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The impact of metabolic syndrome on insulin sensitivity, glucose sensitivity, and acute insulin response after glucose load in early-onset type 2 diabetes mellitus: Taiwan Early-Onset Type 2 Diabetes Cohort Study

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Abstract

Diabetic patients with metabolic syndrome (MetS) have higher lifetime risks for cardiovascular disease, especially in early-onset type 2 diabetes mellitus (EODM). Increased insulin resistance (IR) and impaired insulin secretion are important pathophysiologies in diabetic patients. Therefore, the effects of MetS on IR and insulin secretion in EODM were investigated. Forty-eight EODM (mean age, 22.8 ± 0.6 years) patients were enrolled in this study. Two grouping criteria were used: the first was whether the patient had MetS or not (MetS+ or Met−, with 31 and 17 patients, respectively); and the second was the number of MetS components each group had, that is, MetS (1,2) with 1 to 2, MetS (3) with 3, and MetS (4,5) with 4 to 5 components (17, 17, and 14 patients in each group, respectively). A frequently sampled intravenous glucose tolerance test was performed to measure insulin sensitivity, glucose sensitivity, acute insulin response after glucose load, and disposal index. Severe IR was noted with both homeostasis model assessment and frequently sampled intravenous glucose tolerance test both in MetS+ and MetS−. However, significantly higher acute insulin response after glucose load and disposal index were noted in MetS+ and MetS (4,5) than in Met−, MetS (1,2), and MetS (3), respectively. Early-onset type 2 diabetes mellitus patients with MetS had similar IR to those without MetS. This may be due to early deterioration of insulin action in these subjects. In addition, insulin secretion was higher in subjects with more MetS components, suggesting that EODM patients with MetS had better preserved ability of β-cell compensation for IR than those without MetS.

1. Introduction

Metabolic syndrome (MetS), defined as the clustering of cardiovascular risk factors that include dysglycemia, obesity, dyslipidemia, and high blood pressure, was described in 2001 [1]. It is now considered as a serious clinical and public health problem. The risk for developing cardiovascular disease and type 2 diabetes mellitus in subjects with MetS are 2- and 5-fold higher, respectively, than in individuals without MetS [2]. In adults, the incidence of MetS is estimated to be around 20% in the United States; and it is increasing at an alarming rate [3,4]. The prevalence of MetS in Taiwan is 14.3% to 16.4%, depending on the particular criteria used [5]. It should be noted that, in subjects with type 2 diabetes mellitus, the incidence of MetS increases dramatically to 86% after age 50 years [6]. Not surprisingly, subjects with both type 2 diabetes mellitus and MetS will have a much higher cardiovascular risk than those with only one [6].

In 2000, the American Diabetes Association (ADA) issued a consensus statement to address the increasing occurrence of type 2 diabetes mellitus in children and

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adolescents (early-onset type 2 diabetes mellitus [EODM]) [7]. This phenomenon is observed in many countries, and it is postulated to be linked to the increasing rate of obesity [7]. Despite a lower prevalence of obesity in Asia than in the Western world, obesity has increased from 10.3% to 19.2% in Taiwan in the last decade [5]. Although there is no formal survey of MetS in children at present, it can be premised that the incidence of MetS in EODM is also increasing. Because the complications of diabetes often occur 15 to 20 years after the diagnosis of diabetes, if not well controlled, it can be predicted that these EODM individuals will have complications of diabetes much earlier. This could be a huge burden not only to patients, but also to society. Thus, early detection and proper management for these patients are important issues for health providers.

The ADA also suggested that the initial abnormality of EODM is impaired insulin action that is compounded later by β-cell failure [7]. Our previous report supported this postulation and found that the severities of both defects are similar to those of older type 2 diabetes mellitus patients [8]. Cheal et al [9] have reported that MetS is also related to insulin resistance (IR). Therefore, the purpose of this study was to evaluate whether EODM subjects with MetS should have more severe deteriorated insulin action/and secretion than those without MetS.

2. Materials and methods

2.1. Patients

The Taiwan Early-Onset Type 2 Diabetes Cohort Study was started in 1997 in 3 hospitals: the Tri-Service General Hospital and the Buddhist Tzu Chi General Hospitals in Taipei and Hualien. The diagnostic criteria for EODM were based on the 1997 ADA definition of diabetes [10] and age of onset less than 30 years. The EODM patients enrolled in this study were considered to have type 2 diabetes mellitus rather than type 1 diabetes mellitus or maturity-onset diabetes of the young based on the following: (*a*) although some of the EODM patients had a family history of diabetes, none of their parents had a diagnosis of diabetes before the age of 35 years; (*b*) none of the patients had a history of ketosis; (*c*) diabetes was easily controlled by diet alone or by oral hypoglycemic agents (with mean treatment duration of 2.8 ± 0.4 years) for months before the onset of the study; (*d*) the mean fasting insulin was high, suggesting normal to exaggerated insulin secretion; (*e*) none of the patients had measurable antiglutamic acid decarboxylase autoantibody (GAD-Ab), antimicrosomal antibody, or antinucleotide antibody. After each EODM patient was enrolled, medical history was taken, physical examination was done, blood samples were collected, and a frequently sampled intravenous glucose tolerance test (FSIGT) was performed. Patients were then put on oral hypoglycemic agents according to their condition. They were seen monthly in our clinic, and FSIGT was done biannually. Some of the data have been published previously [8].

There were 48 diabetic (44 men and 4 women) patients enrolled in this study. Before enrollment, 3 individuals had their diabetes controlled by diet alone; and the other 45 subjects took 2 different types of oral hypoglycemic drugs. Each subject took the last dose the day before the study began. Patients were not allowed to receive any medications that are known to affect glucose or lipid metabolism, except for oral hypoglycemic agents, for at least 3 weeks before the study. Three days before the study, patients were placed on a stable diet.

Subjects enrolled in the study were evaluated for the presence of criteria of MetS defined by the National Cholesterol Education Program, Adult Treatment Panel III [11], with the exception of waist circumference; the lower cutoff levels of waist circumstance were 90 cm in male and 80 cm in female patients, according to the recommendation by the official Web site of the Taiwanese Department of Health for the definition of obesity [12]. The other 4 cutoff levels of the criteria include high blood pressure (≥130 mm Hg systolic or ≥85 mm Hg diastolic) or taking antihypertensive medications; plasma triglycerides at least 1.7 mmol/L; high-density lipoprotein cholesterol (HDL-C) less than 0.9 mmol/L in men or less than 1.0 mmol/L in women; and high fasting plasma glucose (FPG) at least 5.6 mmol/L.

To see the effects of having MetS, the study subjects were divided into 2 groups: either with MetS (MetS+) or without (MetS−). Thirty-one patients were classified as MetS+; and 17 patients, MetS−. We further grouped the study subjects according to the number of MetS components exhibited by each patient. Because our study cohort was diabetic, every subject by definition had 1 component of the MetS: elevated FPG. Only 6 subjects had no components other than elevated FPG. Because of the small number, they were included in the group having 2 components (MetS [1,2]). Similarly, only 2 subjects had all 5 components; and they were incorporated into the group with 4 components (MetS [4,5]). The MetS (3)

Table 1
Comparison of clinical characteristics between groups with and without MetS

Clinical characteristics	MetS+	MetS−
n (male/female)	31 (29/2)	17 (15/2)
Age (y)	21.7 ± 0.9	23.7 ± 1.1
BMI (kg/m^2)	27.4 ± 0.9	22.2 ± 0.85*
Systolic blood pressure (mm Hg)	119.6 ± 2.3	110.6 ± 3.2*
Diastolic blood pressure (mm Hg)	78.4 ± 1.5	70.3 ± 2.2*
Waist (cm)	90.8 ± 2.2	78.6 ± 4.2*
FPG (mmol/L)	10.22 ± 0.7	10.5 ± 1
FPI (pmol/L)	188.9 ± 35.6	100 ± 37.8
Glycated hemoglobin A_{1c} (%)	10.9 ± 0.8	10.1 ± 1
Total cholesterol (mmol/L)	4.4 ± 0.3	4.9 ± 0.39
HDL-C (mmol/L)	0.9 ± 0.5	1.1 ± 0.1
Triglycerides (mmol/L)	2.7 ± 0.2	1.4 ± 0.28*
HOMA-IR	10.4 ± 1.9	5.1 ± 2.0
HOMA-B	110.5 ± 29.8	66.6 ± 29.3

Data are shown as mean ± SE.
* $P < .05$.

Table 2
Comparisons of characteristics between 3 groups with different numbers of MetS factors

	MetS (1,2)	MetS (3)	MetS (4,5)
n (male/female)	17	17	14
Age (y)	23.7 ± 1.1	22.4 ± 1.2	20.9 ± 1.3
BMI (kg/m^2)	22.2 ± 0.9†	25.7 ± 1.3	29.4 ± 0.7
Systolic blood pressure (mm Hg)	110.6 ± 3.2	119.7 ± 2.4	119.5 ± 4.3
Diastolic blood pressure (mm Hg)	70.3 ± 2.2*,†	79.1 ± 2.1	77.7 ± 2.1
Waist (cm)	78.6 ± 4.2†	87.3 ± 3.1	95.3 ± 2.8
FPG (mmol/L)	10.5 ± 1	11 ± 1	9.3 ± 0.7
FPI (pmol/L)	100.1 ± 37.8	156.1 ± 37.5	232.7 ± 66.4
Glycated hemoglobin A_{1c} (%)	10.1 ± 1	11.4 ± 1	10 ± 1.2
Total cholesterol (mmol/L)	4.9 ± 0.4	4.9 ± 0.4	3.9 ± 0.3
HDL-C (mmol/L)	1.1 ± 0.1	0.9 ± 0.09	0.8 ± 0.09
Triglycerides (mmol/L)	1.4 ± 0.3*,†	2.4 ± 0.2	2.7 ± 0.3
HOMA-IR	5.5 ± 2.2	10.2 ± 2.4	12.5 ± 3.7
HOMA-B	34.7 ± 13.3	48.8 ± 16.6	78.3 ± 23

Data are shown as mean ± SE.
* $P < .05$ vs MetS (3).
† $P < .05$ vs MetS (4,5).

group, by definition, had 3 components of MetS. In total, there were 17, 17, and 14 subjects in the MetS (1,2), Mets (3), and MetS (4,5) groups, respectively.

The study was approved by the hospital ethics committee, and the purpose and potential risks of the study were explained to the patients before obtaining their written consent to participate.

2.2. Laboratory evaluations

After a 10- to 12-hour overnight fast, intravenous cannulas were placed in both antecubital veins of the subject. A blood sample was drawn at time −10 minutes for the measurement of FPG, fasting plasma insulin (FPI), and lipid levels. An FSIGT was also performed on the same day.

The FSIGT procedure was described in a previous article [8]. Insulin sensitivity (SI), glucose sensitivity (SG), and acute insulin response to glucose load (AIRg) were calculated using a minimal model algorithm [13]. Insulin sensitivity and IR are inversely related. Glucose sensitivity is the effect of glucose, independent of insulin, on the glucose utilization rate. A higher value of SG indicates more glucose is cleared per minute. Acute insulin response to glucose load is the increase in the plasma insulin level after glucose infusion, which represents the first phase of insulin secretion. Disposition index (DI), which is defined as the product of SI and AIRg, is the measurement of insulin-resistance–compensated β-cell function.

The mathematical calculations of the homeostasis model assessment estimating the IR (HOMA-IR) and β-cell function (HOMA-B) were calculated from the FPI and glucose [14]. These algorithms were described in our previous report [8].

Plasma was separated from blood within 1 hour and stored at −30°C until analyzed. The samples obtained from −5 and 0 minute(s) were analyzed for FPG, FPI, and lipid levels.

Plasma glucose was determined using a glucose oxidase method (YSI 203 glucose analyzer; Scientific Division, Yellow Spring Instrument, Yellow Spring, OH). Insulin was measured by a commercial solid-phase radioimmunoassay kit (Coat-A-Count insulin kit; Diagnostic Products, Los Angeles, CA) [15]. Intra- and interassay coefficients of variance for insulin are 3.3% and 2.5%, respectively. The level of glycated hemoglobin A_{1c} (A_{1C}) was evaluated by ion-exchange high-pressure liquid chromatography method (Variant II; Bio-Rad, Hercules, CA).

Triglycerides and total cholesterol were measured using the dry, multilayer analytical slide method and the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan). Serum HDL-C concentration was determined by an enzymatic assay method after dextran sulfate precipitation. The GAD-Ab was measured by a commercial radio-immunoassay kit with ^{125}I (CIS Bio International, Bagnols sur Cèze, France). The intra- and interassay coefficients of

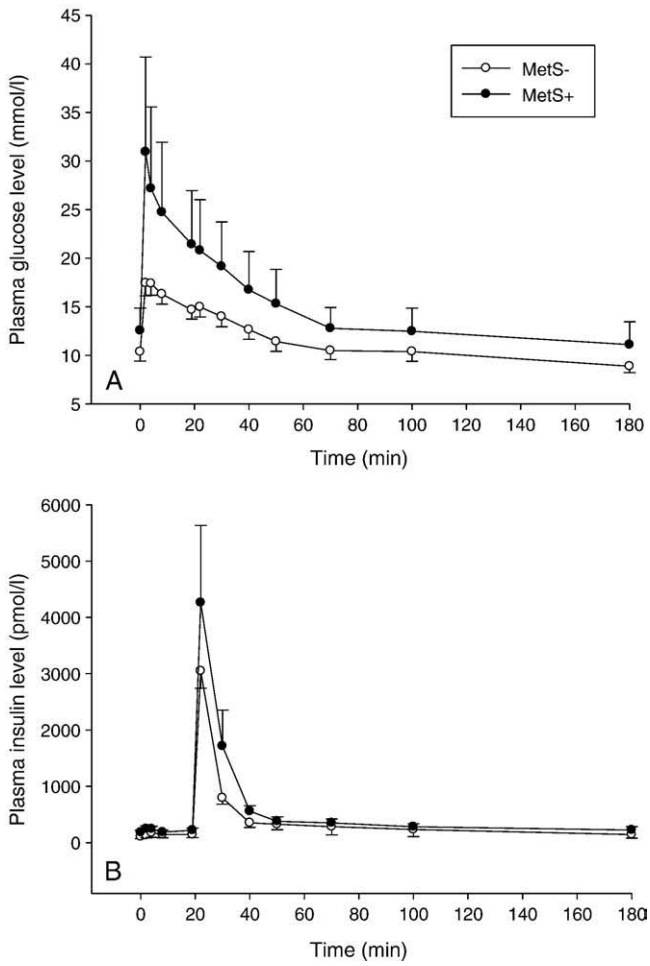

Fig. 1. Changes in plasma glucose and insulin levels during the FSIGT.

variance for GAD-Ab are 3.9% and 7.5%, respectively. Antimicrosomal antibody and anti-thyroglobulin antibody were semiquantified by the Boyden passive hemagglutination (HA) system (Thymune*-M and Thymune-T*, respectively; Abbott, Dartford, United Kingdom) [16]. The correlation between HA and fluorescent antibody titer was also found to be good, showing a linear relationship between titers of up to 1/1 600 000 for the HA test and 1/1280 for the fluorescent antibody titer test [17].

2.3. Statistical analysis

Analysis was performed using SPSS version 10.0 statistical package for Windows (SPSS, Chicago, IL). Data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variance with the Levene test. Continuous variables are expressed as mean ± SEM. Independent-samples *t* test was used to evaluate the differences in demographic characteristics. One-way analysis of variance using the Bonferroni post hoc test was also applied to compare the differences among 3 groups with different numbers of MetS characteristics. To evaluate the relationships between each of the MetS components with AIRg, simple correlation was performed.

Because age, sex, and body mass index (BMI) are considered as confounding covariates, each variable of interest was first adjusted for age, sex, and BMI by using analysis of covariance. The derived residuals (adjusted variables) were then used for analyses.

All statistical tests are 2-sided, and *P* values less than .05 are considered to be statistically significant.

3. Results

Demographic data and metabolic profiles of the subjects with EODM and with or without MetS are shown in Table 1. Glycemic control (FPG and A_{1C}) and plasma HDL-C level were similar in both groups. It is not surprising that other components such as blood pressure, BMI, and triglyceride levels were higher in the group with MetS. To explore the effects of different numbers of MetS components on these parameters, further comparison among groups according to the component numbers were also evaluated (Table 2). Except for diastolic blood pressure, plasma triglyceride levels (lowest in MetS [1,2]), BMI, and waist circumference (lower in MetS [1,2] than MetS [4,5]), other demographic and clinical metabolic characteristics were not different among these 3 groups.

Fig. 1 shows changes in plasma glucose (Fig. 1A) and insulin (Fig. 1B) during FSIGT. There were no differences in plasma insulin and glucose concentrations between these 2 groups. The SI, SG, AIR, and DI derived from the FSIGT are presented in Fig. 2 for MetS+ and MetS−. Although the SI and SG seemed to be higher in the MetS+ group, they were not statistically different (Fig. 2A and B, respectively). In the same time, AIRg was significantly higher in the MetS+ group (Fig. 2C). Because DI is the product of AIRg and SI and the SI was similar in the 2 groups, the significantly higher DI in Met+ was predictable (Fig. 2D).

In Fig. 3, similar results of MetS (1,2), MetS (3), and MetS (4,5) groups are presented. Analogous to the 2-group results, the SI and SG were not different in the 3 groups (Fig. 3A and B, respectively). Again, the AIRg was significantly

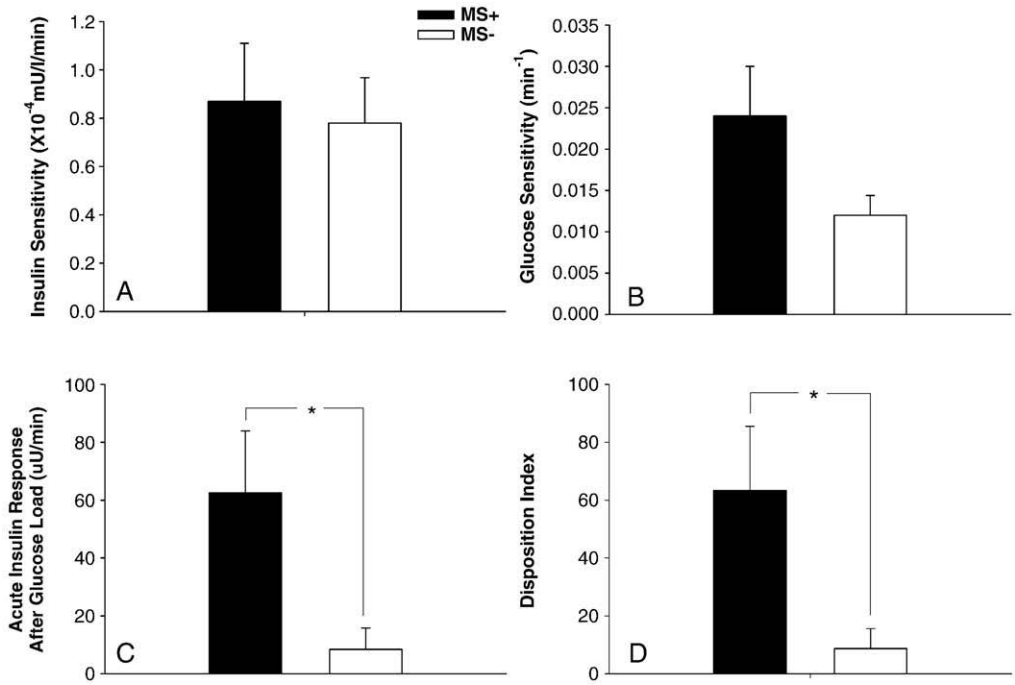

Fig. 2. Insulin sensitivity (A), SG (B), AIRg (C), and DI (D) in subjects with and without MetS. Data are shown as mean ± SE. $^{*}P < .05$.

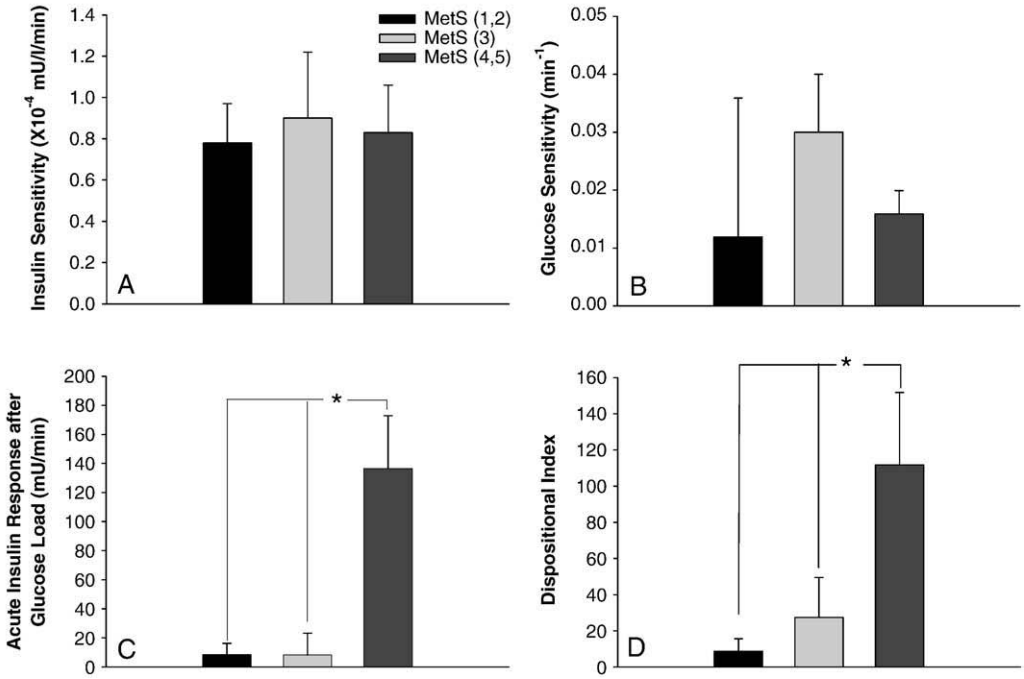

Fig. 3. Insulin sensitivity (A), SG (B), AIRg (C), and DI (D) in subjects with different numbers of MetS components. Diabetes with 1 to 2 (MetS [1,2]), 3 (MetS [3]), or 4 to 5 (MetS [4,5]) components of MetS. Data are shown as mean ± SE. $^{*}P < .05$.

higher in the MetS (4,5) group compared with the other 2 groups (Fig. 3C). It should be noted that no difference was found between the MetS (1,2) and MetS (3) groups. Not surprisingly, the DI was highest in the MetS (4,5) group, which was not surprising considering the effect of AIRg on DI.

The difference of AIRg between groups raised another interesting question about which MetS component had the most profound impact on the AIRg in these subjects. A simple correlation was performed to evaluate this relationship, and the results were shown in Table 3. Among the 5 components, only BMI was significantly correlated with AIRg.

4. Discussion

It is well known that IR plays a central role in type 2 diabetes mellitus. However, not all type 2 diabetes mellitus patients have IR; and not all subjects with IR have diabetes [18]. In our study, we found that subjects who had at least 3 factors of MetS will have similar SI, but higher AIR-g and DI, than those with 2 or less factors in this specific diabetic population, EODM.

It has been well documented that components of the MetS such as hypertension, hypertriglyceridemia, low HDL-C, and obesity correlate with higher IR [19-21]. Indeed, our results showed that HOMA-IR was higher in the MetS+ group and the MetS (4,5) subgroup than in the MetS− group and the other MetS subgroups. However, the differences were not statistically significant. When a more sophisticated method, FSIGT, was applied, there was still no difference in IR between MetS+ and MetS−.

Our results were different from those of Rhee et al [22]. They explored similar relationships between IR, insulin secretion, and MetS in adult-onset type 2 diabetes mellitus (older type 2 diabetes mellitus [ODM]). They found that subjects with both type 2 diabetes mellitus and MetS had significantly higher HOMA-IR than those without MetS (3.45 ± 2.49 vs 2.37 ± 1.37). We found that HOMA-IR values were higher in our study when compared with theirs in both the MetS+ and MetS− subjects (10.4 vs 3.45 for MetS+, 5.1 vs 2.37 for MetS−). The results suggest that IR is more severe in Taiwanese EODM than in Korean ODM. According to published data, the average HOMA-IR for type 2 diabetes mellitus patients is in the range of 5 to 9 [23,24], similar to the HOMA-IR values in the present study. This is compatible with the conclusion in our earlier article that EODM has severe defects like adult-onset type 2 diabetes mellitus, but with earlier age of onset [8].

Table 3
Simple correlation between AIRg and components of the MetS

Component	r	P
BMI	0.318	.045
FPG	−0.118	.245
Systolic blood pressure	0.036	.835
Diastolic blood pressure	−0.061	.728
HDL-C	−0.201	.215
Triglyceride	0.256	.111

Theoretically, having MetS should increase the severity of IR. However, in our study, there is no difference in IR related to MetS status. It is reasonable to explain that a severe deterioration of SI diminishes the role of MetS. At the same time, compared with our study, the Korean study reported less severe IR. Therefore, MetS may contribute to IR in the study of Rhee et al [22].

To our knowledge, few studies have addressed the effects of MetS on insulin secretion. By using the insulinogenic index, Rhee et al [22] showed that, compared with type 2 diabetes mellitus subjects with MetS, those without MetS had higher insulin secretion and higher IR. It could be noted that, in these type 2 diabetes mellitus patients, β-cell compensation was preserved when IR began to increase, albeit 5 times less effectively than in prediabetic subjects [22]. Therefore, they concluded that deterioration in insulin secretory function may be more important than an aggravated IR in the early stage of type 2 diabetes mellitus. In our study, we used AIRg derived from FSIGT to evaluate the effect of MetS on acute phase insulin secretion. Our results did not agree with the results of Rhee et al [22] and showed a higher insulin secretion with more MetS components. These interesting relationships between AIRg and numbers of MetS components could be explained by the possible role of obesity in insulin secretion. The effect of obesity on β-cell function is complex, and information in this field is limited. In a Korean cohort, Park et al [25] showed that fasting serum c-peptide levels were lower in nonobese than obese type 2 diabetes mellitus patients. A similar finding was noted by Prando et al [26]. By observing meal-stimulated c-peptide levels, they suggested that β-cell function was better preserved in obese type 2 diabetes mellitus patients. Finally, in our previous study, we also demonstrated that better AIRg was noted in obese than lean young type 2 diabetes mellitus subjects [8]. At present, there is no hypothesis to explain this finding. However, we propose 2 possibilities. First, the obese subjects may have greater β-cell mass, resulting in better compensatory secretion of insulin. Second, it is well known that a decrease in β-cell function is associated with aging in the presence of IR [27-29]. This process takes years before for full decompensation to occur. Obesity may trigger the cascade of glucose intolerance and earlier progression to diabetes, while preserving β-cell function for some time in these younger subjects.

One may argue that, because the BMI and age were adjusted before the statistic procedures, obesity should not contribute to the difference of the AIRg and DI. However, we have to point out that comparison between the AIRg before adjusting for age and BMI was also performed (data are not shown). Not surprisingly, the differences were also significant. This existence of significance both before and after the adjustment is interesting and suggests both that obesity does have an important role in AIRg and that other MetS components also contribute to the difference. The only significant correlation between the BMI and AIRg shown in Table 3 also supports the role of obesity on AIRg. However, further investigation is warranted; and at present, we can only conclude that, in ODM and EODM, better insulin secretion is noted in obese than in nonobese subjects.

The importance of SG is often overlooked when the pathophysiology of type 2 diabetes mellitus is discussed [30]. In our study, there were no significant differences in SG between MetS+ and MetS−. It is generally agreed that type 2 diabetes mellitus occurs when both insulin action and secretion are impaired. As stated earlier in “Materials and methods,” DI is the product of SI and AIRg and is a good indicator of glucose homeostasis. Our data showed that DI is significantly higher in MetS+ and MetS (4,5) compared with MetS− and MetS (1,2), respectively.

In conclusion, EODM patients with MetS had similar IR to those without MetS. At the same time, the insulin secretion was higher in the presence of MetS. This implies that the ability of β-cell compensation for IR is better preserved in subjects with EODM with MetS.

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