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Obesity Indices Could Predict High Apolipoprotein B/Apolipoprotein A1 Ratio in Non-menopausal Indonesian Adult Females

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ABSTRACT

Previous research has demonstrated associations between high obesity indices with increased risk of metabolic and cardiovascular disorders. It has also been established that abnormalities of lipoprotein metabolism have an important role in atherogenesis and that non-menopausal females are protected from atherosclerotic cardiovascular events relative to males and menopausal females. This study aimed to investigate the relationship between obesity indices such as Body Mass Index (BMI), Waist Circumference (WC), Body Fat Percentage (BF), and Visceral Fat (VF) with apolipoprotein B/apolipoprotein A1 ratio in non-menopausal Indonesian mongoloid adult females. A total of 75 non-menopausal Indonesian adult females were included as subjects in this cross-sectional study. The measured indices in this study were BMI, WC, BF, and VF. Measurement of apolipoprotein B and A1 was performed by immunoturbidimetry, followed by calculation of the ratio. A cut-off value of 0.8 was used to define the high apolipoprotein B/apolipoprotein A1 ratio. Apolipoprotein B/Apolipoprotein A1 ratio was significantly correlated with BMI (r=0.384, p=0.001), WC (r=0.363, p=0.001), BF (r=0.385, p=0.001), VF (r=0.380, p=0.001). The area under the curve of BF (0.754) was slightly larger than BMI (0.722), VF (0.721), and WC (0.686) in predicting high apolipoprotein B/apolipoprotein A1 ratio. A positive weak correlation was observed between obesity indices and the apolipoprotein B/apolipoprotein A1 ratio. Obesity indices could be used to predict high apolipoprotein B/apolipoprotein A1 ratio.

Keywords: Apolipoprotein B/apolipoprotein A1 ratio, obesity, non-menopausal female

INTRODUCTION

The global obesity prevalence has nearly doubled in the last thirty years.[1] Around 2 billion people are categorized as overweight, and one-third of them is considered obese.[1] This rapid increase is observed not only in high-income cough income but also in countries with low- and middle-income countries including Indonesia.[1] According to a previous report, central obesity and obesity prevalence among the adult Indonesian population was 28% and 23.1 respectively, with higher occurrence in females (28.6%) relative to males (16.9%).[2] Obesity, which can be measured by several anthropometric indices, is linked to the progression of metabolic syndrome and cardiometabolic risks.[3]

Obesity affects many facets of human metabolism, including the regulation of lipoproteins. Lipoproteins are involved in many crucial roles, including the distribution of triglycerides as an interorgan fuel, maintenance of endogenous and exogenous cholesterol metabolism, and reverse cholesterol transport. Abnormalities of lipoprotein metabolism have been related to the atherogenesis process, which may lead to coronary heart disease.[4] Apolipoprotein B is contained in Low-Density Lipoprotein (LDL), Intermediate-Density Lipoprotein (IDL), and Very-Low-Density Lipoprotein (VLDL) and has proatherogenic and inflammatory features.[5] Apolipoprotein A1 constitutes 70% of High-Density Lipoprotein (HDL) apolipoproteins and has antioxidant and anti-inflammatory features.[4]

The use of apolipoprotein B/apolipoprotein A1 ratio as a reflection of pro-and anti-inflammatory mechanisms is often used in predicting cardiovascular risk and is a better marker than other lipid markers such as total, HDL, and LDL cholesterol.[4] The apolipoprotein B/apolipoprotein A1 ratio is not only associated with metabolic and cardiovascular disorders but also has been shown as a superior

predictor of type 2 diabetes risk relative to other routine lipid markers.[6] In addition to age, smoking, alcohol intake, and obesity have been frequently reported as important determinants of this ratio.[7]

A report conducted on the Indian population revealed that the apolipoprotein B/apolipoprotein A1 ratio a had significant association with metabolic syndrome and its components.[8] The optimal cut-off points for the prediction of coronary heart disease risk were between 0.80 and 0.90.[9]

An interesting feature regarding cardiovascular risk is that non-menopausal females are protected from atherosclerotic cardiovascular events relative to menopausal females and males. One commonly proposed theory highlights the endogenous protective features of estrogen against cardiovascular diseases, as lipid abnormalities surge along with the decline of endogenous estrogens in menopausal females.[10] Hence, this study aimed to evaluate the relationship between several common obesity indices such as Body Mass Index (BMI), Waist Circumference (WC), Body Fat Percentage (BF), and Visceral Fat (VF) with apolipoprotein B/apolipoprotein A1 ratio in non-menopausal Indonesian adult females as a representative of South East Asia regional population, and to determine which obesity index had better correlation with this ratio. This study focused only on non-menopausal female adults because menopause and male gender might alter lipoprotein metabolism and could have bias potential.

METHODS

This research was a cross-sectional study conducted from September 2018 to February 2019. Ethical approval was obtained from Health Research Ethical Committee, at the Faculty of Medicine, Hasanuddin University, Makassar (approval recommendation number 730/H4.8.4.5.31/ PP36-KOMETIK/2018).

Research subjects were non-menopausal Indonesian mongoloid adult females aged 18-40 years old who voluntarily joined the study with signed informed consent. Exclusion criteria were subjects who suffered from diabetes mellitus or had recently consumed certain medications including corticosteroid drugs or cholesterol-lowering agents within one month before sampling. Subjects with a history of regular smoking and alcohol intake were also excluded.

Obesity indices measurements were performed by a single examiner on the same day as blood sampling. Body mass was measured by a scale (Seca) and height data were collected, and BMI was then calculated by the formula of body mass (kg) divided by height squared (m^2). A measuring tape was used to measure WC at the midway level of the iliac crest and the lower border of the 12th rib. Other obesity indices including BF and VC were determined by the bioelectrical impedance analysis (BIA) method using the Tanita-BC541 (Tokyo, Japan) device. Subjects were categorized as normal weight, overweight, and obese based on the World Health Organization (WHO) criteria for the Asian population.[11]

After an 8-12 hours overnight fasting period, a sample of 3 mL venous blood was obtained from each subject by using a vacutainer, followed by serum separation for direct fasting plasma glucose (FPG) testing (Abx Pentra 400, Horiba, USA) to exclude type 2 diabetes based on the American Diabetes Association (ADA) 2018 criteria.[12] The serum was stored at -20°C until the testing of insulin (Elecsys 2010, Roche, USA), and apolipoproteins B and A1 (Cobas C501, Roche, USA). Insulin resistance was then calculated using the assessment model of insulin resistance (HOMA-IR) index = (fasting plasma glucose [mg/dL] x insulin [µIU/mL] / 405).[13] The apolipoprotein B/apolipoprotein A1 ratio value above 0.80 was considered as high (atherogenic and harmful), based on a previous report.[9]

The normality of data distribution was tested by the Kolmogorov-Smirnov test. The normally distributed numerical variables were analyzed with the one way ANOVA test followed by post-hoc testing using Fisher's for Least Significant Difference (LSD). Parameters with abnormal distribution were analyzed with the Kruskal Wallis test followed by a post-hoc Mann-Whitney test. The Pearson and Spearman tests were used to assess correlation in normally and abnormally distributed parameters, respectively. Further simple linear regression analyses were also performed and R2 was reported. Receiver Operating Characteristic (ROC) curves were created to evaluate the performance of obesity indices as predictors of high apolipoprotein B/apolipoprotein A1 ratio.

The area under the ROC curve (AUC) was analyzed and the optimal cut-off points for predicting the high apolipoprotein B/apolipoprotein A1 ratio of obesity indices were determined by the largest sum of specificity and sensitivity. Logistic regression analysis was then conducted to evaluate the odds ratio of obesity indices in determining the high apolipoprotein B/apolipoprotein A1 ratio. Subjects were categorized as obese, overweight, and normal weight based on BMI, and the odds ratio of having high apolipoprotein B/apolipoprotein A1

ratio between obese and overweight compared to normal subjects was analyzed. All statistical tests were performed using the Statistical Package for the Social Sciences, Version 21.0 (SPSS Inc, Chicago, IL, USA).

RESULTS AND DISCUSSIONS

A total of 75 subjects were recruited for the study and were categorized as normal weight (n=25), overweight (n=18), and obese (n=32). The study subjects age range was 18-40 years. Kolmogorov-Smirnov test showed that age, BF, apolipoprotein B, apolipoprotein A1, and its ratio were normally distributed, while other parameters were not normally distributed. The general characteristics of the subjects within the three groups are presented in Table 1. There was no significant difference in age and height among those groups. FPG, insulin, and HOMA-IR were significantly higher in the obese group compared to normal and overweight groups. Meanwhile, there was no significant difference in apolipoprotein A1 levels among those three groups; apolipoprotein B and apolipoprotein B/apolipoprotein A1 ratio remained higher in the obese compared to normal weight group (post-hoc p=0.005 and 0.010, respectively). The Apolipoprotein B/apolipoprotein A1 ratio was higher in the obese compared to the overweight group (p=0.047), while there was no significant difference in apolipoprotein B between the obese and overweight group.

All obesity indices had a significant correlation with apolipoprotein B but showed no significant correlation with apolipoprotein A1. The correlations were even stronger with the apolipoprotein B/apolipoprotein A1 ratio compared to apolipoprotein B alone (Table 2). Further analysis

Table 1. Characteristics of all, normal, overweight, and obese subjects

Variable	Total (n=75)	Normal (n=25)	Overweight (n=18)	Obese (n=32)	p
Age, year	31.81±4.50	30.92±4.40	31.56±4.78	32.66±4.40	0.342*
BM, kg	61.15±10.26	52.36±3.90	57.08±2.88	70.30±8.76	<0.001#
Height, m	155.75±5.05	156.30±5.89	155.03±3.81	155.72±5.06	0.855#
BMI, kg/m^2	25.21±4.10	21.38±1.17	23.75±0.57	29.02±3.29	<0.001#
WC, cm	83.63±9.35	75.52±5.31	81.06±3.51	91.41±7.81	<0.001#
BF, %	33.30±4.68	29.04±2.33	31.98±3.13	37.36±3.16	<0.001*
VF, unit	7.67±4.97	3.72±1.06	5.67±0.59	11.88±4.96	<0.001#
FPG, mg/dL	89.96±12.25	84.68±9.94	86.34±9.30	96.11±12.85	0.003#
Insulin, µIU/mL	10.96±6.92	8.77±5.58	8.57±1.97	14.01±8.44	<0.001#
HOMA-IR, unit	2.38±1.74	1.82±1.08	1.82±0.44	3.13±2.28	<0.001#
Apo A1, mg/dL	145.60±23.04	144.68±19.83	151.94±21.12	142.75±26.18	0.393*
Apo B, mg/dL	102.21±24.34	92.48±24.07	101.06±17.09	110.47±25.64	0.019*
Apo B/Apo A1	0.72±0.21	0.65±0.22	0.68±0.14	0.79±0.21	0.021*

* One way ANOVA test; # Kruskal-Wallis test

Table 2. Correlation of apolipoprotein B/apolipoprotein A1 ratio with obesity indices, and other laboratory variables

Variables	Apo B		Apo A1		Apo B/Apo A1	
	r	p	r	p	r	p
Univariate						
BMI	0.310	0.007#	-0.130	0.266#	0.384	0.001#
WC	0.314	0.006#	-0.082	0.485#	0.363	0.001#
BF	0.346	0.002*	-0.129	0.200*	0.385	0.001*
VF	0.299	0.009#	-0.143	0.222#	0.380	0.001#
FPG	0.154	0.187#	-0.188	0.107#	0.246	0.034#
Insulin	0.302	0.008#	-0.101	0.388#	0.335	0.003#
HOMA-IR	0.287	0.013#	-0.111	0.344#	0.314	0.006#
Controlling for insulin						
BMI	0.241	0.038	-0.139	0.236	0.289	0.013
WC	0.318	0.006	-0.062	0.599	0.317	0.006
BF	0.320	0.005	-0.161	0.169	0.370	0.001
VF	0.192	0.102	-0.146	0.216	0.245	0.035
Controlling for HOMA-IR						
BMI	0.251	0.031	-0.138	0.241	0.293	0.011
WC	0.323	0.005	-0.069	0.560	0.321	0.005
BF	0.326	0.005	-0.163	0.164	0.372	0.001
VF	0.208	0.075	-0.140	0.234	0.254	0.029

* Pearson correlation test; # Spearman correlation test

revealed that the apolipoprotein B/apolipoprotein A1 ratio also had a significant correlation with insulin and HOMA-IR. Therefore, insulin and HOMA-IR were adjusted to determine their independent effect on the association between obesity indices and apolipoprotein B/apolipoprotein A1 ratio. After controlling insulin and HOMA-IR, the correlation between obesity indices with apolipoprotein B/apolipoprotein A1 ratio remained significant, despite slight decreases in the coefficient correlation values.

Further analysis by simple linear regression in Table 3 showed that each obesity indices could describe apolipoprotein B/apolipoprotein A1 ratio ($p<0.005$) with BF having the greatest effect ($R2 =0.136$) compared to other indices.

A ROC analysis showed that the AUC of all obesity indices had a strong value in predicting the high apolipoprotein B/apolipoprotein A1 ratio (Figure 1). BF had a better predictive value than BMI, VF, and WC. BF and WC had the highest sensitivity with a cut-off of 33.15 and 80, respectively, while VF had the highest sensitivity with a cut-off of f 7.5 (Table 4).

Further logistic regression analysis showed that each 1-point increase of BMI, WC, BF, and VF increased 1.249, 1.090, 1.256, and 1.208 occurrences of high apolipoprotein B/apolipoprotein A1 ratio (Table 5).

Table 5. Logistic regression analysis in determining high apolipoprotein B/apolipoprotein A1 ratio

Variables	OR	95% CI	
		Lower	Upper
BMI	1.249	1.080	1.444
WC	1.090	1.025	1.159
BF	1.256	1.096	1.440
VF	1.208	1.059	1.379

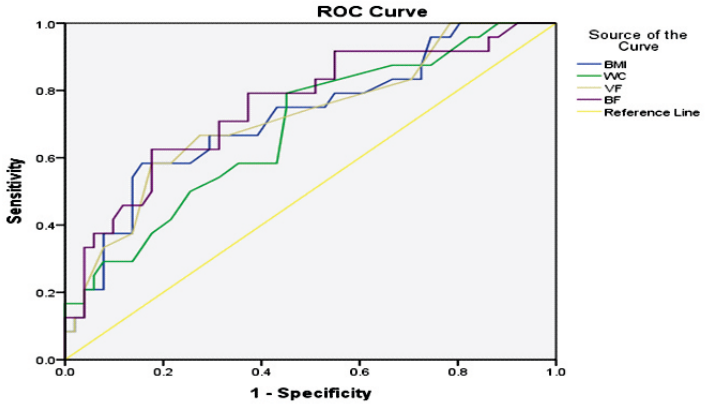

Figure 1. A ROC curve for BMI, WC, VF, and BF as predictors of high apolipoprotein B/apolipoprotein A1 ratio

Table 3. Obesity indices, FPG, insulin, and HOMA-IR simple linear regression with apolipoprotein B/apolipoprotein A1 ratio

Variables	Apo B		Apo A1		ApoB/ApoA1	
	R^2	p	R^2	p	R^2	p
BMI	0.063	0.017	0.002	0.289	0.083	0.007
WC	0.106	0.003	-0.010	0.623	0.101	0.003
BF	0.107	0.002	0.009	0.200	0.136	0.001
VF	0.041	0.045	0.003	0.269	0.061	0.018
FPG	0.025	0.091	0.009	0.201	0.056	0.023
Insulin	0.005	0.241	-0.014	0.979	0.001	0.305
HOMA-IR	0.002	0.290	-0.013	0.852	-0.003	0.370

Table 4. The AUC, cut-off point, sensitivity, and specificity of obesity indices in predicting high apolipoprotein B/apolipoprotein A1 ratio

Variables	AUC (95% CI)	Sensitivity	Specificity	Cut-off Point
BMI	0.722 (0.596-0.848)	0.667	0.706	25.4
WC	0.686 (0.559-0.814)	0.792	0.549	80
BF	0.754 (0.633-0.875)	0.792	0.627	33.15
VF	0.721 (0.595-0.847)	0.667	0.725	7.5

Table 6. The odds ratio of high apolipoprotein B/apolipoprotein A1 ratio among normal, overweight, and obese subjects

		Apo B/ Apo A1 Ratio				p	OR (CI 95%)
		High		Normal			
		n	%	n	%		
BMI	Obese	16	50	16	50	0.020	4.0 (1.20-13.28)
	Overweight	3	16.7	15	83.3	0.782	0.8 (0.17-3.89)
	Normal	5	20	20	80		Reference
Total		24	32	51	68		

Obese subjects had 4.0 times higher risk to suffer from high apolipoprotein B/apolipoprotein A1 ratio compared to the normal-weight subjects (Table 6).

Among the subjects of non-menopausal Indonesian mongoloid adult females in this study, we found a significant correlation between all obesity indices with apolipoprotein B, but none was found with apolipoprotein A1. BF had a slightly stronger correlation compared to other obesity indices. This finding was consistent with another report on the South-East Asian population.[14] Vanavanan *et al*. in Thailand, reported that the percentage of body fat was a good indicator of atherogenic lipoprotein molecules in adults.[14] In one study, which did not include BF and VF in the analysis, BMI was reported as a stronger index for the prediction of atherogenic parameters than other body indices including waist circumferences, waist-to-hip ratio, and waist-to-height ratio.[15]

A stronger correlation was observed between the obesity indices with the apolipoprotein B/apolipoprotein A1 ratio in comparison with apolipoprotein B alone, indicating the interaction of pro- and anti-inflammatory features.[4] Apolipoprotein B/apolipoprotein A1 ratio was also significantly correlated with insulin resistance (HOMA-IR) showing that metabolic disorders occurring in obese states may contribute to lipoprotein abnormality.[8] In fact, a strong correlation existed even after controlling the effect of insulin resistance (insulin/HOMA-IR), indicating that excess fat may solely become an independent factor of lipoprotein metabolic disorders. One study reported that the apolipoprotein B/apolipoprotein A1 ratio was higher in Metabolically Abnormal Obese (MAO) compared to Metabolically Healthy Obese (MHO) individuals. Metabolically healthy obese subjects were obese subjects, which did not have any of the four components of metabolic syndrome criteria (after excluding the WC criteria) based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), in contrast to MAO subjects whose at least one of the four criteria.[16]

Several explanations may describe these study findings. Chronic hyperinsulinemia and insulin resistance in obesity induce the liver to resist from inhibitory effects of insulin on the secretion of VLDL. Fatty liver, a condition frequently found in obese subjects, results in the increased synthesis of triglyceride-rich lipoproteins through the overproduction of VLDL cholesterol.[17] Increased lipid availability in obesity and insulin resistance may also protect apolipoprotein B from local degradation by hepatocytes, induce defect in hepatic VLDL clearance, and will therefore increase the apolipoprotein B and its ratio because each VLDL contains one molecule of apolipoprotein B100.[17,18]

Although all obesity indices correlate significantly with the apolipoprotein B/apolipoprotein A1 ratio, BF has a slightly better value in predicting a high ratio compared to others. This may be explained by the fact that BF tends to reflect all body fat including hepatic fat, which can cause lipoprotein metabolism abnormalities, while BMI may be biased by the possibility of miscalculation of muscle as fat. Additionally, VF and WC only specifically reflect fat in the abdominal region.

In this study, obese subjects (BMI >25 kg/m^2) were found to be 4 times more likely to have a high apolipoprotein B/apolipoprotein A1 ratio compared to those of normal weight. On the other hand, overweight subjects (BMI 23-24.9 kg/m^2) did not demonstrate a higher risk of having high apolipoprotein B/apolipoprotein A1 ratio compared to normal-weight subjects. It seemed that the lipoprotein metabolism of overweight non-menopausal mongoloid adult female subjects in our population was not or only minimally disturbed and might share similar features with normal-weight subjects.

Other interesting findings in our study were the BMI and WC cut-off in defining the high apolipoprotein B/apolipoprotein A1 ratio. This study found that the most optimal BMI cut-off to define the high ratio was 25.4, which was close to 25 as the BMI cut-off used to define the obese state in the

Asian population. Meanwhile, the most optimal WC cut-off to define a high ratio was 80, the same value used to define central obesity in female adults stated by IDF. Therefore, our findings confirmed the BMI and WC cut-off values, which had been proposed previously for defining obesity in the Asian population and gave an impact on predicting lipoprotein abnormalities, especially the apolipoprotein B/apolipoprotein A1 ratio.

The inability of this cross-sectional design to explain the causality of the association between obesity indices and apolipoprotein B/apolipoprotein A1 ratio and the inability of this single-center study to represent multi-ethnic Indonesian populations remained the limitations of this study.

CONCLUSIONS AND SUGGESTIONS

The obesity indices comprising of BF, BMI, VF, and WC were significantly correlated with the apolipoprotein B/apolipoprotein A1 ratio in non-menopausal Indonesian mongoloid adult females and might be used to predict the high ratio. Future multicenter and larger studies should be performed on multiple Indonesian ethnic groups to generalize the cut-off values.

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