METABOLIC SYNDROME COMPONENTS AND PREVALENCE OF CARDIOVASCULAR DISEASE AMONG TYPE 2 DIABETIC PATIENTS IN MALAYSIA

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Abstract. Metabolic syndrome (MetS) is common among patients with type 2 diabetes mellitus (T2DM) and increases the risk of cardiovascular disease (CVD) and all-cause mortality. The objective of this study was to investigate the association between the components of MetS and the prevalence of CVD among patients with T2DM. We studied 313 patients aged ≥30 years diagnosed with T2DM at two tertiary care hospitals. Patients were recruited by systematic random sampling. Clinical data was obtained using an interviewer-administered structured questionnaire and from a review of their medical records. MetS was diagnosed using NCEP ATP III, WHO, IDF and the new Harmonized definitions. Specific MetS components such as BMI, waist circumference, waist-to-hip ratio, hypertension, HDL-C and triglyceride levels were evaluated to determine if they had an association with CVD. Thirty-six point one percent of the subjects had CVD. The mean age of the subjects was 55.7±9.2 years and the mean duration of having diabetes was 10.1±8.1 years. The overall prevalences of MetS (≥3 of 5 components) (95% CI) were 96.1% (94.0-98.3), 95.8% (93.6-98.1), 84.8% (80.8-88.9) and 97.7% (96.1-99.4) using NCEP ATP III, WHO, IDF and Harmonized definitions, respectively. Patients with MetS had a higher prevalence of CVD using NCEP ATP III (98.2% *vs* 93.5%), WHO (98.2% *vs* 93.0%), IDF (87.6% *vs* 82.0%) and Harmonized criteria (98.2% *vs* 96.0%). The greater the number of MetS components, the greater the chance of having CVD using three definitions for diagnosing MetS: WHO, IDF and Harmonized ($p<0.05$). MetS and the combination of the individual components of MetS were significantly associated with CVD among type 2 diabetic patients in Malaysia. Aggressive treatment of MetS components is required to reduce cardiovascular risk in T2DM.

Keywords: metabolic syndrome, cardiovascular disease, type 2 diabetes mellitus, Malaysia

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INTRODUCTION

Cardiovascular disease (CVD) accounts for 60-80% of deaths among patients with type 2 diabetes mellitus (T2DM) (Fox, 2010; AHA, 2012). Despite many developments in managing CVD, it remains the leading cause of mortality and morbidity worldwide (Clark, 2007). Patients with T2DM have a 2-4 times greater risk of CVD mortality than those without diabetes mellitus (DM). CVD mortality among diabetics without a prior history of myocardial infarction (MI) is similar to non-diabetics with a prior history of MI (Schramm *et al*, 2008).

Metabolic syndrome (MetS) is a collection of metabolic abnormalities that includes hyperglycemia, obesity, atherogenic dyslipidemia, and hypertension (WHO, 1999; NCEP Expert Panel, 2001; Alberti *et al*, 2005; IDF, 2006; Alberti *et al*, 2009). Although MetS as a unique pathophysiologic condition and as a predictor of disease has been questioned (Chan *et al*, 2009), most clinicians and researchers agree that certain metabolic risk factors are prone to cluster, and this clustering increases the risk of developing T2DM (by 5 to 9 fold) (Miettola *et al*, 2008), increases the risk of developing CVD by 5 fold, and increases all-cause mortality in a wide variety of populations (Skilton *et al*, 2008; Gelaye *et al*, 2009; Huang, 2009b). Insulin resistance is believed to be the underlying cause for both T2DM and MetS. This explains why MetS is more common among individuals with T2DM and potentially increases the risk of developing diabetic complications, particularly CVD (Isomaa *et al*, 2001a,b; Bonora *et al*, 2003; Orna *et al*, 2004; Guzder *et al*, 2006; Sone *et al*, 2008; AlSaraj *et al*, 2009; Rodríguez *et al*, 2010).

To date, only a few studies have focused on risk for CVD among patients with MetS and T2DM (Isomaa *et al*, 2001a,b; Bonora *et al*, 2003; Bruno *et al*, 2004; Orna *et al*, 2004; Guzder *et al*, 2006; Sone *et al*, 2008; AlSaraj *et al*, 2009; Rodríguez *et al*, 2010). Several, but not all studies suggest MetS is a significant predictor of CVD mortality and morbidity among diabetics (Isomoa *et al*, 2001a,b; Bonora *et al*, 2003; Orna *et al*, 2004; Guzder *et al*, 2006; Sone *et al*, 2008; AlSaraj *et al*, 2009; Rodriguez *et al*, 2010). However, the effect of MetS among Malaysian patients with T2DM on CVD is not well-defined. We hypothesized combination of the component of MetS increased the risk of CVD. To test this hypothesis, we studied patients with T2DM by grouping them according to the four most common MetS components to determine their association with CVD.

MATERIALS AND METHODS

Patients and study design

We conducted a cross sectional study of 313 patients with T2DM at two tertiary government hospitals (Kuala Lumpur General Hospital and Hospital Serdang) in Klang Valley, Malaysia. The subjects were selected by systematic random sampling. The study was carried out in accordance with the Declaration of Helsinki and Malaysian Guidelines for Good Clinical Practice (MOH Malaysia, 2011). The protocol for the study was approved by the Medical Research and Ethics Committee of the Faculty of Medicine and Health Sciences, Universiti Putra Malaysia and Ministry of Health Malaysia. Inclusion criterion was ambulatory patients with a diagnosis of T2DM. Exclusion criteria were having type 1 diabetes mellitus (T1DM) or gestational diabetes mellitus, being pregnant or lactating, having non-atherosclerotic heart disease, such as rheumatic heart disease, having congestive

heart failure secondary to thyrotoxicosis, having atrial fibrillation, having a history of a venous thromboembolism (VTE) (deep vein thrombosis and pulmonary embolism), having non-ischemic cardiomyopathy, having valvular heart disease, having a prosthetic heart valve, having cardiac dysrhythmias, having inflammatory heart disease (endocarditis, pericarditis or myocarditis), having congenital heart disease, having an embolic or hemorrhagic stroke, having a malignancy, having a severe psychiatric illness or having dementia. A trained interviewer administered a questionnaire and recorded the blood pressure, waist circumference, hip circumference, weight, height, body mass index (BMI), waist-to-hip ratio (WHR) and laboratory investigations [hemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides]. A complete medical history, including current pharmacological treatment, duration of diabetes and traditional cardiovascular risk factors, such as dyslipidemia and hypertension, were also obtained.

CVD was defined as having one or more of the following: coronary artery disease (CAD) [having a history of a non-fatal MI, angina, coronary artery bypass graft (CABG) surgery, angioplasty or heart failure due to ischemic heart disease], having a history of a non-fatal ischemic stroke, transient ischemic attack (TIA) or clinically significant peripheral vascular disease (PVD). The presence of CVD was established by clinical examination, face-to-face interview and review of medical history.

We selected the four most popular definitions for MetS per different medical organizations: NCEP ATP III (2001), WHO (1999), IDF (2006), and the Harmonized criteria from the collaboration of the IDF, American Heart Association/ National Heart, Lung, and Blood Institute (AHA/NHLBI), World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity (Alberti *et al*, 2009). To estimate the prevalence of MetS, the glycemic criterion was considered satisfied since all the patients had a diagnosis of T2DM. The blood pressure criterion was satisfied if the subject was taking antihypertensive medications or if the blood pressure was elevated in subjects taking antihypertensives. Dyslipidemia was diagnosed if the subject was taking lipid lowering agents, such as statins, fibrates or nicotinic acid, regardless of HDL-C or triglycerides levels, or if their lipid levels were outside the normal range. MetS was diagnosed when T2DM was present along with ≥2 other components of MetS based on the criteria used for that definition. Subjects were grouped by the number of MetS components they had (Group 2 for two criteria, Group 3 for three criteria and Group 4 for four criteria). Patients with one or no components of MetS were classified as not having MetS (Group 1).

Statistical analysis

All statistical analyses were performed using SPSS (Version 21.0, SPSS, Chicago, IL). Descriptive statistics, such as percentages, means, and standard deviations (SD), were used to describe the data. Categorical variables were expressed as an absolute number (percentage). All normally distributed and transformed variables were expressed as a mean±SD. On bivariate analysis, risk factors were compared between subjects with and without CVD, using the Pearson's chi-square test and independent *t*-test. Trends by CVD

Table 1
Socio-demographic, anthropometric, biochemical and clinical characteristics of subjects by CVD status (N = 313).

Characteristic	All (N = 313)	CVD absent (N = 200)	CVD present (N = 113)	p-value
Age (years)	55.7±9.2	54.7±9.7	57.4±8.1	0.013[a]
Diabetes duration (years)	10.1±8.1	9.2±7.6	11.5±8.7	0.021[a]
Gender				0.005[b]
Male	150 (47.9)	84 (42.0)	66 (58.4)	
Female	163 (52.1)	116 (58.0)	47 (41.6)	
Ethnicity				0.015[a]
Malay	147 (47.0)	106 (53.0)	41 (36.3)	
Chinese	80 (25.6)	47 (23.5)	33 (29.2)	
Indian	86 (27.5)	47 (23.5)	39 (34.5)	
Diabetes treatment (%)				0.890
Only oral agents	190 (60.7)	120 (60.0)	70 (61.9)	
Only insulin	25 (8.0)	17 (8.5)	8 (7.1)	
Oral agents and insulin	98 (31.3)	63 (31.5)	35 (31.0)	
BMI (kg/m^2)	29.0±5.0	29.2±5.4	28.5±4.2	0.259
WC (cm)	96.3±11.2	95.7±11.7	97.3±10.1	0.214
WHR	0.9±0.1	0.9±0.1	1.0±0.1	0.002[b]
HbA_{1c} (%)	8.7±2.1	8.6±2.0	8.9±2.2	0.202
Fasting plasma glucose (mmol/l)	8.8±3.6	8.7±3.5	9.0±3.9	0.575
Total cholesterol (mmol/l)	4.9±1.3	4.9±1.1	5.0±1.6	0.527
LDL-C (mmol/l)	2.9±1.1	2.9±0.9	3.0±1.4	0.465
HDL-C (mmol/l)	1.2±0.3	1.2±0.4	1.1±0.3	<0.001[c]
Triglycerides (mmol/l)	1.8±1.2	1.7±1.2	2.1±1.3	0.013[a]
Dyslipidemia[d] (%)	279 (89.1)	173 (86.5)	106 (93.8)	0.046[a]
Hypertension[d] (%)	251 (80.2)	148 (74.0)	103 (91.2)	<0.001[c]
Systolic blood pressure (mmHg)	137.9±18.9	138.8±17.7	136.5±20.9	0.302
Diastolic blood pressure (mmHg)	80.7±11.8	81.4±11.4	79.4±12.6	0.154

Data presented as n (%) or mean±SD.
CVD, cardiovascular disease; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
[a]p<0.01, [b]p<0.05, [c] p<0.001 independent t-test and chi-square test.
[d] Being treated.

group were analyzed with the chi-square test for linear trends. A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the socio-demographic, anthropometric, biochemical and clinical characteristics of patients. The overall prevalence of CVD among study subjects was 36.1%. Prevalences of CAD, cerebrovascular disease and PVD were 30.7%, 10.2% and 5.1%, respectively. Of the subjects with cerebrovascular disease, 9.6% had a history of a previous ischemic stroke and 4.5% had a history of a tran-

Table 2
Prevalence of MetS among T2DM patients with and without CVD.

MetS prevalence	All (N = 313)	CVD absent (N = 200)	CVD present (N = 113)	χ^2	p-value
NCEP ATP III	298 (96.1)	187 (93.5)	111 (98.2)	2.109	0.146
95% CI	94.0-98.3	91.8-98.0	95.8-99.9		
WHO	297 (95.8)	186 (93.0)	111 (98.2)	2.600	0.107
95% CI	93.6-98.1	91.2-97.7	95.8-99.9		
IDF	263 (84.8)	164 (82.0)	99 (87.6)	1.676	0.303
95% CI	80.8-88.9	78.0-88.5	81.4-93.8		
Harmonized	303 (97.7)	192 (96.0)	111 (98.2)	0.192	0.661
95% CI	96.1-99.4	95.3-99.7	98.2-95.8		

Data presented as n (%).
MetS prevalence are reported in parentheses.
MetS, metabolic syndrome; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; CI, confidence interval.

sient ischemic attack. The mean age of the subjects at the time of recruitment was 55.7±9.2 years, and the majority of the subjects were aged 50-69.9 years. The average duration of T2DM was 10 years. The subjects with CVD tended to have longer duration of DM (t=2.333, p=0.021). Males and females were equally represented. In terms of ethnic variation, one-third of the patients were Malays without CVD. Hence, the prevalence of CVD was highest among the Malays (36.3%), followed by Indians (34.5%) and then Chinese (29.2%). Higher mean WC and WHR values were observed among patients with CVD than those without CVD, but only the WHR was significantly different between the subjects with and without CVD (t=3.202, p=0.002). The mean HDL-C level was significantly lower among T2DM subjects with CVD (t=-3.749, p<0.001) and the mean triglyceride level was significantly higher among CVD patients (t=2.498, p=0.013). The use of medications for dyslipidemia was more common among subjects without CVD. More than 80% of subjects used medication for hypertension and dyslipidemia. The proportion of patients with dyslipidemia was 89.1% and 80.2% were hypertensive, with mean systolic and diastolic blood pressures of 137.9 and 80.7 mmHg, respectively. There was no significant difference in the mean blood pressure between subjects with and without CVD. Lower blood pressure was found among subjects with CVD. This may reflect more aggressive treatment in this group.

The prevalences of MetS among subjects using the criteria by the NCEP ATP III, WHO, IDF and new Harmonized system by presence of CVD are shown in Table 2. A high prevalence of MetS was found using all the four criteria. The overall prevalences of MetS (≥3 of 5 components) (95% CI) were 96.1% (94.0-98.3), 95.8% (93.6-98.1), 84.8% (80.8-88.9), and 97.7% (96.1-99.4) using the NCEP ATP III, WHO, IDF, and Harmonized criteria, respectively. Patients with MetS had a higher prevalence of CVD, though this was not significant for all criteria (Table 2).

Table 3
Prevalence of components of MetS by CVD status[a].

Criterion	NCEP ATP III			WHO			IDF			Harmonized		
	All (*N*=313)	CVD absent (*N*=200)	CVD present (*N*=113)	All (*N*=313)	CVD absent (*N*=200)	CVD present (*N*=113)	All (*N*=313)	CVD absent (*N*=200)	CVD present (*N*=113)	All (*N*=313)	CVD absent (*N*=200)	CVD present (*N*=113)
Obesity												
BMI (%)	-			112 (35.9)	74 (37.2)	38 (33.6)	-			-		
WC (%)	160 (51.3)	103 (51.8)	57 (50.4)	-			267 (85.6)	168 (84.4)	99 (87.6)	267 (85.6)	168 (84.4)	99 (87.6)
WHR (%)	-			270 (86.5)	167 (83.9)	103 (91.2)	-			-		
Hypertension (%)	283 (90.4)	174 (87.0)	109 (96.5)	273 (87.2)	167 (83.5)	106 (93.8)	283 (90.4)	174 (87.0)	109 (96.5)	283 (90.4)	174 (87.0)	109 (96.5)
Low HDL-C (%)	297 (95.5)	186 (93.9)	111 (98.2)	287 (92.3)	178 (89.9)	109 (96.5)	297 (95.5)	186 (93.9)	111 (98.2)	297 (95.5)	186 (93.9)	111 (98.2)
Elevated triglycerides (%)	290 (92.9)	181 (91.0)	109 (96.5)	290 (92.9)	181 (91.0)	109 (96.5)	290 (92.9)	181 (91.0)	109 (96.5)	290 (92.9)	181 (91.0)	109 (96.5)

Data presented as *n* (%).
BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; HDL-C, high-density lipoprotein cholesterol.
[a]Statistically not significant.

Table 4
Proportions of subjects by number of MetS components by CVD status (N = 313).

Number of MetS components	All (N = 313)	CVD absent (N = 200)	CVD present (N = 113)	p-value
NCEP ATP III				0.061
≤ 2 components	12 (3.9)	10 (5.0)	2 (1.8)	
3 components	21 (6.8)	18 (9.0)	3 (2.7)	
4 components	135 (43.5)	81 (40.5)	54 (47.8)	
5 components	142 (45.8)	88 (44.0)	54 (47.8)	
WHO				0.014[a]
≤ 2 components	13 (4.2)	11 (5.5)	2 (1.8)	
3 components	9 (2.9)	8 (4.0)	1 (0.9)	
4 components	62 (20.0)	46 (23.0)	16 (14.2)	
5 components	226 (72.9)	132 (66.0)	94 (83.2)	
IDF				0.019[a]
≤ 2 components	7 (2.3)	5 (2.5)	2 (1.8)	
3 components	14 (4.5)	13 (6.5)	1 (0.9)	
4 components	60 (19.4)	44 (22.0)	16 (14.2)	
5 components	229 (73.9)	135 (67.5)	94 (83.2)	
Harmonized				0.019[a]
≤ 2 components	7 (2.3)	5 (2.5)	2 (1.8)	
3 components	14 (4.5)	13 (6.5)	1 (0.9)	
4 components	60 (19.4)	44 (22.0)	16 (14.2)	
5 components	229 (73.9)	135 (67.5)	94 (83.2)	

Data presented as n (%).
[a]p<0.05 according to chi-square test.

This may have been because of the large number of T2DM patients with MetS both with and without CVD.

The prevalences of the various components of MetS are shown in Table 3. The MetS components in descending order of frequency were low HDL-C, elevated triglyceride level, hypertension, and obesity. The prevalences of obesity, hypertension, low HDL-C and high triglyceride levels were not significantly different between subjects with and without CVD, irrespective of the MetS definition.

The prevalences of the various components of MetS defined by the NCEP ATP III, WHO, IDF and Harmonized criteria are shown in Table 4. Most patients met the criteria for MetS. More than 95% of T2DM subjects had three, four or five components of MetS with all the NCEP ATP III, WHO, IDF and Harmonized definitions. Eighty-three point two percent of subjects with CVD had all five components of MetS following the WHO, IDF and Harmonized definitions. The results suggest patients with all five components of MetS may be more likely to have CVD. When subjects were grouped according to the number of MetS components they had, a significant linear increase in the prevalence of CVD was observed with a corresponding increase in the number of components following WHO (p=0.014), IDF (p=0.019) and Harmonized

(p=0.019) criteria, but was borderline using NCEP ATP III criteria (p=0.061) (Table 4).

DISCUSSION

The high prevalence of MetS among T2DM patients, particularly in those with CVD, is not surprising. Some studies have used different definitions of MetS in diabetic patients to determine the relative risk of CVD morbidity and mortality (Isomaa *et al*, 2001a,b; Bonora *et al*, 2003; Orna *et al*, 2004; Guzder *et al*, 2006; Sone *et al*, 2008; AlSaraj *et al*, 2009; Rodríguez *et al*, 2010) and found MetS is associated with an increased risk of CVD. Several explanations for the link between MetS and CVD are possible. Obesity, elevated blood pressure and dyslipidemia are more common in diabetic patients than in non-diabetic patients; these risk factors for CVD are more prevalent in patients with MetS resulting in the increased prevalence of CVD seen in diabetic patients (Ekoe *et al*, 2001).

There are important differences among the NCEP ATP III, WHO, IDF and Harmonized criteria used for MetS which could explain the weaker association between IDF and Harmonized MetS and CVD (Tables 2, 3). The lower cut-off level for WC as a definition in the IDF and Harmonized definitions compared to the NCEP ATP III definition could lead to people with lower risk factors being diagnosed with MetS; therefore reducing the relative risk of having CVD. WC criterion used in the IDF definition (≥90 cm in males and ≥80 cm in females) could result in a relatively lower prevalence of other risk factors for MetS using that method.

The high prevalence of MetS found in our study along with the finding that the more MetS components, the greater the risk of having CVD among the T2DM patients (p<0.05) using all four definitions of MetS confirms our hypothesis that diabetic patients are more susceptible to CVD (Costa *et al*, 2004). In a study of 318 Spanish patients with T2DM followed for 4.6 years, the presence of all MetS components significantly increased the CVD risk (Relative Risk=5.0%; 95% CI: 1.6-15.9; p=0.006) and the risk of coronary heart disease (RR =7.4; 95% CI: 1.3-41.1; p=0.02) (Orna *et al*, 2004). Other studies have found the coexistence of components of MetS and DM increases the risk of CVD (Bonora *et al*, 2003; Bruno *et al*, 2004; Cull *et al*, 2007; Hanefeld *et al*, 2007; Forst *et al*, 2009; Kanbak *et al*, 2011). Because of the high frequency of MetS in diabetic patients, multi-factorial intervention in these patients seems warranted.

The presence of MetS identifies patients at high risk of developing atherosclerotic CVD among T2DM patients. Understanding the relationships between the components of MetS may help us to better understand the pathophysiology that links those components and increases the risk of CVD. MetS is a disorder that includes important cardiovascular risk factors of hyperglycemia, obesity, dyslipidemia and hypertension. Its incidence is gradually increasing throughout the world (Alberti *et al*, 2009). These components of MetS are interrelated and share underlying mediators, mechanisms and pathways (Huang, 2009a). Patients with MetS may be asymptomatic until significant disease is already present.

There were several limitations of our study. This was a cross sectional study where the temporal relationship between CVD and the components of MetS could not be studied. Longitudinal studies are needed to determine the associations between CVD and MetS. The study subjects were patients attending tertiary referral

hospitals and many had longstanding DM. This could skew the results toward those with diabetic complications, cardiovascular risk factors and more difficult to control problems. This could exaggerate the risks. Due to the large number of cases with multiple criteria for MetS and the number of cases with only a few criteria was minimal making the power of the study insufficient to reach significance in those with only a few criteria. Another limiting factor in the study was patients were often being treated for the individual components of MetS, reducing their effect on risk for CVD.

In conclusion, we found MetS is alarmingly common among patients with T2DM. The more the components of MetS present the greater the risk of developing CVD, no matter what criteria was used to define MetS. The components of MetS should be targeted individually to reduce the risk of CVD in diabetic patients.

ACKNOWLEDGEMENTS

We would like to thank the Research University Grant Scheme and Department of Medicine, Universiti Putra Malaysia (UPM) for financial support (Grant No.: RUGS 9199609).

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