Adiponectin index to assess metabolic syndrome and insulin resistance in obese adolescents

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Abstract

Background: Adiponectin level is decreased in obesity, and is suspected to be the cause of metabolic syndrome (MetS) and even linked with the onset of insulin resistance (IR). Adiponectin index (AI) has been used to determine IR and MetS in polycystic ovary syndrome (POCS).

Objectives: To assess the usefulness of AI to determine IR and MetS in obese adolescents.

Method: A cross sectional study was performed in obese adolescents from January to May 2020 in Sidoarjo and Surabaya Junior/High School, Indonesia.

Results: AI had a weak negative correlation with body weight, waist circumference, hip circumference and body mass index. AI also correlated with triglyceride, systolic blood pressure, fasting insulin, Homeostatic Model Assessment for IR (HOMA-IR) and high-density lipoprotein cholesterol (HDL-c). Obese adolescent with MetS had bigger AI than non-MetS (0.21±0.18 vs. 0.13±0.09, p=0.0000). A similar phenomenon was seen in obese adolescents with IR (0.37±0.51 vs. 0.11±0.07, p=0.000). AI had a better prognostic value to determine IR than MetS, with larger area under curve (AUC), 0.890 vs. 0.606. Cut-off value to determine IR was ≤0.17, with sensitivity 81.3% and specificity 88.5%.

Conclusions: AI is better to determine IR than MetS with a cut-off of <0.17 in obese adolescents.

(Key words: Adiponectin index, Insulin resistance, Metabolic syndrome, Obese adolescents)

Introduction

Adiponectin is one of the adipokines exclusively secreted by adipose tissue. The level is decreased in obesity, and is suspected to be the cause of metabolic syndrome (MetS) and even linked to the onset of insulin resistance (IR)[1-4]. Adiponectin gene expression and the levels in circulation correlated with adiposity[5]. The role of adiponectin is seen not only in energy homeostasis, but also in lipid and carbohydrate metabolism. Adiponectin also has potential anti-inflammatory and anti-atherogenic properties so that it can be detected in skeletal muscle, cardiomyocytes, osteoblasts, lymphocytes and many more[6].

Obesity is marked by excessive lipid accumulation in adipose tissue, which causes an endocrine response of adipose tissue due to a low-grade chronic inflammation, and leads to metabolic alterations, including IR, type 2 diabetes and MetS as the pioneer of cardiovascular disease[7]. Chronic inflammation in obesity leads to the reduction of adiponectin, and at extremely low levels, is termed hypoadiponectinaemia, which has been shown in several studies including obese individuals[8,9]. Intercorrelation has been proposed between obesity, IR and hypoadiponectinaemia. Hypoadiponectinaemia in obesity may accelerate the reaction of tumour necrosis factor alpha (TNFα) of blocking the action of insulin, so IR is supposed to be induced by hypoadiponectinaemia[10]. Others state that hypoadiponectinaemia is the result of obesity and IR, and associated with metabolic alterations[11]. Based on that, adiponectin has been used as an indicator of MetS in the paediatric population[12].

Adiponectin index (AI), defined as adiponectin divided with (fasting blood glucose x fasting insulin), has been used to determined insulin sensitivity and MetS in polycystic ovary syndrome (PCOS) with high sensitivity and specificity[13].

Objectives

To assess the usefulness of AI to determine IR and MetS in obese adolescents where AI = adiponectin ± (fasting blood glucose x fasting insulin)[13].

Method

A cross sectional study was performed in obese adolescents from January to May 2020 in Sidoarjo and Surabaya Junior/High School, Indonesia.

Sample size was calculated using the formula given below:

$$N = \left[\frac{Z1-\alpha/2\sqrt{2\bar{P}(1-\bar{P})} + Z1-\beta\sqrt{P1(1-P1)+P2(1-P2)}}{(P1-P2)^2} \right]^2$$

The calculated sample size of obese subjects was 260.

Anthropometric measurement: For anthropometric measurements, the subjects had to wear light clothes and no footwear (socks and shoes), belt, hat, or other accessories, including a watch. Female students with a ponytail had to undo the ponytail prior to measuring their height. To measure body weight, participants were asked to stand on a weighing scale (Seca Robusta 813). To measure height, participants were asked to stand straight on a stadiometer (Seca 213) without footwear or hat. Waist and hip circumference were measured using non-stretch tape on standing straight posture without pulling in the stomach. Waist circumference was measured halfway between the lower ribs and the iliac crest. Hip

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circumference was measured at the largest circumference around the buttocks. Body mass index (BMI) was calculated using the formula: Body weight (kg)/height $(m)^2$.

Blood collection: Before the blood collection, the subjects were asked to fast for 12-hours after supper. Blood (5 ml) was drawn via cubital vein by a laboratory worker in the morning, and placed in an ethylene-diamine-tetra-acetic acid (EDTA) containing tube with complete identity. The blood was put into a cooling box for transportation to laboratory for further analysis (fasting blood glucose, fasting insulin, lipid profile). Blood pressure was measure using Omron automatic blood pressure HEM-8714.

Metabolic syndrome

IR was determined using the homeostatic model assessment for IR (HOMA-IR) cut-off value ≥5.22 for boys and ≥3.82 for girls in pubertal periods[14] by using the formula:

$$HOMA - IR \equiv \left[Fasting\ blood\ glucose\ \left(\frac{mg}{dL}\right) \times insulin\ \left(\frac{\mu u}{L}\right)\right] \div 405$$

MetS was determined according to International Diabetes Federation (IDF) criteria, where central obesity is accompanied by 2 of 4 criteria described below[15]:

For children aged 10-16 years:

1. Hypertension (systole ≥130mmHg/diastole ≥85 mmHg).
2. Hypertriglyceridaemia (triglyceride levels ≥110 mg/dL).
3. Hypo high-density lipoprotein-cholesterol (HDL-c levels ≤ 40 mg/dL).
4. Hyperglycaemia, (fasting blood glucose ≥110 mg/dL).

For children aged >16 years:

1. Hypertension (systole ≥130 mmHg /diastole ≥85 mmHg).
2. Hypertriglyceridaemia (triglyceride levels ≥150 mg/dl).
3. Hypo HDL-c, (HDL levels ≤ 50 mg/dl).
4. Hyperglycaemia (fasting blood glucose ≥100 mg/dl) (16).

Central obesity is defined as waist circumference:

1. For children aged 10-16 years: ≥88 cm for boys and ≥85 cm for girls.
2. For children aged >16 years: ≥94 cm for boys and ≥80 cm for girls[16].

Ethical issues: The study was approved by the Ethical Committee of Faculty of Medicine, Airlangga University, Indonesia (No. 65/ EC/ KEPK/ FKUA/2020). Before the study was conducted, the researchers presented the importance of this study to the parents, and asked the parents to sign the informed consent form. This study is voluntary, without coercion.

Results

A total of 229 subjects with obesity participated in this study. Male/female ratio was 1.3: 1. MetS was seen in 73 (31.9%) subjects, while IR was detected in 133 (58.1%) subjects. Subject's characteristics are seen in Table 1. There was a significant difference in body weight, height and waist circumference, greater in male than female adolescents, while HDL-c level was significantly higher in female than male ($p<0.05$). The incidence of hypertension was more in male adolescent than female (60.8% vs. 44.4%, p=0.010).

Table 1: ***Subject's characteristics (n=229)***

Characteristics	Total *(n=229)*	Male *(n=130)*	Female *(n=99)*	p-value
Age (months): M ± SD	182.11 ± 18.35	181.86 ± 16.92	182.43 ± 20.14	0.815[1]
Age category: n (%) < 192 months-old	167 (72.9)	98 (75.4)	69 (69.7)	0.209[2]
> 192 months-old	62 (27.1)	32 (24.6)	30 (30.3)	
Body weight (kg): M ± SD	82.57 ± 14.47	85.15 ± 15.11	79.17 ± 12.88	0.002[1*]
Height (cm): M ± SD	161.33 ± 7.85	164.46 ± 7.54	157.22 ± 6.18	0.000[1*]
Waist circumference (cm): M ± SD	96.03 ± 10.85	99.24 ± 10.12	91.82 ± 10.36	0.000[1*]
Abdominal obesity: n (%)	198 (86.5)	115 (88.5)	83 (83.8)	0.206[2]
Hip circumference (cm): M ± SD	107.23 ± 10.32	106.71 ± 9.70	107.92 ± 11.08	0.378[1]
Body mass index (kg/m²): M ± SD	31.61 ± 4.85	31.35 ± 4.82	31.96 ± 4.89	0.388[3]
Total cholesterol (mg/dL): M ± SD	171.70 ± 31.97	168.22 ± 31.07	176.26 ± 32.72	0.059[1]
Triglyceride (mg/dL): M ± SD	112.27 ± 63.30	112.80 ± 64.85	111.58 ± 61.52	0.706[3]
Hypertriglyceridaemia: n (%)	85 (37.1)	80 (61.5)	64 (64.7)	0.366[2]
LDL-c (mg/dL): M ± SD	112.50 ± 28.05	110.31 ± 26.92	115.36 ± 29.36	0.177[1]
HDL-c (mg/dL): M ± SD	43.29 ± 7.63	42.32 ± 7.11	44.58 ± 8.14	0.026[1*]
Hypo HDL-c: n (%)	93 (40.61%)	50 (38.46%)	43 (43.43%)	0.288[1]
Fasting blood glucose (mg/dL): M ± SD	86.01 ± 6.72	86.55 ± 6.29	85.31 ± 7.21	0.185[2]
Hyperglycaemia: n (%)	11 (04.8)	07 (05.4)	04 (04.0)	0.442[2]
Systole blood pressure (mmHg): M ± SD	122.99 ± 13.48	124.19 ± 13.52	121.41 ± 13.33	0.090[3]
Diastole blood pressure (mmHg): M ± SD	81.04 ± 10.49	81.60 ± 10.24	80.30 ± 10.83	0.202[3]
Hypertension: n (%)	123 (53.71%)	79 (60.77%)	44 (44.44%)	0.010[1*]
Fasting insulin (µU/mL): M ± SD	21.77 ± 13.67	21.41 ± 14.22	22.24 ±12.98	0.416[1]
Adiponectin (µg/ml): M ± SD	14.67 ± 7.37	14.34 ± 6.77	15.11 ± 8.11	0.753[3]
Hypoadiponectinemia: n (%)	36 (15.72%)	22 (16.92%)	14 (14.14%)	0.350[2]
HOMA IR: M ± SD	4.64 ± 2.98	4.58 ± 3.13	4.71 ± 2.78	0.484[1]
Insulin resistance: n (%)	133 (44.48%)	73 (56.15%)	60 (60.61%)	0.294[2]
Adiponectin index: M ± SD	0.22 ± 0.36	0.24 ± 0.45	0.20 ± 0.18	0.978[3]

*[1]Independent sample t-test; [2]Fischer's exact test; [3]Mann-Whitney U test; *Significant*

LDL-c: low density lipoprotein-cholesterol; HDL-c: high density lipoprotein-cholesterol; HOMA IR: homeostatic model assessment of insulin resistance

The correlation between AI and obesity parameters is summarized in Table 2. AI has a weak negative correlation with anthropometric parameters body weight, waist circumference, hip circumference and BMI. Negative correlation was also seen between AI and triglyceride, systole blood pressure, fasting insulin and HOMA-IR. AI had a weak positive correlation with HDL-c.

Table 2: ***Correlation of adiponectin index with obesity parameters***

Parameters	Spearman rho correlation	
	r	p
Body weight	-0.262	0.000
Height	-0.038	0.571
Waist circumference	-0.312	0.000
Hip circumference	-0.305	0.000
Body mass index	-0.251	0.000
Total cholesterol	-0.116	0.079
Triglyceride	-0.382	0.000
Low density lipoprotein-cholesterol	-0.113	0.088
High density lipoprotein-cholesterol	0.283	0.000
Fasting blood glucose	-0.097	0.142
Systole blood pressure	-0.232	0.000
Diastole blood pressure	-0.075	0.261
Fasting insulin	-0.784	0.000
Homeostatic model assessment of insulin resistance	-0.784	0.000

Obese adolescent with MetS had bigger AI than non-MetS (0.21±0.18 vs. 0.13±0.09, p=0.0000). Similar phenomenon was seen in obese adolescents with IR (0.37±0.51 vs. 0.11±0.07, p=0.000). Figure 1 represents the area under curve (AUC) of AI to determine MetS. The AUC of AI for predicting MetS was 0.606 (95% CI [0.528 - 0.684], p=0.007). The cut-off value of <0.10, had bigger Youden index to determine MetS, with sensitivity of 70.6% and specificity of 50%.

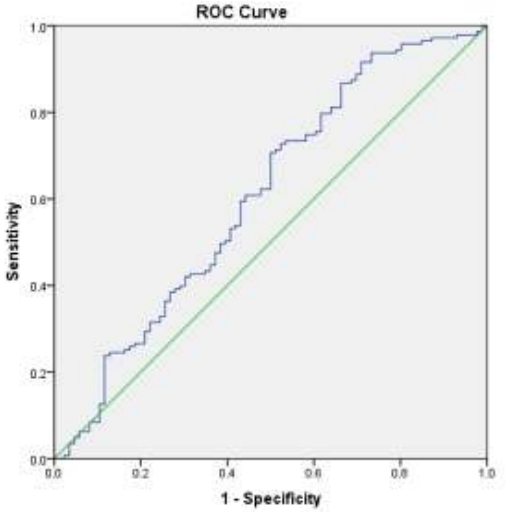

Figure 1: ***ROC of adiponectin index for determining MetS in obese adolescents***

Figure 2 summarizes the AUC of AI to determine IR. The AUC of AI to determine IR was 0.890 (95% CI [0.847 - 0.932], p=0.000). Cut-off value to determine IR was ≤0.17, with sensitivity of 81.3% and specificity of 88.5%.

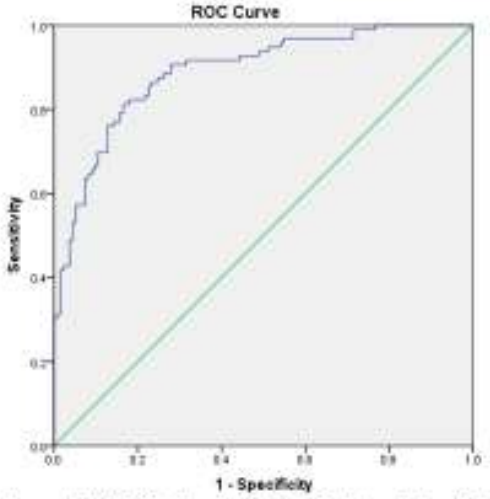

Figure 2: ***ROC of adiponectin index for determining IR in obese adolescents***

Discussion

Sex difference in the incidence of obesity has been reported in several studies, in which being male had a disadvantageous impact[17,18]. Regarding body weight, height and BMI, a study in children aged 8-10 years found that males were taller, heavier and had higher BMI than females and gender contributed 1% to this phenomenon[18], which is in line with the findings. Others also supported this study, which found that boys were taller and heavier than girls[19]. So, being a boy had 2 to 2.9-fold risk of being obese. Girls are more concerned with their appearance than boys, so girls have greater desire to lose weight, and being overweight/obese made their self-esteem lower[17,20]. Moreover, males and females are different in body composition, weight gain pattern and hormones[18].

Male adolescents had greater waist circumference than female, which was also seen in another study, where being male had a 36% risk of having abdominal obesity, and more so in adolescents with sedentary lifestyle[21]. So,

being male also had a higher risk of having cardiovascular disease as found in a study in adults[22]. This phenomenon has been seen since early birth. Male baby with birth weight ≥ 3000 g had a risk of having abdominal obesity in childhood[23]. It was well known that women had higher HDL-c and lower triglyceride than men[24,25], which also is in line with the study.

Our study found that AI correlated negatively with anthropometric indicators of obesity (body weight, waist circumference, hip circumference and BMI), which were also the anthropometric indicators for adiponectin levels. A study has shown that adiponectin, as the indicator of MetS in obese children, correlated with body weight and waist circumference[12]. The similar correlation using AI in regression models also supports this finding as AI correlated with BMI (β=0.177, p=0.000) and strongly correlated with HOMA IR[13]. Adiponectin level in PCOS women also correlated with IR, insulin sensitivity, BMI and adiposity. This finding supported that adiponectin is strongly linked with adiposity mass and visceral adiposity[26], even though the pathology of obesity and PCOS are widely different. This is also supported by the fact that the increment of visceral adiposity in overweight/ obesity had a negative effect on adiponectin levels[8]. Using adiponectin modification in the form of HOMA-adiponectin (HOMA-AD), others showed that HOMA-AD had similar prognostic ability to HOMA-IR for predicting IR in Brazilian adults[27].

This study had limited references as supported evidence of AI in the setting of obese adolescents. So, here we took comparison of serum adiponectin as the supporting evidence. This study also reveals that AI correlates with HDL-c, triglyceride and systolic blood pressure. A study using serum adiponectin as the independent factor showed that adiponectin correlated with triacylglycerols, HDL-c and blood pressure[28,29]. Similar diagnostic tools, named high-molecular weight adiponectin/HOMA-IR ratio has been used to distinguish MetS, and even had negative correlation with waist circumference, blood pressure and triglyceride, but showed positive correlation with HDL-c[30,31] which is in line with this study.

AI had lower AUC to predict MetS in this study compared to the study performed in PCOS women[13]. Another study using adiponectin/ HOMA-IR ratio had better AUC of 0.727 in predicting MetS (0.700)[31]. In predicting IR, AI showed similar ability as shown in PCOS women[13]. In term of AUC, AI is better in predicting IR than MetS, as the AUC below 0.7. an index or tools is determined to be acceptable to use as a diagnostic tool due to it has AUC 0.7 to 0.8, excellent when AUC 0.8 to 0.9 and more than 0.9 is outstanding[32]. The values for the AUC above 0.7 are considered to show good discriminatory capacity[27].

Conclusion

Adiponectin index is better to determine IR than MetS with cut-off value of <0.17 in the population of obese adolescents.

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