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Original article

Acanthosis nigricans, visceral fat, waist-hip ratio in obese adolescents with metabolic syndrome

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Abstract. *Background and Aim:* Metabolic syndrome (MetS) was prevalent in obese adolescents due to insulin resistance (IR), while acanthosis nigricans (AN) was correlated with IR. This study was conducted to analyze the correlation between AN, waist-to-hip ratio (WHR), visceral fat (VF), and the incidence of MetS in adolescents with obesity. *Methods:* From October to December 2023, a cross-sectional study was conducted on obese adolescents aged 15 to 18 in the city of Surabaya. Brief interviews, physical examinations such as AN, blood pressure, waist, hip, visceral fat measurements, and related laboratory examinations were carried out. *Results:* 72 subjects were included in this study. The prevalence of obesity was higher in girls (61.1%) than boys (38.9%). MetS was established in 48%, while AN in 44.4% of subjects. Fat distribution including waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), visceral fat (VF), and total body fat was significantly higher in MetS (p=0.001) and AN (p=0.012). Subjects with non-MetS and non-AN had lower WHtR, total body fat and visceral fat than subjects non-MetS with AN (p<0.05). ROC curve for VF to determine MetS was 13, with a sensitivity of 91.3% and specificity of 33.3%. The cut-off point in obese with MetS for WHR was 0.844, with a sensitivity of 91.3% and a specificity of 33.3%. *Conclusion:* Increased >13 of VF and >0.844 for WHR in obese adolescents presented with AN was associated with a higher risk of developing MetS and can be proposed as a predictor for MetS in obese adolescents.

Key words: metabolic syndrome, acanthosis nigricans, waist-hip-ratio, visceral fat, adolescents

Introduction

Metabolic syndrome (MetS) is a series of physiological, biochemical, and metabolic factors that increase the risk of atherosclerotic cardiovascular disease (CVD) in an individual (1). MetS has a complex pathophysiology involving sedentary lifestyles, unhealthy eating patterns, and insufficient physical activity as risk factors that lead to increased body mass index (BMI) via chronic inflammation and oxidative stress mechanisms (2). It was hypothesized that its relation to CVD was due to the increased production of inflammatory cytokines from metabolically active fatty tissue (3). Dyslipidemia with low levels of High-density lipoprotein-cholesterol (HDL) and hyper-triglyceridemia is frequently encountered in patients with MetS (4). The prevalence of MetS in children and adolescents has drastically increased as a result of increasing obesity rates (5). Global data in 2016 noted that 41 million children under 5 years old are obese (5), and mostly they live in developing and developed countries (6). Overweight/obesity is the result of excess adipose tissue mass in the body, which leads to many chronic complications. Due to a sedentary lifestyle, the onset of these diseases occurs early in childhood and accumulates with age (7), and obese children/adolescents remain obese when they are adults (8). The increasing prevalence of obesity-related non-communicable diseases (NCD) is a burden for patients, families, and healthcare systems (9). As evidence that MetS is

correlated with obesity, MetS screening in overweight/obese children and adolescents becomes very important, especially in the age of 9-11 years (10). So, early diagnosis in children is crucial to prevent an increased risk of cardiometabolic disease (11), as it was evident that pediatric MetS correlated with persistent multiple cardiovascular risk over 8 years (12). BMI is the recommended anthropometric to detect overweight/obesity, but this index does not consider body composition or fat distribution in the body. The gold standard for evaluating visceral fat (VF) using MRI is not cost-effective or feasible in rural areas (13). VF is a proinflammatory endocrine tissue that is suspected to be the cause of cardiometabolic (14), as it is associated with dysglycemia, inflammation, insulin resistance (IR), and myocardial dysfunction. VF constitutes 10% of total body mass in men (15). Waist circumference (WC) was used to access the abdominal fat, as it closely correlated with total abdominal fat mass measured by computed tomography (16). The assessment of WC and waist-to-height ratio (WtHR) has been used to assess obesity in children because they are relatively cheap, easy to use, accurate, and non-invasive (17). WC, WtHR, and waist-to-hip ratio (WHR) indicate the presence of central obesity in children by 14.3% and 16.7%, respectively (18). WHR is considered an early identifier, where a WHR value above 0.891 is found to correlate significantly to MetS (18,19). Abdominal obesity is assessed based on WC and associated with visceral fat, liver fat, CVD risk factors, dyslipidemia, and type 2 diabetes mellitus in children and adolescents. WC measurements can provide a good estimate of VF in adolescents (20), as it is associated with IR and MetS (21,22). Acanthosis nigricans (AN) is a skin discolouration that usually appears in obese patients. It is characterized by thickened, rough skin, wrinkles, and dark pigmentation and can appear on the neck, armpits, knees, elbows, and surfaces of the inguinal region. AN has been closely related to insulin resistance (IR). Thus many studies utilize AN as a clinical marker for IR (23). A recent study revealed that 6.3% of adolescents with AN also had IR (24). It was suspected that chronically high insulin levels induce dermal fibroblasts and proliferation of epidermal keratinocytes, resulting in the development and progression of AN. In recent years, the prevalence of AN in children has increased along with the increase in obesity in children (25). AN is established as a clinical diagnosis and can be classified into: benign, obese, syndromic, malignant, acral, unilateral, treatment-induced, and mixed-type AN (26). Epidemiological study showed that MetS was prevalent in the subjects with AN (27), and can predict the component of MetS in children (28). Even, it is correlated with CVD risk factors, including BMI, HOMA IR and CRP (29). In a univariate analysis, a significant association of AN was found with BMI, WC, hypertension, HDL, and triglyceride (TG). The risk of MetS was found to be eight times higher in cases of AN (27). However, the usage of AN as the risk factor of MetS is still unclear and needs further confirmation, including the correlation of AN with the severity of hyperglycemia, IR, and dyslipidemia (30). Here we enrolled a study to investigate the fat distribution, represented by WHR, WHtR, total body fat and VF concerning AN and MetS in adolescents.

Methods

Study population and design

An observational study with a cross-sectional design with primary data obtained by direct measurement and interview performed between July to August 2023. Subjects of this study are adolescents between the ages of 15 and 18 years old attending senior high schools residing in Surabaya. A total of 107 high school students were categorized as obese or overweight, and 72 were eligible for this study. Brief interviews, physical examinations such as body weight and height measurement and visual evaluation of AN were performed by the author. A sample of this research's population was obtained using simple random sampling. Healthy adolescents aged 13-18 were recruited.

Anthropometry measurements

The qualified medical staff performed the measurements for anthropometry. The subjects were asked to stand on the digital platform barefoot with light clothes. Electronic scales were calibrated to measure weight and body composition with TANITA RD

953-BK, which then recorded BMI, total body fat, muscle mass, bone mass, and visceral fat. A stadiometer SECA 213 was used to measure heights. This stadiometer is used to measure the subject's height from the heel to the vertex, and the result will be presented by 'meter'. The subject's weight (kg) was divided by the square of their height (in m^2) to get their BMI. The CDC defines obesity as having a BMI higher than the 95th percentile for a certain age and gender, and overweight as having a BMI between the 85th and 95th percentile. The subject's waist and hip circumference were measured using a SECA 201®, Germany measuring tape, and WHR was recorded by setting a horizontal tape measure at the approximate middle point between the lower edge of the last palpable rib and the top of the iliac crest at the end of expiration for waist circumference and divided into hip circumference which measured by setting a horizontal tape measure around the widest part of hips.

Physical examination

We observed the present by examining the subject's trunk directly, whether there was a velvet colour or darkening of the skin and presented the result as yes or no. Blood pressure was measured using an OMRON HEM-8712 digital tensimeter in a sitting and relaxed position.

Biochemical measurements

On different days, subjects were asked to fast for 12 hours. The subjects were asked to fast for eight to twelve hours before the blood was taken for the laboratory testing (the last supper at least 7.00 pm, and no more food consumption, except freshwater). Then, a laboratory worker takes a fasting blood sample (5 ml) for examination via vena cubiti. The blood was then placed in a non-EDTA tube and collected into an ice box for further transportation. The analysis involves lipid profile values consisting of total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (lipoprotein (HDL), blood sugar, and insulin. All the blood biochemistry was enrolled by our designated laboratory using ELISA assay. The normal fasting blood glucose level in this study was less than 100 mg/dL, normal total cholesterol was less than 170 mg/dL, Normal HDL was greater than 40 mg/dL, normal LDL was less than 110 mg/dL, and normal TG of less than 150 mg/dL

Diagnosis of obesity and MetS

Obesity was considered based on the CDC 2000 criteria and BMI for age and sex criteria >95^{th} percentile. The metabolic syndrome (MetS) was considered based on the International Diabetes Federation (IDF) criteria for diagnosing the condition in children and adolescents (31,32).

Statistical analysis

The statistical software tool SPSS version 27.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data using descriptive statistics. Test of normality (Kolmogorov-Smirnorv) and homogeneity of variation were enrolled to determine further analysis, which includes an independent sample T-test (or Mann Whitney U test). Pearson chi-squared test or Fisher's exact test (expected value less than 5 >25%) was applied to categorical data. With a *P* value less than 0.05, statistical significance was taken into consideration. Multivariate analysis was enrolled with variate of WHR, WHtR, visceral fat, and total body fat to describe the variable of "fat distribution" in MetS and AN as a variable. We also analyzed WHR, WHtR, VF, and total body fat using the ROC curve and the best trade-off Youden Index (YI) to validate.

Results

The results of this study are as shown in Table 1**,** reveal that the incidence of obesity among males and females is approximately 2:1, with 44 male (61.1%) and 28 female (38.9%) subjects categorized as obese. MetS were found in 35 (48.6%) subjects, while AN was found in 32 (44.4%) subjects.

Those subjects with AN had bigger anthropometric measurements and metabolic profiles such as triglyceride, systole, and diastole blood pressure but lower HDL-c than subjects without AN significantly.

Table 1. Characteristics of subjects between MetS and non-MetS

Patient Characteristics	Mean + SD	MetS (n=35)	Non-MetS (n=37)	*P* value
Age (months-old)	197.21 + 9.814	197.63 + 9.42	196.81 + 10.28	0.862[a]
Gender (n[%]) • Female • Male	 28 (38.9 %) 44 (61.1 %)	 14 (40%) 21 (60%)	 14 (37.84%) 23 (62.16%)	0.851[b]
Acanthosis Nigricans (n[%]) • Present • Not Present	 32 (44.4%) 40 (55.5%)	 23 (65.72%) 12 (34.28%)	 9 (24.32%) 28 (75.67%)	<0.0001[b]
Body weight (kg)	91.39 + 23.64	103.98 + 13.44	79.47 + 25.13	<0.0001[c]
Body height (cm)	164.21 + 7.34	164.14 + 7.32	164.28 + 7.46	0.913[a]
BMI	34.13 + 8.44	38.69 + 3.63	29.85 + 9.41	<0.0001[c]
BMI-for-age	2.57 + 1.55	3.47 + 0.52	1.71 + 1.72	<0.0001[c]
Waist circumference (cm)	97.56 + 97.56	107.96 + 11.40	87.72 + 22.99	<0.0001[a]
Hip circumference (cm)	109.12 + 16.85	118.21 + 8.30	100.52 + 18.40	<0.0001[c]
WHR	0.89 + 0.09	0.91 + 0.07	0.86 + 0.10	0.269[a]
WHtR	0.59 + 0.12	0.66 + 0.05	0.53 + 0.13	<0.0001[c]
HAZ	-0.70 + 0.75	-0.62 + 0.90	-0.77 + 0.58	0.439[a]
Bone Mass (%)	3.76 + 2.76	3.74 + 0.46	3.78 + 3.85	0.002[c]
Visceral Fat (%)	14.78 + 7.44	17.20 + 3.61	12.50 + 9.27	0.011[a]
Body Fat (%)	30.55 + 11.43	35.68 + 8.80	25.70 + 11.62	<0.0001[c]
Muscle Mass (%)	59.01 + 14.79	63.34 + 13.19	54.91 + 15.22	0.015[a]
Systole blood pressure (mmHg)	130.58 + 16.01	137.06 + 14.97	124.46 + 14.65	0.001[a]
Diastole blood pressure (mmHg)	81.89 + 11.54	86.57 + 9.44	77.45 + 11.71	0.001[a]
Central obesity (n[%]) • Present • No	 52 (72.22%) 20 (27.78%)	 35 (100%) 0 (0%)	 17 (45.95%) 20 (54.05%)	<0.0001[b]
Fasting blood glucose levels (n[%]) • High • Normal	 1 (1.39%) 71 (98.61%)	 1 (2.86%) 34 (97.14%)	 0 (0%) 37 (100%)	0.300
Triglyceride levels (n[%]) • High • Normal	 18 (25%) 54 (75%)	 14 (40%) 21 (60%)	 4 (10.81%) 33 (89.19%)	0.006[b]
HDL-c levels (n[%]) • Low • Normal	 38 (52.78%) 34 (47.22%)	 32 (91.43%) 3 (8.57%)	 6 (16.22%) 31 (83.78%)	<0.0001[b]
Hypertension (n[%]) • Present • No	 47 (65.28%) 25 (34.72%)	 34 (97.14%) 1 (2.86%)	 13 (35.14%) 24 (64.86%)	<0.0001[b]
Insulin, (IU/mL)	27.07 + 18.34	32.48 + 14.91	21.96 + 19.96	<0.0001[c]
HOMA IR	5.76 + 4.18	6.87 + 3.12	4.71 + 4.79	<0.0001[c]

[a]Independent sample T-test; [b]Pearson chi-square; [c]Mann Whitney U test. *Abbreviations:* MetS: metabolic syndrome; BMI: body mass index; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; HAZ: height-for-age z-score; HDL-c: high-density lipoprotein cholesterol.

Greater fat distribution was also seen in subjects with AN than non-AN, as seen in Table 2. The presence of MetS components: central obesity, low level of HDL-c, hypertriglyceridemia, and hypertension was significantly more prevalent in subjects with AN than without AN. Table 3 summarized the prevalence of AN with MetS components and showed that abdominal obesity had a strong relationship with AN, followed by hypertension. While low levels of HDL-c had a weak correlation with AN. With MetS, AN had a weak correlation (r=0.384, *P*<0.0001).

Table 4 summarized the multivariate analysis of MetS and AN with fat distribution. Hotelling's Trace test reveals that fat distribution (WHR, WHtR, VF, and total body fat) was significantly higher in MetS and AN (*P*=0.001 and 0.012 respectively), and there was an interaction between MetS and AN (*P*=0.001) on fat distribution. Univariate analysis showed that the component of fat distribution associated with MetS was WHtR and total body fat, not WHR and VF. The interaction between MetS and AN showed a significant difference in variate WHtR and total body fat (P<0.0001 and 0.002, respectively). When the analysis was breakdown into a univariate, non-MetS *non-AN significantly had lower WHtR, total body fat,into a univariate, non-MetS *non-AN had lower WHtR, total body fat, and visceral fat than non-MetS*AN, MetS*non-AN, and MetS*AN (*P*<0.05). WHR were significantly lower in non-MetS*AN than non-MetS*AN and MetS*AN (*P*<0.05).

Figure 1 reflects the ROC of fat distribution to determine MetS in adolescents. The area under the curve (AUC) for WHR to predict MetS in obese adolescents was 0.661, 95% CI [0.512- 0.771], *P*=0.007. The cut-off point to determine MetS using WHR was > 0.89, with a sensitivity of 74.29% and specificity of 59.46%. The positive predictive value (PPV) for WHR was 63.41, and the negative predictive value (NPV) was 70.97%. The AUC for WHtR was 0.753, 95% CI [0.609- 0.849], *P*<0.0001. The cut-off was a point to determine MetS using WHtR was > 0.55, with a sensitivity of 100% and specificity of 54.05%, while PPV was 67.31% and NPV was 100%. The AUC for VF to determine MetS was 0.705, 95% CI [0.557- 0.809], with the cut-off points of > 11.50 (100% sensitivity and 48.65% specificity; 64.81% PPV and 100% NPV). AUC for total body fat in predicting MetS was 0.747 (95% CI [0.607-0.842], *P*<0.0001), with cut-off points of ≥ 25.60% (100% sensitivity, 43.24% specificity; 62.50% PPV and 100% NPV). It was seen that WHtR was the best prediction in predicting MetS in adolescents, as it had a bigger AUC with bigger sensitivity and specificity.

Figure 2 reflects the ROC of fat distribution to determine AN in adolescents. AUC of WHR to determine AN was 0.761 (95% CI [0.627- 0.852], *P*<0.0001), with the cut-off points of ≥ 0.89 (81.25% sensitivity and 62.50% specificity; PPV 63.41% and NPV 80.65%); while AUC for WHtR to determine AN was 0.823 (95% CI [0.698- 0.900], *P*<0.0001). A cut-off value of WHtR for determining AN was > 0.60 (96.88% sensitivity and 62.50% specificity; 67.39% PPV and 96.15% NPV). AUC for VF in predicting AN was 0.760 (96% CI [0.620- 0.853], *P*<0.0001), with the cut-off point of ≥ 13.50 (93.75% sensitivity and 60% specificity; 65.22% PPV and 92.31 NPV), while AUC for total body fat in predicting AN was 0.696 (95% CI [0.555- 0.798], *P*=0.001), with a cut-off point of ≥ 25.60% (100% sensitivity and 40% specificity; 57.14% PPV and 100% NPV). It was seen that all variables had good determination for AN, but the biggest AUC was WHtR, which had good sensitivity and specificity.

Discussion

Pediatric obesity data found sex-related gender in the prevalent prevalence of obesity, in which boys are more prevalent than girls globally (33). The predominant of severe obesity, defined as BMI z-score > 3 SD, increased along with the age increment, from 0.9% (age <5 years old), 2.7% (age 5-9 years old), 2.9% (age 10-14 years old), and 3.7% (15-18 years old), and male was twice more prevalent than female in age of 5-9 years old (34), which in line with this findings, male was predominant in this study. The findings are also in line with global findings obesity is higher in males than females (35–37). The high prevalent of overweight/obesity in males might be that after birth, females typically have higher fat mass and lower fat-free

Table 2. Characteristics of subjects between AN and non-AN

Patient Characteristics	Mean + SD	AN (n=32)	Non-AN (n=40)	*P* value
Age (months-old)	197.21 + 9.81	194.94 + 8.34	199.03 + 10.61	0.079[a]
Gender, (n[%]) • Female • Male	 32 40	 21 11	 23 17	0.482[b]
Body weight (kg)	91.39 + 23.64	105.29 + 11.95	80.27 + 24.88	<0.0001[c]
Body height (cm)	164.21 + 7.34	165.05 + 7.57	163.53 + 7.18	0.386[b]
BMI	34.13 + 8.44	39.37 + 5.00	29.94 + 8.32	<0.0001[a]
BMI-for-age	2.57 + 1.55	3.51 + 0.52	1.81 + 1.69	<0.0001[c]
Waist circumference (cm)	97.56 + 20.83	110.01 + 9.17	87.61 + 22.24	<0.0001[a]
Hip circumference (cm)	109.13 + 16.85	118.73 + 9.40	101.45 + 17.63	<0.0001[c]
WHR	0.89 + 0.09	0.93 + 0.05	0.85 + 0.10	<0.0001[a]
WHtR	0.59 + 0.12	0.67 + 0.05	0.53 + 0.13	<0.0001[a]
HAZ	-0.70 + 0.75	-0.63 + 0.84	-0.75 + 0.68	0.502[a]
Bone Mass (%)	3.76 + 2.76	3.83 + 0.51	3.70 + 3.69	<0.0001[c]
Visceral Fat (%)	14.78 + 7.44	17.83 + 3.18	12.35 + 8.89	0.001[a]
Body Fat (%)	30.55 + 11.56	35.17 + 9.59	26.85 + 9.59	<0.0001[c]
Muscle Mass (%)	59.01 + 14.79	65.27 + 12.10	53.99 + 14.97	0.001[a]
Fasting blood glucose (mg/dL)	84.94 + 7.11	86.66 + 6.78	83.58 + 7.15	0.067[a]
Triglyceride (mg/dL)	104.51 + 51.37	125.00 + 52.44	88.13 + 44.71	0.002[a]
HDL-c (mg/dL)	45.51 + 10.07	42.09 + 7.64	48.25 + 10.99	0.009[a]
Systole blood pressure	130.58 + 16.01	137.84 + 14.52	124.77 + 14.88	<0.0001[a]
Diastole blood pressure	81.89 + 11.54	85.84 + 10.83	78.73 + 11.23	0.008[a]
Central obesity (n[%]) • Present • No	 52 20	 32 0	 20 20	<0.0001[a]
Fasting blood glucose (n[%]) • High • Normal	 1 71	 0 32	 1 39	1.000[d]
Triglyceride levels (n[%]) • High • Normal	 18 54	 11 21	 7 33	0.100[b]
HDL-c levels (n[%]) • Low • Normal	 38 34	 22 10	 16 24	0.015[d]
Hypertension (n[%]) • Present • No	 47 25	 30 2	 17 23	<0.0001[b]
Insulin, (IU/mL)	27.07 + 18.34	41.61 + 18.20	15.44 + 6.06	<0.0001[c]
HOMA IR	5.76 + 4.18	8.96 + 4.33	3.21 + 1.36	<0.0001[c]

[a]Independent sample T-test; [b]Pearson chi-square; [c]Mann Whitney U test; [d]Fischer'sexact test. *Abbreviations:* AN: acanthosis nigricans; BMI: body mass index; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; HAZ: height-for-age z-score; HDL-c: high-density lipoprotein cholesterol.

Table 3. Correlation between AN prevalent with MetS components prevalent using Phi correlation

Variables	AN n=32	Non-AN n=40	r	*P* value
Abdominal obesity **n (%)**	32 (100%)	20 (50%)	0.555	<0.0001
Hyperglycemia **n (%)**	0 (0%)	1 (2.5%)	-0.106	1.000
Low level of HDL-c **n (%)**	22 (68.75%)	16 (40%)	0.286	0.019
Triglyceride **n (%)**	11 (34.38%)	7 (17.50%)	0.194	0.170
Hypertension **n (%)**	30 (93.75%)	17 (42.5%)	0.535	<0.0001

Abbreviations: HDL-c: high-density lipoprotein cholesterol; AN: acanthosis nigricans; MetS: metabolic syndrome.

Table 4. Multivariate analysis of fat distribution (WHR, WHtR, visceral fat and total body fat) with MetS and AN variables

	MetS variable			AN variable		
Variate	**Present**	**Not present**	***P* value**	**Present**	**Not present**	***P* value**
WHR	0.91 + 0.07	0.86 + 0.10	0.327	0.93 + 0.05	0.85 + 0.10	0.003
WHtR	0.65 + 0.05	0.53 + 0.13	0.001	0.67 + 0.05	0.53 + 0.13	<0.0001
VF	17.20 + 3.61	12.50 + 9.27	0.160	17.83 + 3.18	12.35 + 8.89	0.013
Total Body Fat	35.68 + 8.80	25.70 + 11.62	0.008	35.17 + 9.59	26.85 + 11.56	0.029
Multivariate *P* value = 0.012				Multivariate *P* value = 0.001		

Abbreviations: MetS: metabolic syndrome; AN: acanthosis nigricans; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; VF: visceral fat.

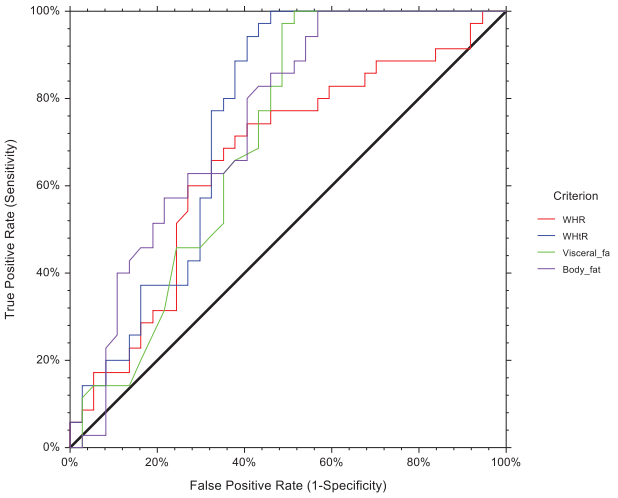

Figure 1. Receiver operating characteristic curve (ROC) to determine MetS for fat distribution (WHR, WHtR, visceral fat, and total body fat) in adolescents. *Abbreviations:* MetS: metabolic syndrome; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio.

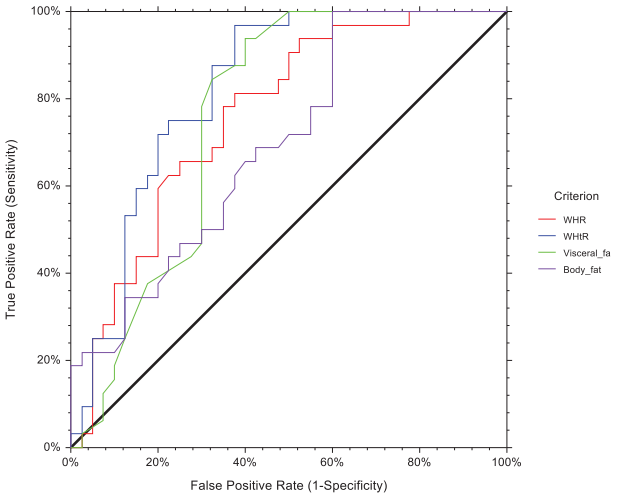

Figure 2. Receiver operating characteristic curve (ROC) to determine AN of fat distribution (WHR, WHtR, visceral fat, and total body fat) in adolescents. *Abbreviations:* AN: acanthosis nigricans; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio.

mass, leading to lower energy intake and calorie needs compared to males, driven by differences in sex steroid hormones and leptin levels influenced by adiposity, BMI, and pubertal status, with androgens in males exerting a suppressive effect on leptin serum concentrations compared to females (33). However, a nationwide survey study conducted in Indonesia showed that the prevalence of young adolescents with overweight and obesity in Jakarta was higher in males. In contrast, in older adolescents, the prevalence was higher in females (37). This may suggest that apart from intrinsic hormonal differences, the different prevalences shown in this study might be attributed to sociocultural influences. Some risk factors have been identified as associated with obesity, namely sedentary lifestyle, eating habits, low physical activity level, long sleep duration and daily computer use, and higher socioeconomic status (38,39).

Diagnostic criteria for MetS were met in 35 (48.6%) subjects, and AN was diagnosed clinically in 32 (44.4%) subjects. A systematic review found that the median occurrence of MetS in the general population was 3.3%, with rates increasing to 11.9% among overweight children and 29.2% among obese individuals, while non-obese, non-overweight populations exhibited a prevalence range of 0-1%; additionally, nearly 90% of obese children and adolescents displayed at least one metabolic syndrome characteristic. (40). No significant difference in MetS prevalent with sex distribution.

Acanthosis nigricans (AN) is commonly found in the posterior neck, axillae, elbows and knees in the form of benign AN which affects 7% of children with obesity, hyperinsulinemia, and IR (41). The most significant AN with a strong association with metabolic impairments were the neck (42), while the axillae region was found in morbid obesity. The presence of AN due to severe IR-related mutation within the insulin receptor (43). Our study found that MetS was more prevalent in AN adolescents, which is in line with others: AN is associated with obesity (61.54%), family history of diabetes mellitus, hypertension, and low physical activity among adolescents aged 13-14, suggesting that regular physical activity may mitigate the onset of AN and potentially reduce the risk of various associated health conditions (44). Acanthosis nigricans (AN) was significantly associated with abdominal obesity, low HDL-c and hypertension in this study. A study noted significantly higher BMI, BMI-for-age z-score, total body fat, WC, systolic and diastolic blood pressure, and lower HDL-c than those without AN in adolescents (45). Others also highlighted its correlation with HOMA IR, CRP and physical fitness score (PFS) in inherited AN, along with lower HDL-c and higher BMI (29). A study in obese children also found a higher value of BMI, systole and diastole blood pressure, triglyceride, insulin and HOMA IR, while lower level of HDL-c in the AN group than in non-AN (46). As noted, the direct relationship of AN in MetS component was mediated by BMI, which then stimulated IR. IR, marked with the Homeostatic Model Assessment for Insulin Resistance (HOMA IR) is suspected as the main cause of metabolic disorders in obesity, which then causes MetS (29). Due to IR-related, AN were mostly found at the neck, axillae and knuckles. Even needs skin biopsy for further diagnostic investigation, it may not be the rule, as IR which manifests with MetS was correlated with AN (47).

Body fat distribution has been found related to CVD There were differences in fat distribution affecting MetS and IR between adults and pediatric populations (48–51). A study noted the role of subcutaneous adiposity as the most significant variate affecting HOMA IR and TG, while BMI affects HDL-c in paediatrics. In adults, WHtR, visceral/subcutaneous fat ratio and BMI affect HOMA IR. BMI and VF affecting TG (48). A previous study found there was a significant relationship between WHR and MetS in obese adolescents, with WHR value > 0.891 had twice the risk of developing MetS than those with lower WHR (OR 2.033; 95% CI = 1.165-3.545). Also, the increased of WHR > 0.89 in adolescents was associated with a higher risk of developing MetS (19). VF was suspected as the cause of MetS due to the anatomic location and peculiar metabolic, hyperlipolytic activity (52), with a 28% greater risk of MetS per increment of 100 m^2/m of FV (53). There was no significant difference between VF and WHR in the MetS group, whether they had AN or not. However, the non-MetS showed significantly greater VF and WHR in the AN subject. VF is associated with the increased release of free fatty acids (FFA) into the portal circulation, resulting in IR

and other MetS characteristics (54). A study noted that VF was associated with MetS in men and women even with normal weight, while subcutaneous and intermuscular fat affected MetS only in normal-weight men (55). A systematic review underlined the cut-off point of WHtR in determining abdominal obesity was 0.49 (95% sensitivity and 88 % specificity) (56), while in Korean adolescents, the AUC of WHtR in determining MetS was 0.794 (95% CI=0.767-0.821) (57), which was similar with this study. A global study noted that the cut-off in determining MetS (≥ 2 or ≥ 3 components) for the European pediatric population was 0.50, 0.46 in Asian, African, and South American youths (58).

Acanthosis nigricans (AN) has been used as the predictor of IR, due to higher HOMA IR in the AN group than non-AN. It predicts IR in 3 points (index of AN severity, Burke quantitative scale), and HOMA IR was increased along with AN severity (23). AN was prone to males, with the neck as the most frequently affected area, with the cut-off point of insulin sensitivity index (ISI) <3.5 to predict IR (66.7% sensitivity and 82.5% specificity; PPV 91% and NPV 48%) (59). We had difficulties finding the literature describing WHtR, WHR, or visceral fat and total body fat with the incidence of AN. However, we try to find the correlation between those fat distribution indicators and AN. As the marker of IR, several body compositions have been enrolled to correlate with IR, including VF and total body fat, with the cut-off point of total body fat (TBF%) being 46.15% and VF cut-off points 15.2% in prediabetes and diabetes subjects (using HbA1C and fasting blood glucose to determine) in pediatric population (60). A study conducted in young adult students found the WHR cut-off to determine "at risk" of diabetes mellitus using postprandial blood sugar level (75 -100 mg/dl of reference range) ≥ 0.90 in males, while in females was ≥ 0.85 (60). In normal adults, AN was predicted by waist, WHR, and fasting insulin (61). Others found AN was associated with increased BMI, WC, WHR, and glucose impairment components. Grade and number of sites were significantly associated with hyperinsulinemia, and AN was the most simple and non-invasive method to identify glucose impairments, which was the risk of diabetes mellitus (62). This study had many limitations, as it did not include the history of NCD in the subjects, race, and ethnicity, although the most prevalent was Javanese.

Conclusion

In conclusion, our findings revealed that the prevalence of MetS was 48% and AN was present in 44.4% of the subjects. We found that the cut-off point in obese with MetS for VF is 13 for WHR is 0.844. Overall, our study highlights the potential importance of considering AN, VF, and WHR as indicators of metabolic health in obese adolescents, particularly in the context of identifying individuals at risk for MetS. These findings may contribute to early detection and targeted interventions to mitigate the health risks associated with obesity and metabolic syndrome in this population.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: KPD: conceptualization, methodology, investigation, and writing original draft; NAW: methodology and investigation.

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