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ORIGINAL RESEARCH REPORT

Metabolic syndrome, HOMA-IR and adiponectin in obese adolescents

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ABSTRACT

Background: Homeostasis model assessment (HOMA) is a method used to measure insulin resistance (IR). Adiponectin is involved in the development of atherosclerosis. **Objectives:** This study aimed to assess metabolic syndrome (MetS) prevalence in adolescents with obesity; correlate HOMA-IR and IR incidence with MetS biochemical parameters and MetS components; as well as correlate adiponectin levels and hypoadiponectinemia incidence with MetS biochemical parameters and MetS components. **Methods:** This study was conducted at the Outpatient Installation Unit of Nutrition and Metabolic Diseases, Child Health Department, Dr. Soetomo General District Hospital, Surabaya, Indonesia with a cross-sectional study design. It lasted for nine months and focused on obese adolescents aged 13-18 years. Anthropometric measurements and blood biochemistry analyses were done. HOMA-IR was calculated using the formula [glucose (mg/dL) x Insulin (µu/L)]/405. **Results:** A total of 216 obese adolescents took part in the study. MetS was found in 81 subjects (37.96%). There was a weak correlation between HOMA-IR with anthropometric measurements, lipid profiles, fasting blood glucose, and serum adiponectin levels ($p<0.05$). IR was found to increase the risk of MetS development by 1.661-times, dyslipidemia b1.845 timeses, and abdominal obesity by 3.077-times. IR increased the risk of MetS incidence with more than three IDF criteria by 9.368 times. There was a correlation between adiponectin levels with the HDL-c. Hypoadiponectinemia was correlated with the incidence of MetS, abdominal obesity, and hypertriglyceridemia. It also increased the risk of developing MetS by 2.220 times. There was a positive relationship between the IR HOMA value and the anthropometric parameters of obesity and MetS parameters. **Conclusions:** IR was found to be associated with dyslipidemia, abdominal obesity, and MetS incidence with more than three IDF criteria. There was a relationship between hypoadiponectinemia and waist circumference, hip circumference, HDL-c, and triglycerides. Insulin resistance and hypoadiponectinemia were associated with Mets and hypertriglyceridemia incidence.

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Highlights

1. Obese adolescents are at risk of MetS, insulin resistance, and hypo-adiponectinemia.
2. HOMA-IR correlated with anthropometric measurements, lipid profiles, fasting blood glucose, and serum adiponectin levels.
3. IR increased the risk of MetS by 1.661-times, dyslipidemia by 1.845-times, and abdominal obesity by 3.077-times.

BACKGROUND

Obesity is defined as being 20% over the ideal body weight (Zimmet et al., 2007a). It is an accumulation of excess adipose tissue that can cause chronic health problems, including cardiovascular disease, type 2 diabetes mellitus (DM), hypertension, stroke, dyslipidemia, and some cancers (Greenberg and Obin, 2006; Must et al., 1999). In obesity, there is chronic low-grade inflammation (Castro et al., 2017) in the adipose tissue, which is marked by increased infiltration and activation of innate and adaptive immune cells. This includes macrophages, which produce proinflammatory cytokines that can damage insulin signals (Zatterale et al., 2020). In addition, adipose tissue is very susceptible to lipolysis, resulting in an increase in free fatty acids (FFA) in plasma that causes insulin metabolism disorder (Ravussin and Smith, 2015) This disorder triggers IR, characterized by an increase in fasting insulin and fasting blood glucose (Cerf, 2013). IR is associated with atherosclerosis, meaning it is very important for early detection of obesity-related degenerative diseases. IR triggers changes in perilipin expression and allows many FFAs to be released into the blood (Zhang et al., 2003).

Adipocyte secretion products are important in determining IR through the influence of hormones and local effects on adiposity. This includes adiponectin, which has an antidiabetic, anti-inflammatory, and cardioprotective role. It is a protein hormone that circulates in the blood in high concentrations, at about 0.01% of the total protein serum (Kern et al., 2003). In obesity, the serum level (in the form of f adiponectin or g adiponectin) is known to decrease both in humans and mice (Greenberg and Obin, 2006). Adiponectin expression in serum has been found to be low in conditions of IR accompanied by low lipid accumulation in muscle and liver or lipodystrophy. Adiponectin acts on several organs. In muscle, adiponectin functions as insulin sensitivity through the AMP kinase (AMPK) and peroxisome proliferator-activated receptor-α (PPARα) pathways. Meanwhile, in the liver, adiponectin activates glucose transport and inhibits gluconeogenesis through the AMPK pathway. This increases insulin sensitivity by triggering the phosphorylation of insulin receptors and insulin receptor substrate 1 (IRS1) protein adapters and activating fatty acid oxidation through the AdipoR1 receptor. In the pancreas, adiponectin acts as a stimulator of insulin secretion in cell proliferation. Meanwhile, in adiponectin, fat tissue increases the uptake of alkaline glucose and increases glucose uptake, which is stimulated by insulin through AMPK activation. Adiponectin is further involved in the development of atherosclerosis, which has been found to decrease in patients with coronary artery disease (Greenberg and Obin, 2006).

Metabolic syndrome (MetS) prevalence increases with the severity of obesity (Zimmet et al., 2007a). Obese adolescents are still a double burden in Indonesia. The prevalence of obese adolescents has increased more than five-fold over three years, from 1.4% in 2010 to 7.3% in 2013. Obese children and adolescents are at risk of developing adult obesity (Lee and Sanders, 2012), meaning early diagnosis and obesity development interventions should be done and to avoid causing long-term health problems.

The homeostasis model assessment (HOMA) is a method used to measure IR, where fasting hyperglycemia is determined by combining β-pancreatic cell deficiency with IR (Borai et al., 2007). Insulin depends on β-cells in glucose levels, while glucose is regulated by hepatic glucose which is insulin-mediated. Thus, IR is described as a decrease in insulin's role in suppressing hepatic glucose production (Singh, 2010). MetS is defined as a cluster of interconnected factors that directly increase the risk of coronary heart disease (CHD), cardiovascular atherosclerotic diseases (CVD), and diabetes mellitus type 2 (DMT2) (Rothstein, 1992). MetS consists of the following components: abdominal

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obesity, dyslipidemia, hypertension, IR, and proinflammatory and prothrombotic state (Al-Hamad and Raman, 2017).

OBJECTIVES

To assess MetS's prevalence in obese adolescents; correlate HOMA-IR and IR incidence with MetS's biochemical parameters and components; as well as correlate adiponectin levels with hypoadiponectinemia incidence, MetS's biochemical parameters, and MetS components.

MATERIAL AND METHOD

Study Design

The study was conducted at the Outpatient Installation of Nutrition and Metabolic Diseases, Child Health Department, Dr. Soetomo General District Hospital, Surabaya Indonesia. The study was conducted over the course of four months, from August until December 2018. The study design was cross-sectional.

Study Population

The study population was obese adolescents aged 13-18 years who were treated at the Outpatient Installation Unit of Nutrition and Metabolic Diseases, Child Health Department, Dr. Soetomo General District Hospital. The research sample was selected randomly. The samples were research subjects, namely obese adolescents aged 13-18 years who were healthy, did not consume corticosteroids six months before the study, did not consume dyslipidemia drugs in the three months before the study, did not take antibiotics, did not smoke, did not undergo hormonal therapy, did not consume alcohol or drugs which affect body composition, and did not suffer from infections or immune and endocrine disorders.

Data Collection

1. Anthropometric measurements

Body weight was measured using digital stepping scales with an accuracy level of 0.1 kg. Height was measured using Seca microtome with an accuracy of 0.1 cm. Waist circumference was measured using metlin with an accuracy of 0.1 cm. BMI was determined by the formula: body weight (kg)/height $(m)^2$.

2. Blood collection and analysis

Blood was drawn via cubiti veins after the subject fasted for 10-12 hours. The blood was stored in an EDTA-containing tube and processed within two hours after the samples were taken, or stored in the freezer at -80^{o}C until the examination were done. Total cholesterol, triglyceride, HDL, LDL, insulin, fasting glucose, and adiponectin levels were analyzed using the ELISA method in the laboratory. Hypoadiponectinemia was determined with a cut-off value of <8.3 µg/ml for females and <8.1 for males (Gilardini et al., 2006). The HOMA-IR measurement index was calculated using the formula: [glucose (mg/dL) x insulin (µu/L)]/405 (Matthews et al., 1985). The cut-off point for healthy children with cardiovascular risk was 3.4 (Jalilolghadr et al., 2015); if they were over 3.4, they were categorized as having IR.

3. MetS determination

MetS in this study had to meet the IDF criteria (Al-Hamad and Raman, 2017; Magge et al., 2017; Zimmet et al., 2007b). This refers to central obesity (or abdominal obesity) accompanied by two of the five criteria for risk factors: hypertension (systole pressure >130 mmHg or diastole >85mmHg); hyperglycemia (fasting); blood glucose >100 mg/dL; hypertriglyceridemia (triglyceride >150 mg/dL); and low-level HDL-c (HLD-c >40 mg/dL for men and 50 mg/dL for women).

This study was submitted to the Health Research Ethics Committee of Dr. Soetomo General District Hospital Surabaya and received approval with the issuance of Ethical Clearance number

0411/KEPK/VII/2018 at July 2018. All study subjects provided written consent from their parents by signing an informed consent form.

Data Analysis

Subjects' characteristics, anthropometric measurements, biochemical examinations, and blood pressure analysis measurements were tested using the paired sample t-test and the Mann-Whitney U test. The tests were based on the normality and homogeneity test with a significance of $p<0.05$. Pearson's correlation was used to determine the strength of the relationships, and the correlation coefficient was used based on Bryman and Cramer (Bryman and Cramer, 2002) with a significance of $p<0.05$.

RESULTS

Subjects' Characteristics, Anthropometry, and Metabolic Obesity Profile

The 216 obese adolescents who took part in this study have their characteristics summarized in **Table 1**. Out of them, 135 did not meet the criteria for MetS (62.14%), while 81 had MetS (37.96%).

Table 1. Subjects' characteristics (n=216)

Subject's Characteristics	Non-Mets (n=134) Mean ± SD	Mets (n=82) Mean ± SD	p
Gender (%)			0.161[3]
- Male	70 (52.99)	51 (62.20)	
- Female	64 (47.76)	31 (37.80)	
Insulin abnormality (%)			0.000[1]
- Hyperinsulinemia >25 µU/mL)	30 (22.96)	38 (45.68)	
- Normal (2.5-24.9 µU/mL)	104 (77.04)	44 (54.32)	
HOMA-IR (%)			0.102[2]
- IR	72 (53.73)	54 (65.85)	
- Normal	62 (46.27)	28 (34.15)	
Age (month)	180.56 ± 17.71	182.26 ± 19.06	0.509[1]
Body weight (kg)	81.14 ± 12.41	88.84 ± 13.71	0.000[1]
Body Height (cm)	159.74 ± 7.01	163.80 ± 8.34	0.000[1]
WC (cm)	95.35 ± 9.97	99.72 ± 10.04	0.001[2]
HC (cm)	107.06 ± 9.61	108.13 ± 9.60	0.033[1]
WHR	0.89 ± 0.07	0.91 ± 0.06	0.085[2]
BMI (kg/m^2)	31.70 ± 4.28	33.02 ± 4.29	0.008[2]

[1]Paired sample T-Test; [2]Mann-Witney U Test; [3]Fischer Exact Test, significant if $p<0.000$
HOMA IR, homeostasis model assessment of insulin resistance; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio

The male-to-female ratio was 1:1.28. Subjects were aged between 147 months (12.25 years) to 226 months (18.83 years), with mean age of 181.12 ± 18.21 months or 15.08 years. The distribution of sex and age was homogeneous and normally distributed, and there was no significant difference between the two groups ($p>0.05$). Insulin levels above the normal threshold were found in 68 subjects (31.48%), with two-times the incidence frequency in obese subjects with MetS (p=0.000) (22.96 vs. 45.68%). IR occurred in 126 subjects (58.33%), and the incidence frequency was higher in obese subjects with MetS (53.73 vs. 65.85%), but there was no significant difference between the groups ($p>0.05$).

Measurements of body weight, height, waist circumference, hip circumference, and BMI showed that obesity with MetS was significantly greater than obesity without MetS among participants ($p<0.05$). Body weight in the non-MetS subjects ranged from 79.03 to 83.26 kg, and 85.81 to 91.88 kg in obese subjects with MetS. Heights ranged between 158.54 to 160.93 cm in obese subjects without MetS, and 161.96 to 165.64 cm in obese subjects with MetS. Waist circumference measurements showed values of 93.66 to 97.05 cm in obese subjects without MetS, and 97.50 to 101.94 cm in obese subjects with MetS. Hip circumference ranged from 105.42 to 108.69 cm and 107.86 to 112.00 cm in subjects with MetS. BMI among MetS subjects was higher (32.07 to 33.96 cm) than in non-MetS subjects (30.97 to 32.43 cm).

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Table 2. Metabolic profile of the subjects (n=216)

Metabolic Parameters	Non-Mets (n=135) Mean ± SD	Mets (n=81) Mean ± SD	p
FBG (mg/dL)	85.70 ± 6.00	86.36 ± 8.08	0.498[1]
Fasting insulin mg/dL	19.67 ± 9.84	27.07 ± 17.60	0.003[2]
HOMA-IR	4.16 ± 2.12	5.80 ± 3.85	0.000[2]
Cholesterol total (mg/dL)	170.27 ± 34.48	177.25 ± 27.12	0.121[1]
HDL-c (mg/dL)	45.68 ± 7.00	38.66 ± 6.57	0.000[1]
LDL-c(mg/dL)	110.59 ± 30.16	118.35 ± 23.56	0.049[1]
Triglycerides (mg/dL)	95.98 ± 54.58	145.81 ± 66.63	0.000[2]
Systole (mmHg)	120.27 ± 12.97	129.86 ± 11.14	0.000[1]
Diastole (mmHg)	78.44 ± 9.42	86.54 ± 9.80	0.000[1]

[1]Paired sample T-Test [2]Mann-Witney Test
FBG, fasting blood glucose; HOMA IR, homeostasis model assessment of insulin resistance

The results of the biochemical examination are summarized in **Table 2**. It shows that glucose levels (84.68-86.72 mg/dL vs. 84.57-88.15 mg/dL) and total cholesterol (164.40-176.14 mg/dL vs 171.25-183.24 mg/dL) were not significantly different between the two groups (p>0.005). Fasting insulin was found to be significantly higher in obese subjects with MetS (27.07 + 17.60 vs. 19.67 + 9.84 mg/dL). Fasting insulin ranged from 17.99 to 21.34 mg/dL in obese subjects without MetS and 23.17 to 30.96 mg/dL in obese subjects with MetS.

Table 3. Metabolic syndrome profile of the obese adolescents (n=216)

Mets	n	%
Hypertension dan dyslipidemia (%)	***56***	***69.14***
- Abdominal obesity, hypertension, low level HDL-c	23	
- Abdominal obesity, hypertension, hypertriglyceridemia	17	
- Abdominal obesity, hypertension, hypertriglyceridemia, low level HDL-c	16	
Hyperglicaemia, hipertension dan dyslipidemia (%)	***1***	***1.23***
- Abdominal obesity, hyperglycaemia, hypertension, low level HDL	1	
Hyperglicaemia and dyslipidemia (%)	***3***	***3.70***
- Abdominal obesity, hyperglycaemia, low level HDL-c	1	
- Abdominal obesity, hyperglycaemia, hypertriglyceridemia, low level HDL-c	1	
- Abdominal obesity, hyperglycaemia, hypertriglyceridemia	1	
Dyslipidemia (%)	***21***	***25.93***
- Abdominal obesity, hypertriglyceridemia, low level HDL-c	21	

HDL-c, high density lipoprotein cholesterol

There were significant differences in HOMA-IR value (3.80-4.52 vs. 4.96-6.66) in both groups. HDL-c (37.21-40.12 mg/dL vs. 44.49-46.87 mg/dL) and adiponectin levels (14.26-16.93 vs. 10.90-13.28 µg/ml) were lower in obese subjects with MetS than obese subjects without MetS. LDL-c (105.45-115.72 mg/dL vs. 113.14-123.56 mg/dL), triglyceride (86.68-105.27 mg/dL vs. 131.08 - 160.55 mg/dL), systolic blood pressure (118.06-122.47 mmHg vs. 127.40-132.32 mmHg), and diastole (76.83-80.04 mmHg vs. 84.38-88.71 mmHg) were significantly higher in obese subjects with MetS.

The distribution of metabolic profile obese adolescents with Mets was presented in **Table 3**. All obese subjects with MetS (81) had central obesity (abdominal obesity) and dyslipidemia. The combination of hypertension and dyslipidemia was the most common type of MetS, whereas 21 subjects (25.93%) had dyslipidemia, 3 (3.70%) and one subject with hyperglycemia, hypertension and dyslipidemia

The Correlation between HOMA-IR Values and IR with the MetS Profile

The Pearson correlation between HOMA-IR values with waist circumference, hip circumference, BMI, GDA, and triglyceride showed a weak positive correlation (p<0.005). Meanwhile, the HOMA-IR with HDL and adiponectin showed a weak negative relationship (r=-0.236; p=0.000; and r=-0.191; p=0.005), as summarized in **Table 4**.

There was a very weak positive correlation between IR and MetS incidence (r=0.112; p=0.025). This was also true of dyslipidemia (r=0.137; p=0.044), which was sufficiently related to abdominal obesity

(r=0.513; p=0.025) and weakly associated with hypertriglyceridemia (r=0.270; p=0.000). There was no correlation between IR and low-level HDL-c, high LDL-c levels, and hypercholesterolemia incidence. Obese adolescents with IR had an increased risk of developing MetS by 1.661-times (95% CI [0.940-2.933]; p=0.081), dyslipidemia by 1.845-times (95% CI [1.014–3.358]; p=0.045), abdominal obesity by 3.077-times (95% CI [0.725 - 8.538]; p=0.415), hypertriglyceridemia by 3.286 -times (95% CI [1.802–5.990]; p = 0.000), hypo-HDL by 1.257-times (95% CI [1.160–2.180]; p = 0.014), hyper LDL-c by 1.604-times (95% CI [0.907–2.835]; p=0.104), and hypertriglyceridemia by 3.377-times (95% CI [1.857–6.140]; p=0.000).

Table 4. Correlation between HOMA-IR value and IR incidence with biochemicals and Mets components (n=216)

HOMA-IR value with anthropometric/biochemicals parameters			
Parameters	**r**	**p**	**OR**
Waist circumference	0.258	0.000	-
Hip circumference	0.226	0.001	-
BMI	0.200	0.003	-
LDL-c	0.133	0.050	-
HDL-c	-0.236	0.000	-
Fasting glucose	0.225	0.001	-
Triglyceride	0.367	0.000	-
Systole	0.206	0.002	-
Diastole	0.080	0.242	-
Adiponectin	-0.191	0.005	-
Odds Ratio of IR incident with MetS and MetS components			
Parameters	**r**	**p**	**OR**
MetS	0.112	0.025	1.661
Dyslipidaemia	0.137	0.044	1.845
Hyperglycaemia	0.005	0.939	1.073
Hypertension	0.023	0.741	1.099
Abdominal obesity	0.513	0.025	3.077
Low level HDL-c	0.055	0.417	1.257
Hyper LDL-c	0.111	0.104	1.604
Hypertriglyceridemia	0.270	0.000	3.286
Hypercholesterolemia	0.032	0.642	0.834

BMI, body mass index; BP, blood pressure; MetS, metabolic syndrome; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol

The risk of hyperglycemia increased by 1.073-times (95% CI [0.176 - 6,558]; p=0.939), hypertension by 1.099-times (95% CI [0.629–1.922]; p=0.119), and hypercholesterolemia by 0.834-times (95% [0.423–1.645]; p=0.601).

The Correlation between Adiponectin Levels and Hypoadiponectinemia with MetS Components

Table 5 shows the correlation results between adiponectin level and hypoadiponectinemia incidence with biochemicals and MetS components. The Pearson correlation showed a very weak negative correlation between adiponectin levels and waist circumference (r=-0.138; p=0.042), hip circumference (r=-0.138; p=0.042), and triglyceride (r=-0.136; p=0.045). Adiponectin levels were significantly, yet weakly associated with HDL-c (r=0.229; p=0.001), and very weakly negatively correlated with triglyceride levels (r=-0.136; p=0.045). However, they did not correlate with BMI, LDL-c, fasting blood glucose, and blood pressure, both systole and diastole. Hypoadiponectinemia had a weak negative association with metabolic syndrome incidence (r=-0.155; p=0.022) and had a weak positive association with abdominal obesity incidence (r=0.137; p=0.044) and hypertriglyceridemia incidence (r=0.141; p=0.038).

Subjects with hypoadiponectinemia had an increased risk of developing MetS by 2.220-times (95% CI [1.085–4.543]; p=0.029), subjects with dyslipidemia by 1.525 -times (95% CI [0.654–3.553]; p=0.328), subjects with hypertension by 0.864-times (95% CI [0.412–1.808]; p=0.377), subjects with hypertriglyceridemia by 2.114-times (95% CI [1.034–4.322]; p=0.040), subjects with hyper-LDL by 1.176-times (95% CI [0.494–2.800]; p=0.713), subjects with low-level HDL-c by 1.790-times (95% CI

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[0.878-3.649]; p=0.109), and subjects with hypercholesterolemia by 1.176-times (95% CI [0.494-2800]; p=0.442).

Table 5. Correlation between adiponectin level and hypoadiponectinemia incidence with biochemicals and MetS components

HOMA-IR value with anthropometric/biochemicals parameters			
Parameters	**r**	**p**	**OR**
Waist circumference	-0.138	0.042	-
Hip circumference	-0.138	0.042	-
BMI	-0.047	0.488	-
LDL-c	-0.101	0.140	-
HDL-c	0.229	0.001	-
Fasting glucose	-0.073	0.283	-
Triglyceride	-0.136	0.045	-
Systole-BP	-0.128	0.061	-
Diastole-BP	0.080	0.242	-
Adiponectin level	-0.039	0.565	-
Odds Ratio of hypoadiponectinemia with MetS and MetS components			
Parameters	**r**	**p**	**OR**
MetS	-0.155	0.027	2.220
Dyslipidaemia	-0.067	0.306	1.845
Hyperglycaemia	-0.026	0.306	-
Hypertension	-0.026	0.699	0.864
Abdominal obesity	-0.137	0.699	-
Low level HDL-c	0.110	0.069	1.790
Hyper LDL-c	-0.025	0.715	1.176
Hypertriglyceridemia	-0.141	0.038	2.114
Hypercholesterolemia	-0.025	0.715	1.176

BMI, body mass index; BP, blood pressure; MetS, metabolic syndrome; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol

The Correlation of MetS with More Than Three IDF Criteria with IR

Spearman's rho correlation showed a very weak association between IR incidence and MetS incidence with more than three IDF criteria (r=0.174; p=0.010). Subjects with IR had an increased risk of developing MetS with more than three IDF criteria by 9.368-times (95% CI [1.196–73.412]; p=0.033). Hypoadiponectinemia did not have a relationship with MetS incidence with more than three IDF criteria. Hypoadiponectinemia was a risk factor for MetS with more than three IDF criteria, with an increased risk of 0.873 -times (95% CI [0.185 - 4.112]; p=0.863).

DISCUSSION

Subjects' Characteristics, Anthropometry, and Metabolic Obesity Profile

The prevalence of MetS in adolescents in this study was still quite high compared to studies in Korea and America (Falkner and Cossrow, 2014; Park et al., 2010). Furthermore, the prevalence of those that met the IDF criteria in Brazil was only 27.6% (Sewaybricker et al., 2013) and in Spain only 5.8% (González et al., 2012) The IR incidence was still high, as 58.33% of all subjects had IR when compared to an Iranian study with only an 18.2% incidence rate (Jalilolghadr et al., 2015). However, studies in Mexico showed a higher IR incidence at 50%, and a 20% incidence of MetS (Murguía-Romero et al., 2012). Being fat was more frequent in individuals with MetS. Research in Jakarta showed a lower proportion (38%) (Pulungan et al., 2013). The difference in IR event proportions is due to differences in the HOMA-IR value's cut-off points in determining IR. However, research on children and adolescents in the Netherlands using the same cut-off HOMA-IR value showed a similar IR incidence proportion (47.34%). Despite this, MetS incidence with the same criteria (IDF criteria) was still low (20.17%) (Lentferink et al., 2017).

Fasting insulin levels are higher in obese individuals with metabolic syndrome. Gender, puberty stage, BMI, and waist circumference have a correlation with fasting insulin levels (Ling et al., 2016). In healthy conditions, glucose is transported into myosin by GLUT-4 under insulin's influence through

the Glut4 translocation process (Brewer et al., 2014) It is then phosphorylated into glucose-6-phosphate. This intermediate product is then stored as glycogen, or becomes a substrate in the glycolytic pathway (Savage et al., 2007). In obesity, fat tissue, especially in the stomach, is prone to lipolysis, which causes an increase in FFA in the body. High concentrations of FFA mediate IR by reducing insulin signals' strength through the insulin receptor substrate (IRS)-1/phosphatidylinositol (PI) 3-kinase pathway (Draznin, 2006). In addition, adipokines produced by adipocytes, such as resistin and retinol-binding protein 4, reduce insulin sensitivity (Klop et al., 2013).

All subjects with metabolic syndrome (81 adolescents) had dyslipidemia and abdominal obesity at the same time. Obesity is characterized by a buildup of lipids in the muscles and liver, causing high triglyceride levels due to increased protein lipase in the muscles and liver, causing selective muscle or hepatic IR (Savage et al., 2007). Obesity, especially abdominal obesity or central obesity, is a cause of metabolic syndrome and dyslipidemia (Di Chiara et al., 2012; Klop et al., 2013). Hypertriglyceridemia and hypo-HDL are strongly associated with IR in children and adolescents due to increased FFA that enters the liver, causing hepatic insensitivity (Magge et al., 2017). In obesity, there is damage to TG lipoprotein (triglycerides) lipolysis due to decreased expression of lipoprotein lipase in adipocyte tissue (Klop et al., 2013).

The clinical profile of hypertension with dyslipidemia was predominant in this study. Hypertension-related obesity is common among obese adolescents, occurring in 30% of them (Falkner, 2017), with three-fold the risk of normal children, increasing with increasing BMI (Sorof and Daniels, 2002). Visceral fat accumulation is associated with blood pressure systole (Matsuzawa et al., 2004). Until now, the relationship between obesity and hypertension remains unexplained. Allegedly, sympathetic nervous system activation, increased renal sodium retention and IR, and proinflammatory cytokines are the cause (Falkner, 2017). Obesity causes overactivation of the sympathetic nervous system (SNS) due to the production of certain cytokines (e.g., leptin); thereby, triggering hyperactivity. This also manifests in the heart (increased heart rate and blood pressure), neurohumoral (elevated catecholamines), and neural areas by increasing peripheral sympathetic nerve traffic (Sorof and Daniels, 2002). Increased BMI increases the amount of norepinephrine manifested in the kidneys (spill over), causes SNS activation, and triggers neural renin release (Brady, 2017). In turn, that triggers vasoconstriction and causes blood pressure to rise due to increased renin–angiotensin–aldosterone system (RAAS) activity. RAAS activity increases with body fat gain (Cat et al., 2016). Insulin increases sodium retention in the kidneys, and the level is increased in adult hypertensive patients. IR increases SNS activity and stimulates vascular smooth muscle growth (Steinberger and Daniels, 2003). Hyperglycemia in obese subjects is a manifestation of defective insulin action, ineffective insulin secretion or clearance, or a combination of other causes. IR causes fasting blood glucose to increase (Lee and Sanders, 2012).

Obesity subjects with MetS have shown significant differences in body weight, BMI, waist circumference, visceral fat, glucose, insulin, LDL-c, total cholesterol, triglycerides, and blood pressure compared to obese subjects without MetS (Masquio et al., 2015), which is consistent with the results of this study. Adiponectin is associated with central obesity and is produced by adipocyte tissue, meaning the levels are associated with adipocyte mass (Pyrzak et al., 2010). Since all subjects with metabolic syndrome had central obesity, the levels were significantly lower than in subjects with non-MetS obesity.

The Correlation between HOMA-IR and IR with Metabolic Syndrome Profiles

IR frequency varies depending on gender and ethnicity/race (Klein et al., 2004), sexual maturating rate, BMI (Singh et al., 2013), puberty stage, waist circumference, and body fat percentage (Ling et al., 2016). HOMA-IR values were found to be weakly related to waist circumference, BMI, and hip circumference. Another study stated that BMI and waist circumference are simple predictors of fasting insulin and IR in overweight and obese adolescents (Ling et al., 2016). Research on children in Korea found a relationship between HOMA-IR values with age, BMI, waist circumference, blood pressure, triglycerides, total cholesterol (Cho et al., 2017) and adiponectin levels (Baratta et al., 2004) these results are in line with this study. Adiponectin has been found to increase insulin sensitivity (Gao et al., 2013). Increased HOMA-IR has been found to reduce adiponectin levels in South Asians (Mori et al., 2006).

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IR and hyperinsulinemia are strongly suspected to be the central key factors in the occurrence of MetS (Di Chiara et al., 2012) meaning IR is associated with MetS incidence in this study. Visceral fat accumulation has been related to excess lipid in the liver, and thought to be the cause of MetS (Di Chiara et al., 2012) since it causes damage to the autonomous cells of insulin signaling (Hardy et al., 2012). IR is strongly associated with dyslipidemia (Lee and Sanders, 2012), especially hypertriglyceridemia (Caceres et al., 2008) and low level HDL-c, in the sense that IR incidence increases the risk of hypertriglyceridemia events. Other studies have shown an association between IR with HDL-c and metabolic syndrome events (Hsu, 2013; Weiss et al., 2004) which is consistent with this study.

The Correlation between Adiponectin Levels and Hypoadiponectinemia with Metabolic Syndrome Profiles

Plasma adiponectin levels range from 3–30 µg/ml, expressed in the liver and correlated positively with insulin sensitivity (Di Chiara et al., 2012). It has been found to decrease in obese individuals and increase after weight loss (Pyrzak et al., 2010). In humans, adiponectin has been found to be higher in women and associated with age (Baratta et al., 2004; Cnop et al., 2003), ethnicity (Mori et al., 2006), BMI z-score (Sparrenberger et al., 2019), pubertal status, and insulin sensitivity (Ryo et al., 2004). Several studies have shown adiponectin levels to be associated with metabolic syndrome variables (low-level HDL-c, hypertriglyceridemia, and high triglyceride-to-high-density-lipoprotein ratio) (Ryo et al., 2004; Shafiee et al., 2015).

In the adult community (mean age of 48.8 years), adiponectin levels are significantly lower in people with metabolic syndrome and are associated with hypertriglyceridemia and low-level HDL-c incidence (Isa et al., 2017). Waist circumference is associated with adiponectin levels, and is an independent determinant, meaning waist circumference changes could be used as a benchmark for adiponectin changes. For every one unit increased, there is a decrease of 0.39 mg/L of adiponectin (Bazanelli et al., 2013). Obese child subjects have shown the same results; hypoadiponectinemia was even associated with the risk of metabolic syndrome and was the best predictor of MetS incidence (Gilardini et al., 2006). Other studies have shown adiponectin concentrations to be negatively related to waist circumference, triglycerides, and fasting insulin, and positively associated with HDL-c, which is consistent with this study (Ryo et al., 2004). Studies show a negative relationship between adiponectin levels with BMI (Steinberger and Daniels, 2003), LDL-c (Cnop et al., 2003), fasting blood glucose (Blaslov et al., 2013) and blood pressure (Li et al., 2008). Even when there is a ten-fold decrease, hypertension risk will increase by 50% (Brambilla et al., 2013).

Serum adiponectin is decreased in patients with MetS and is an independent marker. In obese boys, hypoadiponectinemia (<6.65 µg/ml) is associated with MetS incidence (Ogawa et al., 2005). In adult kidney patients, hypoadiponectinemia is positively associated with HDL-c and BMI, and is an independent predictor of fasting serum adiponectinemia (Tsai et al., 2011). However, for South Asian races, BMI is not correlated with serum adiponectin (Mori et al., 2006). Serum adiponectin is produced in subcutaneous and visceral fat, but the correlation is negative and stronger in visceral adipocytes (Matsuzawa et al., 2004); thus, it is associated with abdominal obesity and abdominal circumference, and strongly correlated with insulin sensitivity.

Individuals with hypoadiponectinemia (adiponectin <4 µg/mL) have an increased risk of experiencing MetS by 7.6 -times ($p<0.001$). This includes experiencing hypertriglyceridemia (OR=3.2; $p<0.05$), low-level HDL-c (OR=1.9; $p=0.29$); hypertension (OR=2.2; $p=0.15$), and hyperglycemia (OR=1.9; $p=0.29$) in the worker community (Mori et al., 2006). In the elderly community, individuals with hypoadiponectinemia (<4.02 µg/mL for men; <5.10 µg/mL for women) are at increased risk of hypertension by 2.62-times (Chow et al., 2007). This study's subjects with hypoadiponectinemia (>8.3 µg/mL for women; >8.1 µg/mL for men) were at increased risk of MetS by 2.22-times, as well as increased risk of dyslipidemia and hypertension by 1.525 and 0.864-times, respectively.

Correlation Between Mets in More than Three IDF Criteria with IR

There was a very weak relationship between IR incidence and MetS incidence with more than three IDF criteria (r=0.174; p=0.010), with an added risk of 9.268-times. The higher the HOMA-IR value, the greater the MetS incidence in more than two criteria. Adult subjects with T2DM at the HOMA-IR index quartile 4 (75%) experienced 13.8-times the MetS incidence with more than two components. Subjects with large waist circumferences and hypertriglyceridemia experienced 6.1-times and 2.6-times the MetS incidence with more than two components, respectively (Hsu, 2013). In this study, the subjects with Mexican hypertension had MetS in more than three IDF categories 10.225 (95% CI [2,205 - 47,412]; p=0.003). Hyperglycemia increased MetS risk with more than three IDF categories by 12.121-times (95% CI [1,832 - 80,183]; p=0.010), hypertriglyceridemia increased the risk by 9.795-times (95% CI [2,113 - 45,399]; p=0.004), and low-level HDL-c increased the risk by 8.456-times (95% CI [1,826 - 39.1589] p=0.006).

Strengths and Limitations

This study did not access the adiponectin receptor on obese adolescents and other markers related with atherogenic events on the endothelial.

CONCLUSION

This study identified a positive relationship between HOMA-IR and anthropometric parameters of obesity and MetS parameters. IR was found to be associated with dyslipidemia, abdominal obesity, and MetS incidence with more than three IDF criteria. There was a relationship between hypoadiponectinemia and waist circumference, hip circumference, HDL-c, and triglycerides. Insulin resistance and hypoadiponectinemia were associated with Mets and hypertriglyceridemia incidence.

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Conflict of interest

All authors have no conflict of interest.

Ethics Consideration

This study was submitted to the Health Research Ethics Committee of Dr. Soetomo General District Hospital of Surabaya and received approval with the issuance of Ethical Clearance no. 0411/KEPK/VII/2018 on July 20th, 2018.

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