Original article

The metabolic syndrome in normal weight Malay subjects.

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Abstract:

Information regarding the prevalence of features of Metabolic Syndrome (MS) in Malaysia has not been previously reported. There are also difficulties in using Western cut-off criteria to define MS in this Asian population. The aim of this study was to determine the prevalence of features of MS in normal body weight normoglycemic Malay subjects. An additional aim was to determine the optimal waist circumference cut-off which best identified MS in this population. We used data from a cross-sectional study carried out in Malay descendants in Kota Bharu a city on east coast peninsular Malaysia. The prevalence of different features of MS was determined using the AHA/NHLBI and IDF criteria. The results showed that even after excluding subjects with diabetes mellitus, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), hypertension, a first degree relative with diabetes mellitus and obesity (BMI >25 kg/m^2), the features of metabolic syndrome were still highly prevalent in this population. Furthermore, the features of the metabolic syndrome were associated with reduced insulin sensitivity in an additive manner. The metabolic syndrome is a biologically relevant construct for the identification of the insulin resistant individual in a Malaysian population.

Keywords: Insulin sensitivity, metabolic syndrome

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Introduction

Over the past few years, the metabolic syndrome has been the subject of much controversy. Some groups have recommended against using the metabolic syndrome while others have suggested that it remains a biologically and clinically relevant construct. The originally stated rationale for the criteria was that the syndrome components are associated with insulin resistance. This seems like a valid reason for attempting to diagnose the metabolic syndrome since insulin resistance has been shown to be a predictor of both diabetes and cardiovascular morbidity[1]. However, as pointed out in a recent statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), there is considerable doubt whether all patients with the metabolic syndrome are indeed insulin resistant. One concern is that the new definitions of the metabolic syndrome overlaps significantly with other well established clinical states that are already known to be associated with increased insulin resistance such as obesity impaired fasting glucose, impaired glucose tolerance, hypertension, and diabetes mellitus. It is possible that the association between the metabolic syndrome and insulin resistance occurs as a consequence of the inclusion of these established disease states. If so, then the metabolic syndrome adds little to our current ability to identify insulin resistant individuals. We therefore felt it was important to determine whether the metabolic syndrome is associated with insulin resistance after the exclusion of these disorders. For this reason, we studied the association between

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features of the metabolic syndrome and insulin resistance in a population of Malay descendant after excluding subjects with diabetes mellitus, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), hypertension, a first degree relative with diabetes mellitus and obesity (BMI >25 kg/m^2).

A secondary aim of the study was to assess the appropriateness of ethnic specific waist circumferences in defining central obesity in an Asian population. Recently the International Diabetes Federation (IDF) and the American Heart Association (AHA)/ National Heart Lung and Blood Institute (NHLBI) proposed an ethnic-specific cut-off limit to define abdominal obesity (waist circumference)[1,2]. A study done in Singaporean population which represented three ethnic populations of Asia also supports this with evidence[3].

Materials and methods

Data for this research was taken from the results of a cross-sectional study which was conducted from mid September 2003 to March 2005. This study was approved by the Research and Ethical Committee, School of Medical Sciences, Universiti Sains Malaysia (USM). Written informed consent was taken from every participant in this study. The study method adhered to the existing Malaysian guidelines for International Committee on Harmonization of Good Clinical Practice (ICH-GCP) Guidelines[4]. Research volunteers were recruited from schools and public offices in Kota Bharu, a city in east coast peninsular Malaysia. An open invitation was posted at each location for an initial screening program.

Selection criteria for entry of volunteers were: 1) adults aged between 30 to 60 years, 2) non-obese with BMI <25kg/m^2 [5], 3) non-diabetic and non-hypertensive, 4) without family history of type 2 diabetes, and 5) non-smoker. Subjects suffering from chronic illnesses, ketosis, chronic liver and renal diseases, and pregnant women were excluded from the study. Subjects taking anti-hypertensive drugs, steroids or traditional supplements were also excluded[6]. The subjects were screened according to the selection criteria, and anthropometric measurements (height, weight, waist circumference, and BMI) and clinical history were recorded. Those who met the selection criteria were invited to come to the Department of Chemical Pathology in USM after overnight fasting (10-12 h) for oral glucose tolerance test (OGTT), liver function test (LFT), renal function test (RFT) followed by lipid profile and insulin sensitivity test in two separate visits. The second visit was arranged for only those who were proven free from diabetes, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), renal and or liver disease. Diabetes and IGT were defined according to the criteria set by the World Health Organization (WHO) Expert Committee[7].

Out of a total of 890 staff from different offices, 561 subjects participated in the screening program for the cross-sectional study (participation rate 63%). Finally, 226 subjects fulfilled the selection criteria and were recruited. All the study subjects were Malaysian Malay by ethnicity.

Body weight (in kg) was measured in subjects wearing casual light clothing. Height (in cm) was measured by using appropriate scales (Standard ZT-120®, Healthometer Inc., USA) in bare feet. Body mass index (BMI in kg/m^2) was calculated as weight in kg divided by height in m^2. Waist circumference (in cm) was measured at the level of umbilicus[8].

Pulse and blood pressure of all subjects were measured by a single person. At least two readings of blood pressure were taken at 5 minutes interval on the right hand using a mercury sphygmomanometer (Baumanometer®, W.A. Baum Co, Inc., New York, USA) in the sitting position and the mean value was noted. A subject was identified as hypertensive if

Table 1. Characteristics of the study population [mean(SD)]

Parameter	Men	Women
Mean (SD)	n=96	n=130
Age (years)	40.54 (6.88)	39.25 (7.07)
Body mass index (kg/m^2)	23.07 (1.99)	22.39 (2.46)
Waist circumference (cm)	85.46 (7.99)	73.85 (7.95)
Total cholesterol (mmol/L)	5.77 (0.11)	5.46 (0.90)
LDL-Cholesterol (mmol/L)	3.62 (0.97)	3.25 (0.89)
HDL-Cholesterol (mmol/L)	1.37 (0.36)	1.71 (0.43)
Triglyceride (mmol/L)	1.82 (1.51)	1.14 (0.70)
Fasting plasma glucose (mmol/L)	4.43 (0.84)	4.22 (0.62)
Insulin (pmol/L)	63 (55)	52 (38)
b-cell function	151 (84)	142 (75)
Insulin sensitivity	116 (71)	135 (84)

he either had a systolic blood pressure at or above 140 mmHg (≥140 mmHg) and/or diastolic blood pressure at or above 90 mmHg (≥90 mmHg)[9].

Blood specimens for lipid profile were collected in 5ml Vacutainer® tubes with SST® Gel and clot activator. Blood for insulin was collected in 5ml plain Vacutainer® tubes. Blood for glucose was collected in 2ml fluoride oxalate tubes (NaF oxalate 2®). All tubes used for blood collection were supplied by Becton Dickinson Vacutainer Systems 15336 (FD), Farklin Lakes, New Jersey, USA . Plasma glucose and lipid levels were performed on the same day of blood collection. Serum for insulin was frozen immediately at -80˚C and was assayed in separate batches within three months of specimen collection.

All blood analyses were performed in ISO-9001 certified laboratories using commercial kits and automated fully enzymatic colorimetric methods on the Cobas Integra 400® automated chemistry analyzer (ROCHE®, Switzerland). Fasting plasma glucose (FPG) was estimated by the glucose oxidase (GOD-PAD) method (inter-assay coefficient of variation (CV) 2.45%). Serum total cholesterol was estimated by the cholesterol oxidase-peroxidase (CHOD-PAP) method (inter-assay CV 1.27%). HDL cholesterol (HDL-C) was estimated following chemical precipitation with phosphotungstic reagent and subsequent CHOD-PAP method (inter-assay CV 1.26%). Triglyceride (TG) was estimated by the glycerol oxidase-peroxidase (GPO-PAP) method (inter-assay CV 1.38%). The LDL cholesterol (LDL-C) level in serum was calculated by using the Friedewald formula[10]. Serum insulin (inter-assay CV 1.39%) was measured by chemiluminescence method on the IMMULITE® analyzer (Diagnostics Products Corporation EURO/DPC, United Kingdom).

Homeostasis model assessment (HOMA) software was used to calculate insulin sensitivity (HOMA%S) and insulin secretory capacity (HOMA%B) of the subjects. Fasting insulin levels (in pmol/L) and fasting plasma glucose (FPG) (in mmol/L) were keyed into the computer using the HOMA software to calculate HOMA%S and HOMA%B[11-13].

The following features of the MS were identified in each subject

a) waist above 90 cm for male and above 80 cm for female;

b) HDL-C <1.00 mmol/L for men and <1.31 mmol/L for women;

c) TG >1.71 mmol/L;

d) Fasting plasma glucose >5.6 mmol/L,

e) Systolic blood pressure ≥130 mmHg and or diastolic blood pressure ≥85 mmHg.

An individual was considered to meet the AHA/NHLBI criteria for the metabolic syndrome if they exhibited at least three out of five criteria. For the diagnosis of the metabolic syndrome under the IDF criteria, the presence of central obesity was required plus 2 additional features.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) for Windows version 11.1[14]. Subjects demographic, anthropometric and biochemical (lipid, FPG, insulin sensitivity) baseline descriptive statistics and prevalence of non-obesity related MS criteria in study population were presented as percentage, mean (standard deviation, sd) and median (inter-quartile range, iqr) whenever appropriate. The insulin sensitivity was log-transformed due to the skewed distribution of data. Association between the number of features of

Table 2. Prevalence of MS criteria in the study population using the American Heart Association/ National Heart Lung and Blood Institute and International Diabetes Federation criteria.

MS criteria	Prevalence (%)
Waist circumference	33.93%
Low HDL-Cholesterol	19.58%
High Triglyceride	25.56%
High fasting plasma glucose	4.15%
High blood pressure	67.41%

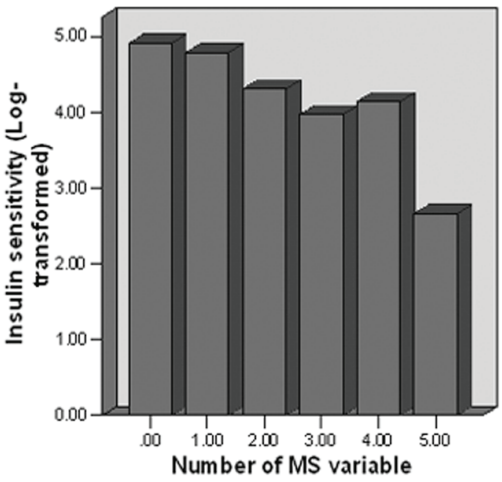

Figure 1. Association between the number of features of the metabolic syndrome and insulin sensitivity

Appendix 1: The ROC analysis data

72.5	0.894737	0.495495	0.504505		1.399241
71.5	0.894737	0.522523	0.477477		1.372214
76.5	0.684211	0.333333	0.666667		1.350877
70.5	0.894737	0.567568	0.432432		1.327169
77.75	0.631579	0.306306	0.693694		1.325273
74.5	0.736842	0.414414	0.585586		1.322428
77.25	0.631579	0.315315	0.684685		1.316264
75.5	0.684211	0.378378	0.621622		1.305832
79.25	0.526316	0.234234	0.765766		1.292082
73.5	0.736842	0.45045	0.54955		1.286392
80.5	0.473684	0.189189	0.810811		1.284495
78.5	0.526316	0.27027	0.72973		1.256046
79.75	0.473684	0.225225	0.774775		1.248459
69.5	0.894737	0.648649	0.351351		1.246088
83.5	0.368421	0.135135	0.864865		1.233286
68.5	0.894737	0.693694	0.306306		1.201043
84.5	0.315789	0.126126	0.873874		1.189663
82	0.368421	0.18018	0.81982		1.188241
67.5	0.894737	0.72973	0.27027		1.165007
64.5	1	0.837838	0.162162		1.162162
65.5	0.947368	0.810811	0.189189		1.136558
86.5	0.157895	0.027027	0.972973		1.130868
66.5	0.894737	0.765766	0.234234		1.128971
85.5	0.157895	0.054054	0.945946		1.103841
63.5	1	0.900901	0.099099		1.099099
62.5	1	0.90991	0.09009		1.09009
61.5	1	0.936937	0.063063		1.063063
60.5	1	0.954955	0.045045		1.045045
58.5	1	0.981982	0.018018		1.018018
56.5	1	0.990991	0.009009		1.009009
55	1	1	0		1
88	0	0	1		1

the MS and HOMA%S was assessed by ANOVA.

Results

Age, anthropometric characteristics, lipid levels, fasting plasma glucose, fasting insulin level, insulin sensitivity and b-cell function of the study subjects are shown in **Table 1**. Results showed that insulin sensitivity in women is higher than men, They also had higher HDL-C and lower TG lower than men. The prevalence of each MS criterion in the study population is shown in **Table 2**. It can be seen that features of MS are highly prevalent among the study population despite the fact that we excluded individuals with states associated with insulin resistance including overweight/obesity, hypertension, IFG/IGT, family history of diabetes Using AHA/NHLBI criteria the prevalence of MS among the study population was 10.18%. The prevalence was 9.29% using IDF criteria.

Figure 1 shows that, with increasing numbers of MS features, the log-transformed insulin sensitivity decreased significantly ($p < 0.001$ for trend).

Discussion

Our study shows that, even after excluding clinical states known to be associated with insulin resistance, each feature of MS was associated with reduced insulin sensitivity. Furthermore, the associations between the features of the metabolic syndrome and insulin resistance is additive ie, a greater number of features was associated with greater insulin resistance. As such, if the aim of defining the metabolic syndrome is to identify those with insulin resistance, then the metabolic syndrome appears to be a biologically valid construct that identifies individuals with insulin resistance which would otherwise have not been identified.

The other aspect of our data that we found interesting was that, in this study population that may be considered non-obese by existing recommendations (BMI < 25 kg/ m2) , the features of the MS remained very common with over half exhibiting at least one feature of the MS. This is in line with the finding that BMI significantly underestimates the degree of adiposity in several Asian populations[15] and the recommendation that lower 'action levels' should be set in these populations[16].

Both the AHA/NHLBI and the IDF, in the new recommendations for the definition of the metabolic syndrome, have included ethnic specific cut-offs for waist circumference. We performed ROC analysis (data shown in Appendix 1) using waist circumference to identify those with at least 2 other risk factors and they arrived at 86.5 cm in men and 72 cm in women. Although the absolute values determined from our ROC analysis differ from those of a previous study carried out in Singapore[2], we recognize that ours is a small study in a highly selected population. Nevertheless, we believe that our findings support the use of lower cut-offs in Asians recommended by both the AHA/NHLBI and the IDF. The American Diabetes Association and the European Association for the Study of Diabetes

have criticized this approach on the basis that there is little or no evidence that the same intra-abdominal fat mass carries different risk in different ethnic groups. However, it should be appreciated that the rationale for lowering the thresholds for defining central obesity in populations of Asian Ethnicity has little to do with the belief that the same degree of adiposity connotes a higher risk of CVD in these populations. It has been reported that waist circumference underestimates the degree of abdominal adiposity in Asians compared to Caucasians[17]. Therefore, it is believed that waist cirumference, as a tool used to estimate the level of central obesity, underestimates the degree of abdominal adiposity obesity present in these populations and the lower thresholds are designed merely to account for this measurement error.

In Malaysia, lifestyles have evolved from being predominantly manual to being more sedentary. Traditional diets have been replaced by diets that contain more refined and less fiber containing foods. These changes are associated with rapidly increasing rates of diabetes and cardiovascular disease in the Malaysian population[18-19]. In this setting, early detection of individuals with insulin resistance using simple clinical criteria, such as the metabolic syndrome, may facilitate the institution of preventive strategies to prevent diabetes and cardiovascular disease before the onset of disease. However, the authors appreciate that the benefits and cost-effectiveness of such strategies have not been clearly documented and we believe that the development of interventional trials to assess these aspects of the metabolic syndrome should form major priorities in the future.

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