

The Impact of Metabolic Syndrome Defined by IDF or Revised NCEP on Glycemic control in Malaysians with Type 2 Diabetes

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Abstract

Background

Chronic complication of Type 2 diabetes mellitus such as macrovascular disease is amplified with the increase in the number of the metabolic syndrome (MeS) risk factors. Specific criteria for diagnosis of metabolic syndrome are essential to help in glycemic control and reduce cardiovascular morbidity and mortality in diabetic patients with metabolic syndrome.

Methods

The study involved 485 Type 2 DM patients who are receiving treatment at the University Kebangsaan Malaysia Medical Center (UKMMC), Kuala Lumpur, Malaysia. Metabolic syndrome among the Type 2 DM patients was diagnosed based on IDF and NCEP-R criteria. The C-peptide and glycosylated hemoglobin (HbA1c) levels were determined by an automated quantitative immunoassay analyzer and high-performance liquid chromatography respectively. The metabolic syndrome factors, glucose, triglyceride and HDL cholesterol were measured by spectrophotometer

Results

Application of IDF and NCEP-R criteria respectively resulted in 73% and 85% of Type 2 DM subjects being diagnosed with metabolic syndrome. The concordance of these criteria in diagnosing metabolic syndrome among Type 2 DM was low ($\kappa=0.33$, $P<0.001$). Both IDF and NCEP-R criteria indicated that Type 2 DM with five criteria of metabolic syndrome had higher insulin resistance ($P=2.1\times 10^{-13}$, $P=1.4\times 10^{-11}$), C-peptide ($P=1.21\times 10^{-13}$; 4.1×10^{-11}), blood glucose ($P=0.01$; 0.021) and HbA1c ($P=0.039$; 0.018) than those Type 2 DM without metabolic syndrome respectively.

Conclusion

However, there is a low concordance between IDF and NCEP-R criteria in the diagnosis of metabolic syndrome among Type 2 DM, both criteria showed that type 2 DM with five criteria of metabolic syndrome had higher insulin resistance, blood glucose and HbA1c.

Background

The burden of non-communicable disease in the developing countries is increasing, and leading to high mortality rates (Islam et al., 2014). Nowadays Type 2 DM is pandemic. According to international diabetes federation report indicates that more than 415 million of people worldwide adults have diabetes and is expected to rise to 642 million by 2040 (Ogurtsova et al., 2017). The metabolic syndrome (MetS) is a complex with high socioeconomic impact due to its association with increased morbidity and mortality (Misra & Khurana, 2008). Metabolic syndrome has attracted increased attention due to its significant impact on cardiovascular diseases (CVD) and its high prevalence in Type 2 DM patients (Basol et al., 2011; Ford, 2005; Grundy, 2008; Nsiah, Shang, Boateng, & Mensah, 2015; Shin et al., 2013; Yadav et al.,

2013). Metabolic syndrome can be defined as a cluster of interconnected cardio-metabolic dysfunctions which is characterized by the increase in fasting blood sugar, abdominal circumference, blood pressure, triglycerides (TG), and reduction in high-density lipoprotein cholesterol (HDLc) (Alberti, Zimmet, & Shaw, 2005; Eckel, Grundy, & Zimmet, 2005).

Globally, 20-25% of the adult population has MetS and they are twice as likely to die from it; and they are three times more likely to have a heart attack or stroke compared with people without the syndrome (Ogurtsova et al., 2017; WHO, 2018). This increase in MetS globally is associated with the worldwide epidemic of obesity and diabetes. Obesity and physical inactivity are the driving force for metabolic syndrome and a person with metabolic syndrome has 5-fold relative risk to develop diabetes (DeBoer et al., 2017; Grundy, 2008; Gurka, Guo, Filipp, & DeBoer, 2018; O'Neill & O'Driscoll, 2015). Overweight and obesity lead to adverse metabolic effects on blood pressure, cholesterol, triglycerides (TG) and impaired glucose tolerance (IGT) (Rassool, 2003).

The National Cholesterol Education Programs Adult Treatment Panel III (NCEP-ATPIII) proposed a simple set of diagnostic criteria for metabolic syndrome based on waist circumference, triglycerides, HDL-C, blood pressure, and fasting glucose level (Expert Panel on Detection, 2001). In 2005, the International Diabetes Federation (IDF) modified the metabolic syndrome definition, which stated that abdominal obesity is necessary for the diagnosis of metabolic syndrome along with any two of the other metabolic syndrome parameters that were suggested by NCEP while IDF included the treatment of the above parameters as well (Zimmet, Magliano, Matsuzawa, Alberti, & Shaw, 2005). In the same year the American Heart Association and the National Heart, Lung, and Blood Institute revised the NCEP criteria and affirmed its overall utility and validity and proposed that it continued to be used with minor modifications and clarifications (Grundy et al., 2005) (Table 1).

In 2009, a meeting between several organization: International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity attempt to unify criteria (Alberti et al., 2009). In this meeting, the IDF criteria was modified and it was agreed that waist circumference should not be an obligatory component and three abnormal findings out of 5 would qualify a person for the metabolic syndrome. However, application of this harmonizing definition of the metabolic syndrome on type 2 DM resulting in more than 97% of Type 2 DM with metabolic syndrome, thus this definition could not include in this study. However, there is no consensus on the definition of MS worldwide. Studies revealed that the impact of different definitions of MetS on the risk of future CVD and diabetes is discrepant (Kastorini et al., 2016; Khosravi-Boroujeni et al., 2015).

Several studies have assessed the metabolic syndrome among normal individual in different populations whereas few studies assessed the metabolic syndrome among Type 2 DM. Taking into consideration, diabetic patients who had MetS also have cardiovascular risk factors, therefore the diagnosis of MetS in those patients is very important for detection, prevention, and treatment of the underlying risk factors and

for the reduction of the cardiovascular disease burden in the general population (Galassi, Reynolds, & He, 2006; Han & Lean, 2016). This research aims to study the effect of metabolic syndrome, diagnosed by International Diabetes Federation or the revised National Cholesterol Education Programs (NCEP-R) criteria, on glycemic control including fasting glucose, glycated hemoglobin, C-peptide and insulin resistance in type 2 DM patients.

Methods

Study design and subjects

The current study was analytical observation study. Four hundred eighty-five previously diagnosed Type 2 DM patients aged between 30 and 70 years attending the University Kebangsaan Malaysia Medical Center, Kuala Lumpur, Malaysia were randomly recruited into the study after obtaining their informed consent. Ethical approval was obtained from the National University of Malaysia Research and Ethics committee.

Sample and data collection

Waist circumference was measured midway between the lower rib margin and the superior iliac spine at the end of gentle expiration in a standing position. Blood pressure (BP) measurements were taken from each patient's right arm in the seated position by using an Omron IntelliSense Automatic Blood Pressure Monitor after 10 min of rest in a quiet room. Two to three successive BP readings were obtained at 5 minutes intervals and averaged. Fasting blood (5ml) was collected from each subjected and divided into two tubes, EDTA tube for HbA1c measurement and plain tubes for biochemical investigations. The plain tubes were centrifuged for 10 minutes at 3000 × g within 30 minutes of blood collection and the serum from each sample was separated into two Eppendorf tubes and immediately kept at -20°C until analysis. The treatment for each participant was collected from the patient data record in University Kebangsaan Malaysia Medical Center,

Biochemical analyses and Glycated hemoglobin (HbA1c) measurements

Kits for the measurement of glucose, triglyceride and HDL cholesterol (reference number 10260, 10724, 10028 and 10018 respectively) were purchased from Human Company (Human GmbH, Wiesbaden, Germany). Human company elevated control sera (Humatrol P Reference number 13512) was used as quality control for these parameters. C-peptide was measured in an automated quantitative immunoassay analyzer (Immulite, DPC, Los Angeles, USA) using IMMULITE C-peptide kit (catalogue number LKPE1). Glycated hemoglobin (HbA1c) levels were determined by high performance liquid chromatography (VARIANT Hemoglobin A1c Reorder Pack, catalog no. 270-0003, Bio-Rad Laboratories, Inc., Richmond, California, USA) with lyphochek diabetes Bi-level controls (Catalogue number 740) as quality control. Insulin resistance was calculated using the Homeostasis Model Assessment (HOMA2) Calculator v2.2 available from Oxford Center for Diabetes, Endocrinology and Metabolism. This program used fasting C-peptide or insulin and blood glucose levels to calculate insulin resistance.

Assessment of metabolic syndrome

Metabolic syndrome was diagnosed based on the IDF and NCEP-R criteria. All subjects included in this research were previously diagnosed with Type 2 DM and therefore the blood glucose was excluded from the five metabolic syndrome criteria. The metabolic syndrome in Type 2 DM was diagnosed according to NCEP-R that included two or more of the following abnormalities:

1. Central obesity: waist circumference ≥ 102 cm for men or ≥ 88 cm for women
2. Raised blood pressure: systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension
3. Raised triglyceride level: ≥ 7 mmol/l or specific treatment for this lipid abnormality
4. Reduced HDL cholesterol: men < 1.03 mmol/l, women < 1.29 mmol/l or HDL cholesterol treatment.

While according to the IDF criteria, metabolic syndrome was defined by the presence of central obesity (waist circumference in Asian male ≥ 90 cm and female ≥ 80 cm) together with one of the other metabolic syndrome criteria which includes; blood pressure, triglyceride, and HDL cholesterol with the same cut off point as NCEP-R.

Statistical analysis

The analyses were assessed by SPSS version 11.5 software (SPSS, Inc, Chicago, USA). The fasting blood glucose, glycated hemoglobin, C-peptide, insulin resistance, were log transformed as they were not normally distributed. Mean and 95% confidence intervals were transformed back and reported. The Kappa test was used to study the concordance between the IDF and NCEP-R criteria. The general linear model adjusted for age, sex, race and history of diabetes (as covariates) was used to study the correlation of metabolic syndrome with glycemic control; fasting blood glucose, glycated hemoglobin, C-peptide and insulin resistance (as a set of dependent variables).

Results

Four hundred eighty-five previously diagnosed Type 2 DM subjects agreed to participate in this project. These patients were on insulin and/or oral antidiabetic medications (98%) followed by antihyperlipidemic agents (65%) and antihypertensive medications (64.5%). Three hundred fifty-six (73%) and 415 (85%) out of the 485 Type 2 DM had metabolic syndrome when defined by the criteria of IDF and NCEP-R respectively (Table 2). When new criteria of metabolic syndrome, harmonizing definition, was applied on type 2 DM resulting in more than 97% of Type 2 DM participated in this study with metabolic syndrome, thus this definition could not include in this study.

The IDF and NCEP-R criteria concurred the diagnosis of metabolic syndrome in 331 (68%) Type 2 DM, while 25 (5%) were diagnosed as metabolic syndrome by IDF but not by NCEP-R and 84 (17%) by NCEP-R criteria but not by IDF (Kappa 0.33, $P < 0.001$). The prevalence of metabolic syndrome was higher in women (82%, 87% Kappa= 0.34, $P < 0.001$) than in men (62%, 84% Kappa= 0.31, $P < 0.001$) using both IDF

and NCEP-R criteria respectively. In general, the highest prevalence of metabolic syndrome (83%, 85% Kappa= 0.24, P= 0.024) was found among Malaysian Indians followed by the Malays (74%, 88% Kappa= 0.35, P<0.001) and the lowest was among the Malaysian Chinese (67%, 81% Kappa= 0.32, P<0.001) again using IDF and NCEP-R criteria respectively. Both criteria showed a higher prevalence of the metabolic syndrome among women than in men within the three races with low concordance particularly among the Malaysian Indians women (kappa=0.08, P=0.54).

Both IDF and NCEP-R criteria showed that multivariate analysis of covariance revealed a significant main effect for metabolic syndrome, Wilks lambda = 0.865 and 0.855 P= 4.8×10^{-10} and 4.7×10^{-11} with powers to detect effect were at 0.99998 and 0.99997 respectively. Type 2 diabetic patients with 5 metabolic syndrome factors defined by IDF or NCEP-R criteria had significantly higher FBG ($P= 0.01$, $P=0.021$) than Type 2 DM without metabolic syndrome (Table 3 and 4). While both criteria did not show statistical difference between Type 2 DM with 4 or 3 metabolic syndrome parameters and Type 2 DM without metabolic syndrome. HbA1c was higher in Type 2 DM with five criteria of metabolic syndrome than Type 2 DM without metabolic syndrome ($P= 0.039$, $P= 0.018$) when IDF and NCEP-R criteria were applied respectively. Whereas IDF criteria showed that diabetic patients with 5 criteria of metabolic syndrome had a significantly higher HbA1c than diabetes with 4 or 3 criteria of metabolic syndrome ($P= 0.034$, $P= 0.005$ respectively).

C-peptide was significantly higher in Type 2 DM having five metabolic syndrome factors ($P= 1.21 \times 10^{-13}$, $P= 4.1 \times 10^{-11}$) or four metabolic syndrome factors ($P= 2.33 \times 10^{-5}$, $P= 1.5 \times 10^{-7}$) than those who were Type 2 DM without metabolic syndrome using both IDF and NCEP-R criteria respectively (Table 3 and 4). The NCEP-R criteria showed that Type 2 DM with three metabolic syndrome criteria had a significantly higher C-peptide than Type 2 DM without metabolic syndrome ($P= 0.004$), whereas the IDF criteria showed no difference ($P= 0.096$). Both IDF and NCEP-R criteria showed a significantly higher C-peptide in Type 2 DM who had five metabolic syndrome parameters than those who had 4 ($P= 0.006$; 0.005) or 3 criteria of metabolic syndrome ($P= 7.1 \times 10^{-5}$; 1.4×10^{-6}).

Type 2 DM with five metabolic syndrome factors had higher insulin resistance than those who had no metabolic syndrome ($P= 2.1 \times 10^{-13}$; 1.4×10^{-11}), and those who had three ($P= 5.9 \times 10^{-5}$; 7.6×10^{-8}) or four metabolic syndrome ($P= 0.0002$, $P= 0.0003$) when IDF or NCEP-R criteria were applied respectively. Both, IDF and NCEP-R criteria showed that insulin resistance was significantly higher in Type 2 DM with 4 metabolic syndrome factors ($P= 7.65 \times 10^{-5}$; 3.1×10^{-6}) than those without metabolic syndrome respectively. NCEP-R criteria showed that diabetics with 3 factors of metabolic syndrome had higher insulin resistance than diabetics without metabolic syndrome ($P= 0.01$) while application of IDF criteria did not show a significant association ($P= 0.110$).

Discussion

In the present study, the prevalence of metabolic syndrome among Type 2 DM was higher according to NCEP-R criteria compared to IDF and the concordance between these two criteria was low. However, in

German Type 2 diabetes, IDF criteria showed more metabolic syndrome than NCEP-R with a higher concordance (0.69) (Koehler, Ott, Benke, & Hanefeld, 2007). Whereas in United Kingdom the modified NCEP Criteria (BMI 28.8 kg/m² used instead of waist circumference) showed a higher prevalence than IDF with 0.60 concordance between these criteria (Song & Hardisty, 2008). Recent study among Ethiopians showed that NCEP Criteria was higher than IDF (70% vs 60% with moderate concordance $K=0.54$) (Wube, Nuru, & Anbese, 2019). The difference in concordance between the MetS diagnostic criteria in different populations is probably due to ethnic characteristics, dietary habits, and lifestyle, thus making it difficult to use a single diagnostic criterion for all populations.

The prevalence of metabolic syndrome in our Malaysian Type 2 DM defined by IDF was similar to that reported in Ethiopians (Birarra & Gelayee, 2018), Nepalese (Pokharel et al., 2014), Iranian (Foroozfar, Najafipour, Khanjani, Bahrapour, & Ebrahimi, 2015), sub-Saharan Africans (Kengne, Limen, Sobngwi, Djuogo, & Nouedoui, 2012), and White American (70%) but higher than the Black (65%) and Mexican Americans (62%) (Lin & Pi-Sunyer, 2007) even though NCEP criteria were used in their study. Recently, the highest prevalence of MetS was reported in India (97%) using WHO criteria (Aziz, 2020).

On the other hand, a lower prevalence of MetS was reported from India 45.8, 57.7 and 28% using NCEP-ATP III, WHO and IDF criteria respectively (Yadav et al., 2013) and Ghana 43.83% with NCEP-ATP III, 63.58% with WHO, and 69.14% with IDF criteria (Osei-Yeboah et al., 2017). Similarly, lower prevalence of MetS was reported in recent studies from Ethiopia 53.5% in IDF whereas 66.7% in the NCEP-ATP III criteria (Biadgo et al., 2018) and from Sri Lanka 28.9%, 43.8%, and 70.6% using NCEP-ATP III, IDF, and WHO criteria, respectively (Herath, Weerasinghe, Weerathna, & Amarathunga, 2018). A previous study reported higher prevalence of MetS in Malaysia Type 2 diabetics (96.1%), (84.8%) (Tan et al., 2013) according to NCEP ATP III and IDF definitions, respectively.

The increased waist circumference was more frequent in women (89% and 59%) than men (68% and 23%) when defined by IDF and NCEP-R respectively resulted in a higher prevalence of metabolic syndrome in women than men this result in agreement with previous study (Gebremeskel et al., 2019; Herath et al., 2018; Ogedengbe & Ezeani, 2014; Pokharel et al., 2014; Song & Hardisty, 2008). According to a large population survey conducted, female diabetics were more obese compared to male diabetics (13% and 10%, respectively) (Alamgir, Javid, Hameed, & Mustafa, 2015). In addition, diabetic women are more likely than men to have hypertension, low levels of HDL cholesterol and high levels of triglycerides (Legato et al., 2006). Higher prevalence of MetS in females may be due to the higher HDL cut-off and lower waist circumference cut-off values in females as compared to males. Hence, more females than males can be recognized as having metabolic syndrome.

In general, IDF and NCEP-R criteria are the most applicable for epidemiological studies and clinical diagnosis of metabolic syndrome. However, the concordance between these two criteria was low for the diagnosis of metabolic syndrome among Malaysian Type 2 DM. NCEP-R criteria utilized American data while IDF criteria based on accumulated international data. There is an ethnic difference in waist circumference, which was considered by IDF. Although IDF and NCEP-R criteria were in low concordance

for the diagnosis of metabolic syndrome among Malaysian Type 2 diabetes, there was a similar effect of metabolic syndrome particularly in the patients with 5 criteria, as defined either by IDF or NCEP-R, on glycemic parameters (insulin resistance, C-peptide, blood glucose and HbA1c). Type 2 diabetic patients with metabolic syndrome have higher central obesity, which is associated with higher insulin resistance and higher blood pressure (Rassool, 2003). Accumulation of lipids in the liver and muscle of Type 2 DM has been shown to aggravate the insulin resistance (Shulman, 2000). This resulted in increased glucose production by the liver and less glucose conversion into glycogen by muscles. Consequently, beta cells compensated the insulin resistance via increased insulin production.

Conclusion

The effect of metabolic syndrome, as defined by either IDF or NCEP-R criteria, on insulin resistance and poor glycemic control were similar however, there was a low concordance between IDF and NCEP-R criteria in the diagnosis of metabolic syndrome among type 2 DM. Based on the finding of our study as well as many other studies, it is clear that the different definitions of MetS give rise to different prevalence. In fact, the difference in the two criteria is in the definition of metabolic syndrome thus requires more consideration as chronic complication of type 2 DM is amplified with metabolic syndrome.

Abbreviations

IDF: International Diabetes Federation; NCEP-ATPIII: The National Cholesterol Education Programs Adult Treatment Panel III; NCEP-R: Revised National Cholesterol Education Programs; WHO: World Health Organisation; DM: Diabetes mellitus; MetS: Metabolic syndrome; CVD: Cardiovascular diseases; BP: Blood pressure; HDL: High-density lipoprotein; TG: Triglycerides; FBG: Fasting plasma glucose; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Declarations

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Contributions

RSA and WZWN participated in study design, sample collection, experimental tests, conducted statistical analyses, interpreted results, and wrote the draft of the manuscript. NAK sample collection and study design, MA and SAA critically revised and edited the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved was by National University of Malaysia Research and Ethics committee. Written informed consent was obtained from each participant before the sample collection.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Tables

Table 1: Diagnostic criteria of metabolic syndrome

Parameters	Revised NCEP	IDF
Definition	Any three of the following 5 features	Increased waist circumference
Elevated waist circumference	≥ 102 cm in men ≥ 88 cm in women	men ≥ 90 cm, women ≥ 80 cm along with any 2 of following features
Triglyceride	≥ 1.7 mmol/l or TG treatment	
HDL cholesterol	Men < 1.03 mmol/l or women < 1.29 mmol/l or HDL cholesterol treatment	
Blood pressure	Systolic ≥ 130 mmHg or Diastolic ≥ 85 mmHg or hypertension treatment or previously diagnosed hypertension	
Glucose	≥ 5.6 mmol/l or treatment for elevated glucose or previously diagnosed type 2 diabetes	

^aSub-Saharan Africans, Eastern Mediterranean and Middle East (Arab) populations use European and Ethnic South and Central Americans Use South Asia.

Table 2: Concordance of International Diabetes Federation and reversed National Cholesterol Education Program criteria in the diagnosis of metabolic syndrome among type 2 diabetes

	No	% prevalence of metabolic syndrome in type 2 diabetes		Concordance (Kappa, P-value)
		NCEP-R	IDF	
Total	485	85	73	0.33, P<0.001
men	206	84	62	0.31, P<0.001
women	279	87	82	0.34, P<0.001
Malaysian Malays	253	88	74	0.35, P<0.001
Men	113	88	63	0.35, P<0.001
women	140	89	81	0.33, P<0.001
Malaysian Chinese	143	81	67	0.32, P<0.001
Men	65	85	57	0.25, P=0.01
Women	78	78	76	0.42, P<0.001
Malaysian Indians	89	85	83	0.24, P=0.024
Men	28	68	64	0.28, P=0.13
Women	61	93	92	0.08, P=0.54

Table 3: The effect of metabolic syndrome diagnosed by International Diabetes Federation criteria on glycemic control among type 2 diabetes

Parameters	Diabetes without metabolic Syndrome (n=129)	Diabetes with 3 criteria of metabolic syndrome (n=68)	Diabetes with 4 criteria of metabolic syndrome (n=146)	Diabetes with 5 criteria of metabolic syndrome (n=141)
Fasting glucose (mmo/L)	7.7 (7.24-8.20)	8.0 (7.33-8.71)	7.9 (7.48-8.39)	8.6 (8.15-9.16)
	p-value	0.516	0.526	0.01 , (^a 0.042)
Glycated hemoglobin (%)	7.7 (7.40-8.0)	7.6 (7.18-8.02)	7.6 (7.28-7.83)	8.2 (7.85-8.47)
	p-value	0.69	0.507	0.039 , (^a 0.034, ^b 0.005)
C-peptide (pmol/l)	489 (441-542)	569 (493-656)	667 (605-735)	809 (735-893)
	p-value	0.096	2.33×10⁻⁵	1.21×10⁻¹³ , (^a 7.1×10 ⁻⁵ , ^b 0.006)
Insulin resistance	2.4 (2.23-2.54)	2.6 (2.39-2.85)	2.9 (2.69-3.03)	3.4 (3.16-3.56)
	p-value	0.110	7.65×10⁻⁵	2.1×10⁻¹³ , (^a 5.9×10 ⁻⁵ , ^b 0.0002)

The result presented as geometric mean and 95% confidence interval of mean adjusted to age, sex, race and history of diabetes. ^a, Diabetes with 5 criteria of metabolic syndrome versus 3 criteria of metabolic syndrome; ^b, Diabetes with 5 criteria of metabolic syndrome versus diabetes with 4 criteria of metabolic syndrome.

Table 4: The effect of metabolic syndrome diagnosed by reversed National Cholesterol Education Program criteria on glycemic control among type 2 diabetes

Parameters	Diabetes without metabolic Syndrome (n=70)	Diabetes with 3 criteria of metabolic syndrome (n=136)	Diabetes with 4 criteria of metabolic syndrome (n=196)	Diabetes with 5 criteria of metabolic syndrome (n=82)
Fasting glucose (mmo/L)	7.8(7.03-8.23)	8.0(7.54-8.5)	8.0(7.62-8.42)	8.8(8.11-9.49)
	p-value	0.395	0.356	0.021
Glycated hemoglobin (%)	7.6(7.25-8.07)	7.5(7.24-7.82)	7.7(7.49-7.98)	8.4(7.96-8.80)
	p-value	0.624	0.747	0.018,^a0.001,^b0.009)
C-peptide (pmol/l)	443(385-509)	569(515-628)	688(633-747)	857(752-975)
	p-value	0.004	1.5×10⁻⁷, (^c0.004)	4.1×10⁻¹¹ (^a1.4×10⁻⁶,^b0.005)
Insulin resistance	2.3 (2.01-2.49)	2.6(2.46-2.79)	2.9(2.77-3.07)	3.5(3.21-3.78)
	p-value	0.01	3.1×10⁻⁶, (^c0.01)	1.4×10⁻¹¹ (^a7.6×10⁻⁸,^b0.0003)

The result presented as geometric mean and 95% confidence interval of mean adjusted to age, sex, race and history of diabetes. ^a, Diabetes with 5 criteria of metabolic syndrome versus diabetes with 3 criteria of metabolic syndrome; ^b, Diabetes with 5 criteria of metabolic syndrome versus diabetes with 4 criteria of metabolic; ^c, diabetes with 4 metabolic syndrome criteria versus diabetes with 3 criteria of metabolic syndrome.