant group

The prevalence of MetS in the MetSa group was 73.6%, with 68.2% using the KSSO WC cut-off (Table 1). The prevalence of MetS in the MetSi group was 62.2%, with 54.5% using the KSSO WC cut-off. The discordant group thus included 11.4% of subjects and 11.7% when the KSSO WC cut-off value applied. All subjects in the MetSi group satisfied the ATP III criteria for MetS regardless of the cut-off value. Thus, in this study, MetSi has the same meaning as MetS defined by both the ATP III and the IDF criteria.

### Baseline characteristics

The baseline characteristics were not significantly different between the MetSi subjects and the discordant group, except for WC and BMI (Table 2). Because the presence of central obesity (i.e., WC) is mandatory in the IDF criteria, WC and BMI were significantly higher in the MetSi group than in the discordant group.

### Differences in cardio-metabolic parameter between the MetSi and discordant groups

There was not significantly difference in HOMA-IR level between the MetSi and the discordant groups. Plasma levels of aspartate aminotransferase, alanine aminotransferase, and uric acid were not significantly different between the MetSi and the discordant groups (Table 3).

The prevalence of microalbuminuria and CVD was not significantly different between the two groups. These results were similar using the KSSO cut-off value of WC (Table 4).

The prevalence of fatty liver was not significantly different between the two groups. However, when WC was examined per the KSSO cut-off value, it was significantly higher in the MetSi group than in the discordant group ( $P=0.039$ ).

## DISCUSSION

Although there are some differences in the prevalence of MetS in T2DM according to the criteria used, a previous report stated a 58.5%, prevalence of MetS using the IDF criteria [17]. Similarly, we found a MetSi prevalence of 62%. Another previous report found a prevalence of MetSa in T2DM of 77.9% [18], and our result was 73%. The IDF proposed WC cut-off values for South Asians (plus Chinese and Japanese) as 90 cm

**Table 4.** Prevalence of cardiovascular disease, microalbuminuria, fatty liver in the discordant and MetSi groups

WC	No.	Cardiovascular disease	Microalbuminuria	Fatty liver
90 cm/80 cm				
MetSi	104	15 (14.4)	38 (36.5)	71 (68.3)
Discordant <sup>a</sup>	19	4 (21.1)	8 (42.1)	9 (47.4)
90 cm/85 cm <sup>b</sup>				
MetSi	91	14 (15.3)	35 (38.5)	65 (71.4)
Discordant <sup>a</sup>	23	5 (21.8)	9 (39.2)	11 (47.8) <sup>c</sup>

Values are presented as number (%).

MetSi, metabolic syndrome by the IDF criteria; WC, waist circumference (male/female).

<sup>a</sup>A group of patients who were satisfying the ATP III criteria but not the IDF criteria; <sup>b</sup>By the Korean Society for the Study of Obesity (KSSO); <sup>c</sup> $P$  value=0.039, prevalence of fatty liver in discordant vs. MetSi groups according to KSSO cut-off value.

**Table 3.** Comparison of HOMA-IR and plasma levels of AST, ALT, and uric acid between the discordant and MetSi groups

WC	No.	HOMA-IR		AST		ALT		Uric acid	
		Mean±SD	$P$ value	Mean±SD	$P$ value	Mean±SD	$P$ value	Mean±SD	$P$ value
90 cm/80 cm									
MetSi	104	3.7±5.3	0.42	27±13	0.22	34±7	0.53	5±1	0.64
Discordant <sup>a</sup>	19	2.9±3.4	0.42	23±12	0.22	31±22	0.53	5±1	0.64
90 cm/85 cm <sup>b</sup>									
MetSi	91	3.9±5.6	0.18	28±13	0.088	35±17	0.25	5±1	0.48
Discordant <sup>a</sup>	23	2.7±3.1	0.18	23±11	0.088	30±21	0.25	5±1	0.48

$P$  value: discordant vs. MetSi, according to each cut-off value.

HOMA-IR, homeostasis model assessment of insulin resistance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MetSi, metabolic syndrome by the IDF criteria; WC, waist circumference (male/female); SD, standard deviation.

<sup>a</sup>A group of patients who were satisfying the ATP III criteria but not the IDF criteria; <sup>b</sup>By the Korean Society for the Study of Obesity.

for men and 80 cm for women; however, the KSSO proposed WC cut-off values of 90 cm for men and 85 cm for women [14,19]. Until now, there has been no consensus on which WC cut-off value is more accurate in describing Korean obese subjects. We also tried to apply the KSSO WC cut-off and assess the prevalence of MetS. In that case, the prevalence of MetS and MetSa decreased to 54% and 68%, respectively. This slightly lower prevalence of MetS is due to the higher WC cut-off for women, whereas the KSSO WC cut-off for men is the same as the ATP III and IDF value.

The prevalence of the discordant group (11.4%) did not change with the KSSO WC cut-off value (11.7%). This similarity suggests that a male dominant exists in this group. This interpretation is described in Table 2.

We found that the surrogate markers of insulin resistance and cardio-metabolic parameters in the MetSi subjects were very similar to those in the discordant group. Also, the prevalence of cardiovascular disease was not significantly different between subjects in the MetSi and discordant groups. These findings did not change when the KSSO WC cut-off was applied.

There have been reports evaluating the association between MetS and nonalcoholic fatty liver [20,21]. T2DM subjects with nonalcoholic fatty liver frequently accompany MetS [22]. There has even been a report that MetS was a strong predictor of nonalcoholic fatty liver disease [23]. In this study, we found that there were no significant differences in the prevalence of fatty liver between the MetSi and discordant groups; however, the prevalence of fatty liver in the MetSi group was slightly higher than in the discordant group when the KSSO WC cut-off was applied. We presume these contrary findings on the prevalence of fatty liver may be less reliable because of the small sample size and we need further study to solve this confusing problem.

All of these results, except for those on the prevalence of fatty liver, suggested that the discordant group showed a similar phenotype to that of the MetSi group.

Many other studies have suggested similar opinions regarding this. There have been reports that the ATP III criteria have a higher predictive power of CVD risk than the IDF criteria [10-12]. The Joint Interim Statement (JIS) identified specific criteria for the clinical diagnosis of MetS [24]. This statement was an attempt to eliminate some of the confusion regarding how to identify subjects with MetS. Now WC is just one of the criteria that a physician can use when diagnosing MetS by JIS.

There are several limitations to the present study. First, this study was a cross-sectional study involving subjects who were registered at a university hospital. The subjects may not be representative of a general T2DM population. Second, recall bias might have been introduced because the prevalence of CVD was retrospectively obtained and self-reported, and the prevalence of fatty liver was obtained by medical records. Thus under-reporting and misreporting could be a source of bias. The other limitation is the relatively small sample size of the discordant group compared to the MetSi group. Further studies prospectively investigating the cardio-metabolic features of discordant subjects in both general and diabetic populations are needed.

In conclusion, among T2DM subjects, the discordant group had very similar cardio-metabolic features to subjects with MetS as diagnosed by both the ATP III and IDF criteria.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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