Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Prevalence of Metabolic Syndrome and its Associated Risk Factors in Pediatric Obesity

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Abstract

Objective. We aimed to study the prevalence of metabolic syndrome (MetS) and the factors associated with metabolic syndrome among obese children.

Methodology. We recruited 175 subjects, aged 7 to 18 years old, referred for obesity. We studied their demography (age, gender, ethnicity, family background), performed clinical/auxological examinations [weight, height, body mass index (BMI), waist circumference (WC), blood pressure (BP)], and analyzed their biochemical risks associated with metabolic syndrome [fasting plasma glucose (FPG), fasting lipid profile (FLP), fasting insulin, liver function tests (LFT)]. MetS was identified according to the criteria proposed by the International Diabetes Federation (IDF) for pediatric obesity. Multiple logistic regression models were used to examine the associations between risk variables and MetS.

Results. The prevalence of metabolic syndrome among children with obesity was 56% (95% CI: 48.6 to 63.4%), with a mean age of 11.3 ± 2.73 years. Multiple logistic regression analysis showed age [adjusted odds ratio (OR) 1.27, 95% CI: 1.15 to 1.45] and sedentary lifestyle (adjusted OR 3.57, 95% CI: 1.48 to 8.59) were the significant factors associated with metabolic syndrome among obese children.

Conclusion. The prevalence of metabolic syndrome among obese children referred to our centers was 56%. Older age group, male gender, birth weight, sedentary lifestyle, puberty and maternal history of gestational diabetes mellitus (GDM) were found to be associated with MetS. However, older age group and sedentary lifestyle were the only significant predictors for metabolic syndrome.

Key words: prevalence, metabolic syndrome, risk factors, obese children

INTRODUCTION

Obesity is one of the major public health problems in both developed and developing countries. Over 340 million children and adolescents age 5 to 19 years were overweight or obese in 2016, according to the World Health Organization (WHO).[1] An estimated 38.2 million children under the age of 5 years old were either overweight or obese. Half of the estimated children with obesity were from Asia.[1] The prevalence of obesity in South America was as high as 41.8% in Mexico, 19.3% in Argentina and 22% in Brazil.[2] In the Asia-Pacific region, the prevalence of obesity among children and adolescents was 16.3% in New Zealand, 14.1% in Brunei Darussalam, and 12.7% in Malaysia.[3] The estimated prevalence of obesity in the United States was 19.3% or about 14.4 million children and adolescents.[4] The high prevalence of obesity is most often related to excessive consumption of a high-calorie diet and poor lifestyle.[5] More important, it is reported that a third of obese children and 80% of obese adolescents remain obese when they reach adulthood.[6]

Obesity is associated with multiple co-morbidities/complications. The most serious endocrine complication is metabolic syndrome.[7,8] In the National Health Survey in China (2002), the prevalence of MetS among adolescents was 3.7%, and the prevalence rates of obesity, overweight and normal weight in children were 35.2%, 23.4% and 2.3%, respectively.[2] The prevalence of MetS among Turkish students with obesity was ten times more than lean students (21% versus 2%).[2] MetS prevalence was as high as 36% among children with obesity in Bolivia compared to children in South Korea, with a prevalence of only 9.1%.[2]

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines
Copyright © 2022 by Sabri et al.
Received: August 29, 2021. Accepted: November 15, 2021.
Published online first:
https://doi.org/10.15605/jafes.037.01.05

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There are numerous publications related to pediatric obesity in Malaysia. In 2011, the South-East Asia Nutrition Survey (SEANUTS) revealed that the prevalence of overweight and obesity in children six months to 12 years of age was 21.6%.[9] The 2015 National Health and Morbidity Survey (NHMS) reported that the prevalence of obesity among children age 10 to 14 years in Malaysia was 14.4%.[10] The study by Fadzlina et al., showed a 16.0% and 9.4% prevalence of overweight and obese status among 13-year-old adolescents respectively.[11] The MyBreakfast study found that the prevalence of overweight and obesity in Malaysian children age 6 to 12 years was 14.7 %.[12] Compared to other Southeast Asian countries such as the Philippines, Thailand and Vietnam, there are more overweight and obese Malaysian adolescents.[13-15]

Metabolic syndrome is defined as the clustering of risk factors of dyslipidemia, abnormal glucose metabolism and high blood pressure. If left untreated, the syndrome would result in cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).[16,17] According to Andrabi et al., the prevalence of MetS among children and adolescents was 3.8%, with obese subjects having the highest proportion of MetS compared with those at risk for overweight and average weight (30.7% vs. 2.5% and 0.5%, respectively).[18] A review of MetS research in Malaysia by Lim et al., using the IDF criteria found the prevalence of metabolic syndrome among overweight and obese children was 1.3% to 5.3%.[19,20] Using the same criteria, Fadzlina and colleagues found a 10% prevalence of metabolic syndrome among 280 overweight and obese 13-year old school children.[11] None of those with average weight had metabolic syndrome.

Despite the increasing prevalence of pediatric obesity in Malaysia, there are few studies on the factors associated with MetS. Most of them are mainly population-based studies among school children with a much lower prevalence of metabolic syndrome. In contrast, ours is a hospital-based study which sought to identify risk factors for MetS that will be essential to prevent the consequent CVD and T2DM among at-risk patients. This study aimed to determine the prevalence of MetS and to identify risk factors associated with MetS among recruited and referred obese children in a hospital-based setting.

METHODOLOGY

Study design and setting

This is a cross-sectional study conducted from May 2019 to August 2021 at the Hospital Universiti Sains Malaysia (HUSM) and Hospital Raja Perempuan Zainab II (HRPZII). The study was approved by the Human Research Ethics Committee USM (reference: USM/JEPeM/18120807) and Medical Research and Ethics Committee Kementerian Kesihatan Malaysia (NMRR-20-3213-56314 (IIR).

Patients and procedures

The study involved 175 patients using consecutive sampling method from the two study sites. The inclusion criteria included the following: age 7 to 18 years; waist circumference more than 90th percentile; diagnosis of exogenous or primary obesity, defined as BMI more than 95th percentile according to age and gender; and with assent to join the study. Patients with secondary causes of obesity (monogenic disorders, syndromic forms of obesity, neurogenic, endocrine and drug-induced) were excluded.

All subjects underwent measurements of height, weight, BMI, WC and BP. Waist circumference was measured over the skin midway between the tenth rib and iliac crest at the end of normal expiration, using the same measuring tape. Body weight was recorded to the nearest 0.1 kg, measured using a standard weighing scale while the subject was barefoot and clad in light clothes. Height was measured to the nearest 0.5 cm in a standing position without shoes using a standard stadiometer. Blood pressure was measured with a digital BP monitoring device and an aneroid sphygmomanometer. Each device was calibrated regularly. Doctors evaluated pubertal maturation according to standardized Tanner staging.

BMI was expressed in kg/m^2. Obesity was defined as BMI >95th percentile of the standard WHO BMI. The diagnosis of MetS was based on the 2007 IDF pediatric definition: WC ≥90th percentile and at least two components above or under a single cut-off point (triglyceride ≥1.7 mmol/L; high-density lipoprotein cholesterol <1.03 mmol/L; fasting plasma glucose ≥5.6 mmol/L; and systolic or diastolic BP ≥130 or ≥85 mmHg, respectively).For biochemical measurements, a 10 mL venous blood sample was obtained in the morning using standard venipuncture after an overnight fast by trained health staff. Blood was analysed for fasting plasma glucose, fasting lipid profile, fasting insulin, liver function tests and renal profile.

A questionnaire on age, gender, race, birth weight, feeding history, family history of diabetes mellitus or GDM, hypertension, cardiovascular disease, physical activity, and sedentary lifestyle was provided on enrollment in the study. According to the WHO recommendation, a sedentary lifestyle was defined as more than 2 hours of screen time and less than 60 minutes of moderate to vigorous physical activity per day.[1] The questionnaire took 15-20 minutes to complete, and was answered by the parents of children less than 13 years old; older subjects answered together with their parents.

The recruited participants were then followed up at the Endocrine Clinics every three months.

Sample size estimation

The sample size was calculated using a single proportion formula for the estimation of the proportion and prevalence odds ratios for the factors considered in the study. The largest sample size obtained was for breastfeeding as one of the factors associated with metabolic syndrome. The information used for the sample size computation using Power and Sample Size Program were as follows: (a) 37% of pediatric patients with metabolic syndrome were breastfed based on the study by Sangun and colleagues, (b) the expected prevalence difference was 25% (since proportion with metabolic syndrome was assumed to be higher among patients who were not breastfed), (c) the level of significance was set at 5%, (d) the power of the test was set at 80%, and (e) the ratio between patients with metabolic syndrome to those without metabolic syndrome in the sample was set at 3.[6] This resulted in a minimum sample size of 165 patients. Anticipating a non-response rate of 10% among prospective respondents, the sample size was adjusted to 182 obese patients.

Statistical analysis

All categorical variables were presented as frequencies and percentages. For numerical (quantitative) variables, the distribution was evaluated by examining the skewness and kurtosis values as well as the histogram with overlaid normal curve and the box whisker plot. Numerical variables with normal distribution were presented as mean and standard deviation (SD). Non-normally distributed numerical variables were presented as median and inter-quartile range (IQR). The point and 95% confidence interval estimates of the prevalence of MetS among obese pediatric patients were calculated.

Logistic regression analysis was used to determine factors associated with MetS. Simple logistic regression analysis was used to identify factors to be included in the multiple regression analysis. Cut-off was set at $p<0.25$ in determining variables to be included in the full model. The forward selection method was used for the variable selection procedure. Probability to enter the model was set at $p<0.05$. All the assumptions of the test were examined. The fitness of the model was assessed using the Hosmer-Lemeshow test. Outlier and influential observations were examined using Cook's influential statistics, while linearity was examined using the Box-Tidwell procedure. The factors that remained in the final model were presented using a table with its corresponding adjusted odds ratio, 95% CI, and *p* value. Data were analyzed using IBM® SPSS® Statistics 26.0.

RESULTS

Baseline characteristics are summarized in Table 1. There were 98 (56%) male patients and 77 (44%) female patients. The predominant race was Malay (n=172, 98%). The subject's mean age was 11.3 years (SD 2.73): 96 patients (54.9%) were between 7 to 11 years old, and 79 (45.1%) were between 12 to 18 years. The mean birth weight of the subjects was 2.9 kg (SD 0.43). Of the 175 children, 104 (59.4%) received exclusive breastfeeding until the age of 6 months, 55 (31.4%) were fed with milk formula during infancy, and 16 (9.1%) were given mixed feeding. A total of 170 subjects (97.1%) had a sedentary lifestyle.

Table 1. Sociodemographic, clinical and biochemical characteristics

Variables	n (%)
Gender	
Male	98 (56.0)
Female	77 (44.0)
Age, year	11.3 ± 2.73[a]
7 to 11	96 (54.9)
12 to 18	79 (45.1)
Race	
Malay	172 (98.0)
Chinese	2 (1.1)
Indian	1 (0.6)
Birth weight, kg	2.9 ± 0.43[a]
Feeding	
Breastfeeding	104 (59.4)
Formula milk	55 (31.4)
Mixed	16 (9.1)
Lifestyle	
Active	5 (2.9)
Sedentary	170 (97.1)
Family history of obesity	
Yes	170 (97.1)
No	5 (2.9)
Family history of medical illness	
None	4 (2.3)
Diabetes	68 (38.9)
Hypertension	19 (10.9)
Heart disease	6 (3.4)
Hypertension + diabetes	66 (37.7)
Hypertension + diabetes + heart disease	12 (6.9)
Gestational diabetes mellitus	
Yes	130 (74.3)
No	45 (25.7)
Weight, kg	62.0 ± 21.89[a]
Height, cm	139.1 ± 21.75[a]
Body mass index, kg/m^2	30.2 ± 4.00[b]
Waist circumference, cm	89.6 ± 13.65[a]
Fasting plasma glucose, mmol/L	4.9 ± 1.20[b]
Triglycerides, mmol/L	1.5 ± 0.60[b]
High-density lipoprotein cholesterol, mmol/L	1.0 ± 0.36[b]
Aspartate aminotransferase, IU/L	26.0 ± 15.00[b]
Alanine aminotransferase, IU/L	36.0 ± 30.00[b]

[a] Age, birth weight, weight, height and waist circumference are normally distributed and presented as mean ± standard deviation (SD)
[b] Body mass index, fasting plasma glucose, triglycerides, high-density lipoprotein cholesterol, aspartate aminotransferase and alanine aminotransferase are non-normally distributed and presented as median ± interquartile range (IQR)

The majority of the subjects had a family history of obesity (n=170, 97.1%). In this study, 130 subjects (74.3%) were born to a mother with gestational diabetes mellitus (GDM). Almost all children had a family history of chronic illnesses; 68 (38.9%) had a family history of diabetes, 66 (37.7%) had family history of diabetes and hypertension, 19 (10.9%) had hypertension alone, six (3.4%) had ischemic heart disease, and 12 (6.9%) reported diabetes, hypertension and ischemic heart disease in their family. Four subjects (2.3%) reported no family history of chronic illnesses.

The mean weight and height were 62.0 kg (SD 21.89) and 139 cm (SD 21.75), respectively. The median BMI was

Table 2. Simple and multiple logistic regression analyses to determine factors associated with metabolic syndrome

Variables	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Age in years	1.30 (1.15 to 1.48)	<0.001	1.27 (1.15 to 1.45)	<0.001
Age category in years				
7 to 11	1.00			
12 to 18	2.09 (1.13 to 3.86)	0.018		
Gender				
Female	1.00			
Male	1.62 (0.88 to 2.96)	0.117		
Birth weight in kg	1.80 (0.88 to 3.70)	0.107		
Sedentary lifestyle				
Active	1.00		1.00	
Sedentary	4.48 (1.94 to 10.35)	<0.001	3.57 (1.48 to 8.59)	0.005
Puberty				
No	1.00			
Yes	2.85 (1.42 to 5.70)	0.003		
Gestational diabetes mellitus				
Yes	1.00			
No	0.47 (0.23 to 0.93)	0.030		

OR, odds ratio
Forward LR variable selection method applied.
R^2 = 0.198, classification table = 68.0% overall percentage of correct prediction, Hosmer and Lemeshow Test χ^2 (7) = 5.00, *p* = 0.660,
Area under ROC curve = 72.8% (95% CI: 65.3 to 80.3%)
No multicollinearity and no interaction were found between age and sedentary lifestyle status
A linear relationship was found between age and the logit transformation of the dependent variable as assessed by the Box-Tidwell procedure
Cook's influential statistics indicate no significant outliers, high leverage points or highly influential points

30.2 kg/m^2 (QR 4.00) and the mean WC was 89.6 cm (SD 13.65). In our cohort study, the prevalence of metabolic syndrome among children with obesity was 56% (95% CI: 48.6% to 63.4%).

On simple logistic regression analysis, age, older age group (12 to 18 years), male gender, birth weight, sedentary lifestyle, puberty, and maternal GDM were the important factors associated with metabolic syndrome among obese children. However, multiple logistic regression analysis revealed only age (adjusted OR 1.27, 95% CI: 1.15 to 1.45) and sedentary lifestyle (adjusted OR 3.57, 95% CI: 1.48 to 8.59) to be significant factors (Table 2).

DISCUSSION

Our study recruited 175 obese children who attended the endocrine clinic in tertiary hospitals in Kota Bharu, Kelantan (HUSM and HRPZII). We analyzed the prevalence of metabolic syndrome in obese children aged 7 to 18 years old. Using the 2007 IDF criteria, the prevalence of MetS in our cohort was 56%. The prevalence of MetS has been reported to be higher in severely obese (49.7%) than moderately obese children (38.7%); none of the overweight or normal-weight children had MetS.[20] This is consistent with the results of Simunovic et al., which showed that the risk of MetS increases with obesity.[22] Compared to our findings, there were lower prevalence rates of MetS in other groups of obese children in previous studies by Fadzlina et al., (10%) and Wee et al. (5.3%).[11,20]

Most pediatric obesity studies in Malaysia were mainly population-based studies on school children. Our study had a higher prevalence of MetS since we recruited only obese subjects referred to our hospitals. Majority of our subjects had BMI consistent with morbid obesity or BMI >30 kg/m^2. A higher BMI increases the likelihood of MetS as a metabolic complication of obesity.

Friend et al., analyzed 85 pediatric obesity studies in a systematic review: 63 applied the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) variants, 26 used the International Diabetes Federation (IDF) criteria, and 15 adopted WHO criteria. The study found that the median (range) prevalence of MetS in the whole population was 3.3% (0% to 19.2%), 11.9% (2.85 to 29.3%) in overweight and 29.9% (10.0% to 66.0%) in obese subjects.[23] The authors concluded that the prevalence of MetS varies considerably depending on the criteria used. Prevalence rates were higher when age-specific criteria were applied to children compared to adult criteria. Childhood prevalence differed when childhood and adolescent criteria were applied.[23]

Metabolic syndrome was present in 30.7% of obese subjects based on the modified ATP III criteria among 8- to 18-year old school-going children of Srinagar city of Kashmir, India.[18] In one Myanmar hospital-based study, the MetS prevalence was 39.1% among the obese group using IDF criteria.[24] The prevalence of MetS was also different when other definitions were applied to the same population: the rate was 66.2% based on NCEP ATP III criteria and 42.5% using the definition by Weiss et al.[25] In China, the prevalence of MetS in all moderately and severely obese children and adolescents was 10.3%, and 22.1%, respectively, using ATP III criteria.[26] The overall prevalence of MetS in hospital-based studies varied between 18% to 66.2% using the IDF criteria (2007).[22,24,26-30]

Our present study showed that most obese children were male (56%). A study done by Caceres et al., demonstrated that the prevalence of MetS was 36%, with a higher rate among males (40%) than females (32.2%) (p=0.599).[31] The odds of developing MetS in females were nearly 70% lower than the odds among males in 354 overweight and obese school-aged adolescents (age 10 to 19 years) in the city of Piracicaba, Brazil.[32] Male sex was a significant predictor of metabolic syndrome (adjusted OR 2.338, 95% CI: 1.204 to 4.540).[33] More significant abdominal fat deposition in males than females may be one of the contributing factors for increased MetS.[34] An increase in visceral adiposity would lead to a higher rate of free fatty acid influx into the liver, resulting in increased production of very low-density lipoproteins (VLDL). Under normal circumstances, insulin inhibits the secretion of VLDL into the systemic circulation. In the setting of insulin resistance, an increased influx of free fatty acids into the liver increases hepatic triglyceride synthesis.[35]

Sangun et al., reported that the prevalence of MetS was significantly higher in children with a family of diabetes, hypertension, coronary artery disease and hyperlipidemia.[6] The risk of MetS was 2.4 times higher in children with a family history of chronic medical problems.[36] Our study population had family members with diabetes (38.9%); a combination of diabetes and hypertension (37.7%); hypertension alone (10.9%); a combination of hypertension, diabetes and coronary artery disease (6.9%); and coronary artery disease (3.4%). Only 2.3% had no family history of chronic illnesses. Among the 175 subjects, 97.1% had a family history of obesity. This observation may indicate the interplay of genes with environmental risk factors. A patient with a family history carries some potential genes which would be expressed with poor lifestyle choices and unhealthy diets.

The other risk factor of metabolic syndrome in children was a history of maternal gestational diabetes mellitus. Tam et al., reported that maternal GDM increases cardiometabolic risk in children who had significantly higher systolic and diastolic blood pressure values and lower high-density lipoprotein cholesterol levels.[37] *In utero* hyperinsulinemia is an independent predictor of abnormal glucose tolerance in childhood.[37] A similar study by Boney et al., showed that infants of mothers with diabetes were at significant risk of developing MetS in childhood.[38] Our study showed that 74.3% of the children were born by mothers with GDM. Those without a history of GDM had 53% reduced odds of having metabolic syndrome compared to those with GDM mothers.

There were only two significant predictors for MetS from the multiple logistic regression analyses: older age and sedentary lifestyle. Obese children in the older age range had 1.27 times higher odds to have MetS. Those with sedentary lifestyles had 3.57 times higher odds of having metabolic syndrome than those who were non-sedentary. Our findings were similar to other studies. Wee et al., found that children in the older age group were more likely to have metabolic syndrome compared to those in the younger age group (OR 2.8, 95% CI: 0.7 to 10.6).[20] This is most likely related to hormonal changes associated with puberty. The levels of sex hormones, growth hormone and insulin-like growth factor-1 (IGF-1) are higher during puberty than in the prepubertal period because of hypothalamic-pituitary-gonadal and -IGF-1 axes activation. Sex hormones work synergistically with growth hormones. Pubertal growth spurts coincide with peak secretion of growth hormone, leading to worsening insulin resistance.[39-41] It is estimated that there is a 25-50% decline in insulin sensitivity which recovers upon completion of pubertal development.[42,43]

Dejavitte et al., found that insufficient physical activity was associated increased odds of MetS compared to those who were active (OR 4.60, 95% CI: 1.01 to 20.96).[32] A study in Thailand by Siwarom et al., showed that increased duration of physical activity was associated with decreased odds of MetS (OR 0.96, 95% CI: 0.92 to 0.99).[44] The Third Korea National Health and Nutrition Examination Survey concluded that screen time for more than 2 hours a day was associated with increased odds of having MetS (adjusted OR 2.001, 95% CI: 1.008 to 3.972).[33]

A possible mechanism for this relationship is due to exercise-induced mitochondrial biogenesis in skeletal muscle, representing about 80 to 90% of all insulin-sensitive tissues and accounting for approximately 50% of basal metabolic rate.[45] Increased mitochondrial biogenesis by increased volume and functional capacity is of fundamental importance. It leads to greater rates of oxidative phosphorylation and an improved ability to utilize fatty acids during submaximal exercise.[46] Additionally, physical activity also directly improves insulin sensitivity by facilitating substrate uptake in muscle and adipose tissue.

This study found a significant prevalence of metabolic syndrome among obese children referred to our centers. With more than half of them with MetS at a mean age of 11 years, they already have the most serious complication of obesity. This is a serious public health issue, as untreated MetS may progress to cardiovascular and metabolic diseases such as hypertension, dyslipidemia and type 2 diabetes. More efforts are needed to educate the public about healthy lifestyles to prevent obesity and its complications.

Limitations of the Study

Our study has a few limitations. The selection of cases was limited to referrals to our hospital, which might not be truly representative of the pediatric population in our state. In the future, we may need to include more hospitals in the state to obtain a more accurate representation. Movement restrictions associated with the COVID-19 pandemic may have resulted to fewer referrals from other district hospitals. The short-term design of the study was also a limitation. It would be ideal to have a longer study duration designed to evaluate the effectiveness of the hospital-based weight reduction program.

CONCLUSION

The prevalence of metabolic syndrome among obese children referred to our centers was 56%. The factors associated with MetS included older age group, male gender, birth weight, sedentary lifestyle, puberty and maternal history of gestational diabetes mellitus. However, older age group and sedentary lifestyle were the only significant predictors for MetS.

Acknowledgments
The authors would like to thank their supervisors, fellow lecturers, colleagues, supporting staff, family and the team of authors used as references.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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