ORIGINAL ARTICLE

METABOLIC PHENOTYPING USING METABOLIC SYNDROME CRITERIA AND CARDIOMETABOLIC DISABILITIES CRITERIA IN BANGLADESHI ADULT POPULATION

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ABSTRACT

Obesity has become a global epidemic and has been found to be associated with numerous co-morbidities. Body mass index (BMI) based classification of obesity is simple but co-morbidities do not affect all obese and overweight people. The present study was aimed to find out the frequency of metabolic phenotypes in different BMI groups using metabolic syndrome (MetS) criteria and cardiometabolic disabilities (CA) criteria and also to find out an appropriate method for defining metabolic health among adult population attending out patient department of Bangabandhu Sheikh Mujib Medical University (BSMMU). This cross-sectional analytical study was carried out in the Department of Biochemistry, Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2016 to February 2017. By non probability sampling, a total of 1023 study subjects were selected from apparently healthy adult individuals attending outpatient department of BSMMU. The study subjects were grouped into three body mass index classes and also further categorized into six groups according to metabolically unhealthy or healthy phenotypes by presence or absence of metabolic syndrome (MetS) criteria as well as cardiometabolic disabilities (CA) criteria respectively. Then agreement among different metabolic phenotypes based on these two criteria were observed. Frequency of different metabolic phenotypes i,e metabolically healthy normal weight (MHNW), metabolically obese normal weight (MONW), metabolically healthy over weight (MHOW), metabolically obese over weight (MOOW), metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO) were 12.3%, 6.9%, 21.4%, 27.7%, 7.7%, 23.9% by MetS criteria and 7.7%, 11.5%, 11.6%, 37.4%, 6.1%, 25.6% by CA criteria respectively. MOOW followed by MUO were found to be predominant among all phenotypes. Fare agreement was found between two criteria in case of normal weight and overweight groups and good agreement was found in case of obese groups. From this study, it may be concluded that, attention should be given to the metabolically obese phenotypes in different BMI classes to reduce co-morbidities.

Key Words: Metabolic phenotypes, MHNW, MONW, MHOW, MOOW, MHO, MUO, Metabolic syndrome (MetS), Cardiometabolic disabilities (CA)

Introduction

Obesity and overweight has now become one of the most common problem related to lifestyle. New scientific studies and data from life insurance companies have shown that, even relatively small increase in body weight without having marked obesity, is associated with obesity related health risks[1].

A systematic analysis (1980-2013) for the "Global Burden of Disease Study 2013", conducted by an international consortium of researchers stated that about 2.1 billion people accounting for about one-third of the world's population are overweight or obese. The number of overweight and obese individuals in the world has increased from 857 million (~20%) in 1981 to 2.1 billion (~30%) in 2013[1]. In Bangladesh, 17% adults are obese or overweight[2].

Overweight and obesity are caused by many factors including genetic factors, environmental factors, sedentary lifestyles, ageing, pregnancies, biological factors (hormonal factors), stress and drugs etc[3]. Health risks, such as cardiovascular disease, cancer, diabetes, osteoarthritis and chronic kidney disease increase when a person's BMI is 23 or more[2].

Body Mass Index (BMI), defined as the weight in kilograms divided by the square of the height in meters (kg/m^2) is established by the World Health Organization (WHO) in 1997 and updated in 2015, is a useful, convenient, cheap, and easy to measure tool commonly used by doctors to determine normal weight (18.5-24.9), overweight (25-29.9) and obesity (⩾30) in adults. But it has some limitations as BMI-based classification of obesity cannot measure total body fat content directly nor can distinguish fat from lean (bone) mass, also cannot measure adipocyte dysfunction. It has been observed that normal weight individuals (according to BMI) may have abnormal metabolic profiles to be at increased risk of developing obesity associated diseases[4]. These individuals are called metabolically obese normal weight individuals (MONW). On the other hand, some obese and overweight individuals may have insulin sensitivity, normal blood pressure, favorable lipid profile, lower proportion of visceral fat, less liver fat and a normal glucose metabolism[5]. They are known as "metabolically healthy obese"(MHO) and "metabolically healthy overweight"(MHOW).

The term metabolic obesity (MO) has been floated to solve this issue. MO may be defined as individuals with unhealthy metabolic profile irrespective of BMI. Some researchers used components of metabolic syndrome (MetS) (waist circumference, TG, HDL-C, FBS, BP) to classify metabolically healthy and metabolically unhealthy phenotypes in different BMI group (normal weight, overweight, obese)[6,7]. Individual having ⩾3 components abnormal is regarded as metabolically unhealthy and individual having 0-2 components abnormal regarded as metabolically healthy. Wildman *et al.* in 2008 evaluated metabolic health by the components of cardiometabolic disabilities (CA). Individual having 2 or more abnormal components of CA out of 6 components (BP, FBS, HOMA-IR, TG, HDL-C, hsCRP) is regarded as metabolically unhealthy; whereas, presence of less than 2 components of CA regarded as metabolically healthy[8].

Therefore in each BMI group metabolically healthy and unhealthy phenotypes are categorized using both MetS criteria and CA criteria and thus six metabolic phenotypes are identified: MHNW (metabolically healthy normal weight), MONW (metabolically obese normal weight), MHOW (metabolically healthy overweight), MOOW (metabolically obese

overweight), MHO (metabolically healthy obese), MUO (metabolically unhealthy obese).

It is very important to find out frequency of different metabolic phenotypes in our population so that due attention can be given to those, who need special attention regarding life style modification and treatment to reduce morbidity and mortality. Again there are different methods proposed by different researchers to classify the metabolic phenotypes but yet to achieve a consensus. So a unified method to categorize metabolic phenotypes is needed to search out.

Materials and Methods

This cross-sectional analytical study was conducted in the Department of Biochemistry and Molecular Biology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from March 2016 to February 2017 after receiving Institutional Review Board approval from BSMMU. By non probability sampling, a total of 1023 study subjects of both sexes, age range between 20 to 60 years were selected from apparently healthy adult individuals attending outpatient department of BSMMU. The subjects with BMI less than 18.5 kg/m^2, pregnancy, previous H/O stroke, IHD, chronic liver disease, chronic kidney disease and malignancy were excluded. Initial evaluation by history taking and clinical examination was performed and blood pressure, height, weight and waist circumference were recorded in a preformed data sheet. With all aseptic precautions, fasting blood samples were collected from each study subject. Fasting plasma glucose was measured using hexokinase method (CI 4100 ARCHITECT, USA) whereas HDL-C was measured using enzymatic color test (Beckman Coulter Inc., USA); triglyceride was measured using enzymatic glycerol phosphate oxidase method (Beckman Coulter Inc., USA) and fasting insulin was measured by Chemilminescent Microparticle Immunoassay (CI 4100 ARCHITECT, USA) to measure HOMA-IR[9]. The study subjects were grouped into three body mass index classes (normal weight, overweight and obese according to BMI 18.5- 24.9, 25-29.9 and $\geqslant$30 kg/m^2 respectively) and also further categorized into metabolically unhealthy or healthy phenotypes by presence or absence of metabolic syndrome (MetS) crieteria and cardiometabolic disabilities (CA) crieteria respectively. According to the modified NCEP ATP III (2001) definition[10], metabolic syndrome (MetS) was considered to be present if three or more of the following five criteria were met: central obesity i.e. waist circumference $>$ 102 cm (men) or $>$ 88 cm (women), blood pressure $\geqslant$ 130/85 mm Hg or taking medication for hypertension, fasting triglyceride (TG) level $\geqslant$ 150 mg/dl, fasting high-density lipoprotein (HDL-C) cholesterol level $<$ 40 mg/dl (male) or $<$ 50 mg/dl (female) or taking medication for dyslipidemia and fasting blood sugar $\geqslant$ 5.6 mmol/L or taking medication for DM. Again according to cardiometabolic disabilities (CA) criteria modified from Wildman's (2008) individual having 2 or more abnormal components of following 5 components was regarded as metabolically unhealthy; i,e BP ($\sim$130/85 mm Hg), fasting TG $>$ 150 mg/dl, HDL-C $<$ 35 mg /dl (male), and $<$ 40 mg/dl (female), FBS $>$ 5.5 mmol/L, HOMA-IR $>$ 2.5[8].

Thus using these criteriae all the subjects finally were categorized into six metabolic phenotypes; metabolically healthy normal weight (MHNW), metabolically obese normal weight (MONW), metabolically healthy overweight (MHOW), metabolically obese overweight (MOOW), metabolically healthy obese (MHO) and metabolically unhealthy obese (MUO). The statistical analysis was carried out using the software IBM SPSS version 22. Quantitative data were expressed as mean and standard deviation (mean $\pm$ SD). The prevalence of

different obesity phenotypes were expressed at 95% confidence interval. Categorization of obesity phenotypes by two methods were evaluated by agreement test (kappa test). P-value <0.05 was regarded as significant.

Result

In this study, frequency of normal weight, overweight and obese individuals were 19.3%; 49.1%, 31.7% respectively (Table-I). Here overweight followed by obese group were found to be predominant. Frequency of different metabolic phenotypes such as MHNW, MONW, MHOW, MOOW, MHO, MUO were 12.3%; 6.9%; 21.4%; 27.7%; 7.7% and 23.9% (according to MetS criteria) and 7.7%; 11.5%; 11.6%; 37.4%; 6.1%; 25.6% (according to CA criteria) respectively (Table-II). In both criteria MOOW followed by MUO groups were found to be predominant.

Among different metabolic phenotypes, characterized by MetS criteria; MONW found to be more in male but MHO and MUO found to be more in female; whereas, MOOW, MHO, MUO were found to be significantly more in younger age group than older age group (Table- III).

MONW, MOOW, MUO groups showed increasing trend of HOMA-IR values according to BMI, but MHOW and MHO groups showed comparatively better insulin sensitivity despite of being overweight and obese according to BMI classification (Table- III).

After doing agreement test, kappa value was found 0.53 in normal weight individuals and 0.47 in overweight individuals indicating fair agreement and kappa value was found 0.67 in obese individuals indicating good agreement between MetS criteria and CA criteria, for categorization of subjects into six different metabolic phenotypes (Table- IV).

Table-I: Distribution of study subject according to BMI (n=102)

BMI classes	frequency	Percent (%)
Normal weight (18.5-24.9)	197	19.3
Over weight (25-29.9)	502	49.1
Obese ($\geqslant$30)	324	31.7

Table-II: Frequency of metabolic phenotypes categorized by Metabolic syndrome (MetS) and Cardiometabolic Disabilities (CA) among 1023 individuals N=1023

Metabolic	According to MetS		According to CA	
phenotypes	Frequency	Percent (%)	Frequency	Percent (%)
MHNW	126	12.3	79	7.7
MONW	71	6.9	118	11.5
MHOW	219	21.4	119	11.6
MOOW	283	27.7	383	37.4
MHO	79	7.7	62	6.1
MUO	245	23.9	262	25.6

MHNW, metabolically healthy normal weight, MONW, metabolically obese normal weight, MHOW, metabolically healthy overweight, MOOW, metabolically obese overweight, MHO, metabolically healthy obese, MUO, metabolically unhealthy obese

Table-III: Baseline characteristics of metabolic phenotypes in different BMI classes characterized by MetS criteria (n=1023)

Parameters	MHNW	MONW	MHOW	MOOW	MHO	MUO	p-value
Frequency (percent %)	126(12.3)	71(6.9)	219(21.4)	283(27.7)	79(7.7)	245(23.9)	0.00
Number of cases (male/female)	88/38	46/25*	141/78*	132/151	21/58*	57/188*	0.00[a]
Distribution in different age groups (20-40 years/ 41-60 years)	98/28	36/35	150/69*	154/129*	56/23*	157/88*	0.00[a]
Age (mean±SD)	33.95±7.2	38.47±8.9	35.44±7.7	38.23±8.1	33.61±7.4	36.27±8.1	0.00
Weight (mean±SD)	61.76±7.9	61.45±7.2	71.38±7.9	70.91±7.6	81.10±9.5	82.04±11.5	0.00
WC (mean±SD) (Waist circumference)	83.90±5.9	87.69±5.2	98.48±5.5	94.42±5.5	101.05±7.6	102.74±9.1	0.00
SBP (mean±SD) (systolic blood pressure)	115.41±13.8	127.10±11.7	117.45±11.5	126.84±12.7	117.27±10.8	125.82±13.5	0.00
DBP (mean±SD) (diastolic blood pressure)	78.11±9.1	80.97±7.2	80±7.3	83.42±7.4	81.88±7.4	83.41±8.1	0.00
FBG (mean±SD) (Fasting blood glucose)	4.73±0.7	5.56±2	4.8±1.2	5.37±1.8	4.50±0.6	5.3±0.41	0.00
HDL (mean±SD) (high density lipoprotein)	41.51±8.2	37±8.1	40.40±8.2	37.37±7.1	41.06±8.6	39.70±7.8	0.00
TG (mean±SD) (triglyceride)	137.98±68.5	199.51±75.3	147.63±65.1	132.12±74.7	112.38±26.5	130.08±72.6	0.00
HOMA-IR (median/IQR)	1.5/ 1.1- 2.3	2.1/ 1.4-3	1.9/ 1.4-2.7	2.5/ 1.8-3.9	2/ 1.5-2.9	3.3/ 2.4-4.6	0.00[b]

Continuous variable reported as mean±SD and median/ IQR (in case of nonprametric data) whereas categorical variables as absolute and relative frequencies. One way ANOVA was carried out to find out the level of significance. [a]*Chi-square test was done to find out the level of significance. *Significant difference was found by proportion test.* [b]*Kruskall-Wallis test was done to find out the level of significance.*

Table-IV: Agreement between metabolic syndrome (Mets) criteria and cardiometabolic disabilities (CA) criteria for categorization of obesity phenotypes in different BMI classes

Normal weight (n=197)				
Category by Mets	Category by CA		Kappa-value	p-value
	MHNW	MONW		
MHNW	78	48	0.53	0.00
MONW	1	70		
Overweight (n=502)				
Category by Mets	Category by CA		Kappa-value	p-value
	MHOW	MOOW		
MHOW	104	115	0.47	0.00
MOOW	15	268		
Obese (n=324)				
Category by Mets	Category by CA		Kappa-value	p-value
	MHO	MUO		
MHO	50	29	0.67	0.00
MUO	12	233		

Agreement has done by kappa test. Interpretation of kappa (κ) statistic: <0.00 (no agreement), 0.01- 0.2 (poor agreement), 0.21- 0.40 (slight agreement), 0.41-0.60 (fair agreement), 0.61-0.80 (good agreement), 0.81-0.92 (very good agreement), 0.93- 1.0 (excellent agreement)

Discussion

This cross-sectional analytical study was aimed to find out the frequency of metabolic phenotypes in different BMI groups among adult and apparently healthy individuals aged 20 to 60 years attending OPD of BSMMU. Total 1023 study subjects were selected from adult individuals attending Bangabandhu Sheikh Mujib Medical University (BSMMU) out patient department (OPD).

The frequency of overweight (BMI-25-29.9), and obese (BMI 30) were found to be predominant among 1023 study subjects. The frequency of overweight (49%) and obese (31.7%) documented in this study was comparatively higher than previous studies done in Bangladesh. The age standardized frequency of overweight and obese at rural population of Bangladesh were found to be 17.7% and 26.2% in 2013[11]. Reason behind this difference may be due to the fact that different researchers used different study design and conducted the studies at different points of time using different anthropometric measurement to categorize overweight and obesity. Moreover many of these studies focused on particular segment of population which do not represent the whole population[11-13]. But the previous studies also showed the increasing trend of overweight and obesity[11,12]. Rapid urbanization, affluency, high educational level, shifts from manual labor to more sedentary occupations and the related decline in physical activity were claimed to be associated with higher prevalence of overweight-obesity[13].

In this study, we have used metabolic syndrome (MetS) criteria and cardiometabolic disabilities (CA) criteria to categorize metabolic phenotypes in total study population as well as in every BMI classes. Frequency of MOOW followed by MUO were found to be predominant in our study subjects after categorization by both criteria. Our study showed frequency of MOOW and MUO to be 27.7% and 23.9% according to MetS criteria whereas, 37.4% and 25.6% according to CA criteria respectively and study also showed very low percentage of MONW or MHO which agree with many other studies[6-8].

MetS criteria and CA criteria were evaluated for categorizing metabolic phenotypes as well as for defining metabolic health in every BMI classes. Both the criteria's (MetS and CA) were found to show fare agreement in case of normal weight and overweight groups; good agreement in case of obese group for categorizing metabolic phenotypes possibly due to overlaps among the components of MetS criteria and CA criteria used to define metabolic health. Studies where very low degrees of agreement were found among Mets criteria, HOMA-IR criteria,

combined MetS and HOMA-IR criteria may be due to fact that they used different clinical profile[14,15]. MetS criteria, for categorization, is more convenient, simple and cost effective than CA criteria. So we suggest Mets criteria to define metabolic health as well as to categorize metabolic phenotypes.

Our study showed different metabolically obese phenotypes (MOOW, MHO, MUO) to be more in female than male except for MONW which was found to be more in male. It might be due to life style differences, physical activity and smoking habit. Different researchers used different criteria's to define metabolic health using different study design with different study population and hence showed different pattern of gender difference[15,16].

In this study MOOW and MONW found more in older age group (41-60 years). But MHO and MUO, showed higher tendency (non significant) in younger age group (20-40 years) which do not agree with many other studies[6,8]. But Popkin *et al.*(2001), mentioned about the increasing prevalence of obese and overweight among the adult age group (20-45) that might be due to change in dietary habit and less physical activity in their study population[17].

Among all the metabolic phenotypes, MHO group were presented with better insulin sensitivity. This is consistent with previous study where MHO group did not show increased CVD risk or cancer mortality when compared with normal weight insulin sensitive individuals5. Again MONW individuals shows insulin resistance and early detection of which may help prevent the development of type 2 diabetes and other obesity related comorbidities[18].

One limitation of our study is that we had collected our sample from apparently healthy population attending out patient department of BSMMU which truly do not represent our whole Bangladeshi population.

A WHO expert consultation group debated about interpretation of recommended body-mass index (BMI) cut-off points for determining overweight and obesity in Asian populations, and recommended for a population-specific cut-off points for BMI. They reviewed scientific evidence that suggests that Asian populations have different associations between BMI, percentage of body fat, and health risks than do European populations. The consultation group also agreed that the WHO BMI cut-off points should be retained as international classifications, because the available data did not necessarily indicate one clear BMI cut-off point for all Asians, for overweight or obesity[19]. So to avoid this dispute we had used WHO classification of BMI for categorization of metabolic phenotypes.

In conclusion MOOW followed by MUO groups were found predominant among all metabolic phenotypes and MHOW and MHO groups are showing better insulin sensitivity despite of being overweight and obese.

This study concludes that, there is good agreement between metabolic syndrome (MetS) criteria and cardiometabolic disabilities (CA) criteria in case of obese groups and fare agreement in case of normal weight and overweight for categorization of different metabolic phenotypes. Between the two, we suggest to use MetS criteria to categorize obesity phenotypes because MetS criteria is more convenient, simple and cost effective compared to CA criteria for defining metabolic health.

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