Original Article

Sexual dimorphism in interleukin 17A and adipocytokines and their association with insulin resistance among obese adolescents in Yogyakarta, Indonesia

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Background and Objectives: Pro-inflammatory cytokines interleukin 17A (IL-17), leptin, and adiponectin have been associated with obesity and insulin resistance. Moreover, differences in sex and ethnicity as well as plasma concentration of adipocytokines and cytokines have been associated with the risk of insulin resistance. This study was conducted to elucidate whether sex differences exist in the risk of insulin resistance in Indonesian adolescents and to determine how plasma leptin, adiponectin, and IL-17 predict insulin resistance. **Methods and Study Design:** The study participants were 69 obese–overweight boys, 53 obese–overweight girls, 59 non-obese boys, and 50 non-obese girls aged 15–18 years. Insulin resistance was determined using the homeostatic model assessment of insulin resistance index. Plasma IL-17, leptin, and adiponectin were measured using ELISA. Data were analysed using one-way ANOVA and linear regression analysis. Odd ratios [ORs; 95% confidence intervals (CIs)] were analysed to estimate the risk of insulin resistance; the significance level was set at 95%. **Result:** The OR (95% CI) for insulin resistance was higher in obese–overweight boys than in obese–overweight girls. The plasma IL-17 was higher in boys, whereas plasma adiponectin and leptin were significantly higher in girls. In all participants, obesity status and plasma leptin were the most efficient predictors of insulin resistance, whereas the IL-17 could not significantly predict insulin resistance. **Conclusion**: Sexual dimorphism exists in IL17 as well as leptin and adiponectin in adolescents. Plasma IL-17 cannot be used to predict insulin resistance in adolescents of both sex.

Key Words: sexual dimorphism, obesity, interleukin 17, adipocytokine, insulin resistance

INTRODUCTION

The global increase in the incidence of obesity in children and adolescents contributes to the increased risk of many diseases during adulthood. In developing countries, the prevalence of overweight and obesity in children and adolescents increased from 8.1% (7.7–8.6) in 1980 to 12.9% (12.3–13.5) in 2013 in boys and from 8.4% (8.1–8.8) in 1980 to 13.4% (13.0–13.9) in 2013 in girls.[1] Moreover, the prevalence of obesity in Indonesian children and adolescents increased to 10% in 2013.[2] Obesity is not the only predictor of insulin resistance; however, obese patients are known to have an increased risk of insulin resistance,[3] a condition that leads to cardiometabolic disorders.

Several biomarkers for assessing the risk of cardiometabolic disorders in obese children and adolescents have been extensively studied. A higher leptin and lower adiponectin have been reported in obese people, and these are associated with insulin resistance in several populations.[3,4] However, reports on Indonesian adolescents are very limited. Obesity is a chronic inflammatory condition; therefore, inflammatory cytokines are potential markers of the pathophysiology of obesity related diseases. Some inflammatory markers, such as interleukin 6 (IL-6) and tumor necrosis factor (TNF)-α, reportedly increased in obese children.[3]

IL-17A (IL-17), a pro-inflammatory cytokine, has been reported to increase in obese adults[5] and hypertensive patients.[6] A high IL-17 is associated with an increased risk of inflammation-related diseases such as inflammatory bowel diseases, respiratory tract hypersensitivity, auto-

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immune diseases, and cancer in obese individuals.[7-9] The serum IL-17 has been reported to decrease in obese individuals after antidiabetic,[10] vitamin D,[11] and melatonin therapies.[12] Therefore, in addition to its use as screening and risk analysis purposes, the serum or plasma IL-17 can be used as a therapeutic marker. A specific anti-IL-17 therapy has been tested for several diseases, such as autoimmune diseases, and might be implemented for other diseases involving high serum IL-17. Unlike the role of other pro-inflammatory markers, such as TNF-α and IL-6, that of IL-17 in human diseases has been scarcely reported. IL-17 was suggested to be associated with obesity because it is involved in adipogenesis and glucose homeostasis.[13] However, another study reported a negative correlation between serum IL-17 and central obesity.[14] IL-17 was also reported to inhibit adipogenesis in mice, and mice with IL-17 deficiency were more prone to obesity.[15]

The adipogenesis process is more complicated in adolescents than in adults. Sexual dimorphism plays a major role in adipose tissue distribution during puberty.[16] The differences in adipose distribution and body fat composition are reflected in varying concentration of leptin and adiponectin between adolescent boys and girls.[17] This sex difference induces a differential risk of obesity-related diseases including the risk of developing insulin resistance.[18]

Some studies have reported ethnic differences in adipocytokine concentration, leading to a differential risk of insulin resistance among ethnicity.[19] According to our review of relevant literature, no study has reported an association of IL-17 and adipocytokines with insulin resistance in Indonesian adolescents and the role of sex in this association. Therefore, this study was conducted to elucidate whether any sex differences exist in insulin resistance risk, central obesity status, and concentration of adipocytokines and IL-17 in obese Indonesian adolescents. If a sex difference was confirmed, the differential strength of each parameter in predicting the insulin resistance status was investigated.

METHODS
In this cross-sectional study, obese–overweight and non-obese adolescents constituted the test and control groups, respectively. For inclusion in the study, 3004 adolescents (1230 boys and 1774 girls) were screened for obesity in Yogyakarta, Indonesia. Among these adolescents, 363 boys (13%) and 195 girls (8%) were obese, and 180 boys (9%) and 219 girls (9%) were overweight.

With a two-sided confidence interval (CI) of 95% and power of 90%, to detect 30% differences in the prevalence of insulin resistance, we required 49 participants in each group. We sampled 122 obese–overweight adolescents (69 boys and 53 girls) and 109 non-obese adolescents (59 boys and 50 girls). The participants were excluded if they smoked; consumed alcohol; or were diagnosed as having chronic diseases such as diabetes, heart disease, kidney diseases, autoimmune diseases, asthma, cancer, or infectious diseases 14 days before data collection.

Informed consent and assent were signed by parents and the participants. The study was approved by the Med-

ical and Health Research Ethic Committee of the Faculty of Medicine, Universitas Gadjah Mada (no KE/FK/383/EC).

Body weight and height were measured in the morning, with the participants wearing light clothes. Weight was measured using digital scales (precision, 0.1 kg), whereas height was measured using a microtoise to the nearest 0.1 cm. The body mass index (BMI) was calculated as the body weight (kg)/height (m).[2] Obesity status was determined on the basis of the sex-specific BMI for age z-scores. The participants were considered obese–overweight if their BMI-for-age z-scores were 1 or exceeded 1, whereas they were not considered obese–overweight when their scores were lower than 1.[20]

Peripheral blood was obtained after the participants fasted for 10–12 h. Blood glucose of specimens collected in plain tubes was measured using the glucose oxidase–paramind phenazone method. Blood specimens were also collected in EDTA tubes. Plasma was obtained after centrifugation and was stored at −80°C before the execution of an ELISA; this assay was performed for insulin (DRG 2935, DRG International, NJ, USA), IL-17 (EK0430, BosterImmunoleader, CA, USA), adiponectin (R&D SHWAD0, R&D Systems, Inc, MN USA), and leptin (DRG EIA-2395, DRG International, NJ, USA) in duplicate, according to manufacturer instructions. Insulin resistance was determined using the homeostatic model assessment of insulin resistance (HOMA-IR) index, which can be calculated as HOMA-IR = [fasting insulin (µIU/mL) × fasting glucose (mg/dL)/405].[21] The participants were considered to be in the insulin-resistance state when their HOMA-IR index exceeded 3.2.[22]

The data are reported as means (95% CI). One-way ANOVA was used to compare the means, and chi-square analysis was used to investigate odds ratios for insulin resistance. Regression analyses were performed to assess the association of HOMA-IR with its predictors, either individually (simple linear regression analyses) or in combination (multiple regression analyses). All analyses were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). All tests were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS
The study included 122 obese–overweight participants (69 boys and 53 girls) and 109 non-obese participants (59 boys and 50 girls). The mean age did not vary between the groups. For each sex, the obese–overweight group had higher BMI z-scores, waist circumferences, waist-to-height ratios (WHtRs), fasting plasma insulin, and HOMA-IR index scores than did the non-obese group ($p<0.001$; Table 1).

When HOMA-IR >3.2 was used as the cut-off point, the prevalence rates of insulin resistance were 70% and 67% in obese–overweight boys and girls, respectively. Compared with the ORs (95% CI) for insulin resistance in non-obese girls and boys, those in obese–overweight girls and boys were 11.7 (4.5 vs 33.2; $p<0.001$) and 24.0 (8.8 vs 76.4; $p<0.001$), respectively.

Plasma IL-17 were 3 to 4 times higher in boys than in girls, in both the obese–overweight and non-obese groups. However, plasma IL-17 did not significantly vary be-

Table 1. Characteristics of every groups, i.e. obese-overweight boys vs. non-obese boys vs obese-overweight girls vs. non-obese girls, compared with One-Way ANOVA

	Boys (mean; 95% CI)		Girls (mean; 95% CI)		*p* value			
	Obese-overweight	Non obese	Obese-overweight	Non obese	a	b	c	d
n	69	59	53	50				
Age (year)	16.8 (16.7; 17.0)	16.8 (16.7; 17.0)	16.7 (16.6; 16.9)	16.8 (16.6; 16.9)	0.631	0.959	0.641	0.350
BMI z-scores	3.6 (3.3; 3.9)	-0.4 (-0.6-; -0.2)	3.4 (3.1; 3.8)	-0.3 (-0.5-; -0.1)	<0.001	<0.001	0.341	0.588
Waist circumference (cm)	97.9 (95.4; 100.4)	71.9 (69.4; 74.3)	89.4 (86.6; 92.2)	68.0 (65.7; 70.3)	<0.001	<0.001	0.024	<0.001
Waist to height ratio (%)	58.1 (56.7; 60.0)	42.5 (41.1; 43.9)	56.9 (55.1; 58.6)	44.0 (42.3; 45.6)	<0.001	<0.001	0.488	0.277
Fasting blood glucose (mmol/L)	84.7 (82.1; 87.4)	85.6 (82.9; 88.2)	82.6 (80.1; 85.0)	81.4 (79.0; 83.8)	0.565	0.603	0.025	0.239
Fasting serum insulin (mU/L)	21.5 (19.0; 24.1)	10.9 (9.1; 12.7)	20.6 (18.6; 22.6)	11.7 (10.8; 12.7)	<0.001	<0.001	0.432	0.595
HOMA-IR	4.5 (3.9; 5.0)	2.3 (1.9; 2.8)	4.2 (3.8; 4.7)	2.4 (2.1; 2.6)	<0.001	<0.001	0.899	0.454
Plasma leptin (ng/mL)	7.3 (5.9; 8.7)	2.4 (1.8; 3.0)	20.2 (17.1; 22.4)	5.2 (4.1; 6.2)	<0.001	<0.001	<0.001	<0.001
Plasma adiponectin (µg/mL)	2.0 (1.6; 2.3)	4.0 (3.2; 4.7)	3.9 (3.1; 4.6)	7.5 (6.0; 9.0)	<0.001	<0.001	<0.001	<0.001
Leptin to adiponectin ratio	7.1 (4.8; 9.4)	2.3 (0.2; 4.8)	12.4 (4.6; 20.2)	1.1 (0.8; 1.4)	0.005	0.005	0.363	0.148
IL-17 (pg/mL)	208 (132; 284)	244 (141; 346)	53.9 (21.0; 86.7)	84.5 (31.7; 137)	0.319	0.576	0.010	0.001

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance.
a. Obese overweight – non-obese girls; b. Obese overweight – non-obese boys
c. Non-obese boys – non-obese girls; d. Obese overweight boys – obese overweight girls

Table 2. Linier regression analysis for every predictor of HOMA-IR, stratified by sex

Variabel	Unstandardized coeff. (95%CI)	p value	Adjusted R square[‡]
Girls			
Obesity status[†]	1.84 (1.34; 2.34)	<0.001	0.34
Waist to Height ratio	0.10 (0.07; 0.13)	<0.001	0.31
Plasma adiponectin (µg/mL)	-0.10 (-0.17;-0.04)	0.003	0.08
Plasma leptin (ng/mL)	0.08 (0.06; 0.11)	<0.001	0.36
Plasma IL-17 (pg/mL)	-0.000 (-0.002; 0.002)	0.95	-0.01
Leptin to Adiponectin Ratio	0.01 (-0.001; 0.03)	0.08	0.02
Boys			
Obesity status[†]	2.47 (1.79; 3.14)	<0.001	0.29
Waist to Height ratio	0.12 (0.08; 0.16)	<0.001	0.25
Plasma adiponectin (µg/mL)	-0.23 (-0.39; -0.08)	0.003	0.06
Plasma leptin (ng/mL)	0.18 (0.11; 0.25)	<0.001	0.16
Plasma IL-17 (pg/mL)	0.00 (-0.001; 0.001)	0.85	-0.01
Leptin to Adiponectin Ratio	0.05 (0.01; 0.09)	0.02	0.04

[†]Obesity Status: 0= non-obese (BMI-z score <1), 1=overweight/obese (BMI z score ≥1).
[‡]Adjusted R square for every predictor.

tween the study groups. Among all the participants, the obese–overweight girls had the highest plasma leptin, which reached statistical significance. The plasma leptin were similar between obese–overweight boys and non-obese girls. Plasma adiponectin were the highest in non-obese girls; these concentration were similar between obese–overweight girls and non-obese boys. The leptin-adiponectin ratio was higher in obese groups compared to non-obese groups in both sex. However, there was no significant difference of the leptin to adiponectin ratio between sex.

Because of sexual dimorphism in the risk of insulin resistance, as well as plasma IL-17, leptin, and adiponectin, subsequent analyses were stratified by sex. The mean BMI z-scores; waist circumferences; and fasting insulin, leptin, and adiponectin concentration were significantly higher in the insulin-resistance groups than in the non-insulin-resistance groups (data not shown). The plasma IL-17 did not differ significantly between the insulin-resistance and non-insulin-resistance groups in both sex. However, the plasma leptin and adiponectin were inversely associated with the plasma IL-17 [i.e. Pearson correlation (ρ)=−0.17, p=0.01 and ρ=−0.14, p=0.04, respectively].

Linear regression analysis revealed both associations between every predictor and HOMA-IR (Table 2) and co-associations between all predictors and HOMA-IR (Table 3). Because BMI z-scores were significantly associated with the WHtR (i.e. ρ=0.84, p<0.001 for girls and ρ=0.88, p<0.001 for boys), the regression models revealed either the obesity status or WHtR (Table 3). Eliminating variables to obtain the most efficient regression model showed that only the obesity status and plasma leptin were the strongest predictors of the fasting plasma insulin (adjusted R^2=0.44 for girls and 0.35 for boys); table 3 model 1 and 2). Replacing plasma leptin and adiponectin into leptin to adiponectin ratio did not improve the strength of the prediction (model 3 and 4).

Individually, the plasma leptin, obesity status, and WHtR yielded the highest coefficients of determination (adjusted R^2: 0.36, 0.34, and 0.31 for girls and 0.16, 0.29,

and 0.25 for boys, respectively). Combining all relevant variables into the models yielded slightly increased coefficients (i.e. 0.38 and 0.41 for girls and 0.27 and 0.31 for boys).

DISCUSSION

More than 60% of obese–overweight participants were in an insulin-resistance state. Studies have reported that most obese children and adolescents are metabolically unhealthy.[23,24] We observed that the fasting blood glucose in obese adolescents was still in the reference range, whereas the fasting plasma insulin had increased. Therefore, the fasting plasma insulin must be measured to determine the risk of cardiometabolic disorders in obese adolescents. However, consensus is required on the HOMA-IR cut-off point after stratification by sex, age, and ethnicity.

In this study, the fasting plasma insulin did not significantly vary between the sex; nevertheless, Bellerini et al reported a higher fasting plasma insulin in pubertal girls.[25] Furthermore, boys had a higher risk of insulin resistance than did girls; this observation supports the reports of a previous study.[26] After puberty, changes in the production of sex hormones may alter the metabolic profile and risk of metabolic and cardiovascular diseases in adolescents. Oestrogen is reported to be a protective factor, because menopause increases the risk of metabolic and cardiovascular diseases.[7] A study reported that the plasma testosterone increased insulin sensitivity.[27] However, the plasma testosterone was lower in obese male adolescents than in their non-obese counterparts.[28,29] A lower plasma testosterone is correlated with insulin resistance, whereas testosterone supplementation increases insulin sensitivity.[30]

Obesity status alone, as determined by the BMI z-score, was a strong independent predictor of insulin resistance in both sex. Among adipocytokines and cytokine concentration measured in this study, the plasma leptin was determined to be the most efficient independent predictor of HOMA-IR in both sex, thus supporting the finding of a previous study.[31]

Table 3. Multiple regression models for predictors of HOMA-IR stratified by sex

Variabels	Model 1 Unstandardized coeff. (95% CI)	p	Model 2 Unstandardized coeff. (95% CI)	p	Model 3 Unstandardized coeff. (95% CI)	p	Model 4 Unstandardized coeff. (95% CI)	p
Girls								
Obesity status[†]	1.04 (0.40; 1.68)	0.002	-		1.84 (1.32; 2.37)	<0.001	-	
Waist to Height ratio	-		0.04 (0.002; 0.08)	0.04	-		0.10 (0.07; 0.13)	<0.001
Plasma leptin (ng/mL)	0.05 (0.03; 0.08)	<0.001	0.06 (0.03; 0.09)	0.43	-		-	
Plasma adiponectin (µg/mL)	-0.10(-0.07; 0.05)	0.72	-0.02(-0.08; 0.04)	<0.001	-		-	
Leptin to adiponectin ratio	-		-		0.002 (-0.01; 0.14)	0.79	0.004 (-0.01; 0.17)	0.52
Plasma IL-17 (pg/mL)	0.001(0.001; 0.002)	0.23	0.001(-0.001; 0.002)	0.4	0.001 (-0.001; 0.002)	0.39	0.001 (-0.001; 0.002)	0.84
Adjusted R square[‡]	0.41		0.38		0.33		0.3	
Boys								
Obesity status[†]	2.02 (1.22; 2.82)	<0.001	-		2.37 (1.67; 3.07)	<0.001	-	
Waist to Height ratio	-		0.09 (0.05; 0.14)	<0.001	-		0.12 (0.08; 0.15)	<0.001
Plasma leptin (ng/mL)	0.09 (0.01; 0.16)	0.77	0.08 (0.02; 0.16)	0.52	-		-	
Plasma adiponectin (µg/mL)	-0.22(-0.17; 0.13)	0.02	-0.05 (-0.20; 0.10)	0.04	-		-	
Leptin to adiponectin ratio	-		-	0.54	0.02 (-0.02; 0.06)	0.25	0.02 (0.02; 0.06)	0.37
Plasma IL-17 (pg/mL)	0.00(-0.001; 0.001)	0.49	0.00(-0.001; 0.001)		0.00 (-0.001; 0.001)	0.53	0.00 (-0.001; 0.001)	0.51
Adjusted R square[‡]	0.31		0.27		0.28		0.25	

[†]Obesity Status: 0= non-obese (BMI-z score <1), 1=overweight/obese (BMI z score ≥1).
[‡]Adjusted R square for the best regression model.

The data confirm the reports on sexual dimorphism in leptin and adiponectin in adolescents.[26,28] The plasma leptin were the highest in obese–overweight girls, whereas they were similar in obese–overweight boys and non-obese girls. The plasma adiponectin declined in obese–overweight participants, and they were similar in obese–overweight girls and non-obese boys. This observation supports previous reports on sexual dimorphism in the adipocytokines concentration[17] that may result in sex-specific muscle metabolism.[32] Therefore, sex differences must be considered in the management of obesity in adolescents.

Adiponectin signalling was reported to induce insulin sensitivity.[33] Therefore, as expected, the plasma adiponectin were lower in the obese–overweight group than in the non-obese group, thus confirming the finding of a previous study.[34] A study reported a negative correlation of adiponectin with insulin resistance.[35] In addition to lower plasma adiponectin, insulin resistance can be manifested through the downregulation of adiponectin receptors in obese patients, as previously reported.[36] In both sex, adiponectin was a weaker predictor of insulin resistance than was leptin. However, because adiponectin is a protective factor, the plasma adiponectin is a stronger predictor of cardiovascular diseases.[37]

Our study confirms a previous report that boys have lower plasma adiponectin than do girls.[29] However, ethnicity may be an important determining factor.[38] A European children and adolescent study reported no difference in the plasma adiponectin in both sex.[39] Because adiponectin in adolescents has been reported to be positively correlated with subcutaneous fat and negatively correlated with visceral fat,[28,30] lower plasma adiponectin in boys may be because of lower subcutaneous fat and higher visceral fat. Central obesity has been associated with lower adiponectin secretion in boys.[34,35] However, in the current study, the central obesity, as indicated by the WHtR, was equal in both sex, and data regarding more detailed examination of body fat, such as bio-impedance analysis (BIA), dual energy X-ray absorptiometry (DXA), air displacement plethysmography, and quantitative magnetic resonance[40] are not available. The increased plasma testosterone after puberty has been reported to be negatively correlated with the plasma adiponectin,[41] decreased adiponectin secretion,[27] and decreased mitochondrial biogenesis in cultured adipocytes, whereas an oestrogen signal induced a contrasting effect.[42] Testosterone might contribute to the lower plasma adiponectin in boys and subsequently increase the risk of insulin resistance.

Leptin, along with obesity status, was observed to be the strongest predictor of insulin resistance in both sex. A positive correlation of leptin with insulin resistance and insulin concentration was previously reported.[43] The mechanism through which the plasma leptin predicts insulin resistance, despite leptin being reported to inhibit insulin secretion,[44] warrants elucidation. Several studies have reported that leptin cannot suppress appetite and body weight gain in obese individuals[45] because of leptin resistance in the hypothalamus. Leptin resistance may occur in pancreatic beta cells[46] in obese individuals, resulting in high insulin secretion, despite a high leptin concentration in blood circulation. Contrastingly, insulin signalling has been reported to upregulate leptin expression and induces leptin secretion; this phenomenon is known as an adipoinsular axis.[47]

Compared with boys, girls showed a higher plasma leptin, but lower mean of fasting plasma insulin and HOMA-IR index; the risk of insulin resistance was lower in girls. Because the female fat mass is distributed more as subcutaneous fat instead of visceral fat,[28] the higher secretion of leptin from subcutaneous fat may not directly affect the secretion of pancreatic beta cells. The expression of the leptin receptor was reported to be higher in girls than in boys,[48] hence facilitating effective leptin signalling. The male sex hormone testosterone was shown to downregulate the expression of the leptin receptor.[49] By contrast, oestradiol administration induces leptin receptor expression in the skeletal muscle of ovariectomised rats.[50] Sex hormone signalling may be the factor preventing leptin resistance and subsequent insulin resistance in girls, despite the higher plasma leptin secretion. Moreover, leptin signalling inhibits testosterone production.[51] Therefore, the higher plasma leptin in obese male participants may contribute to the lower plasma testosterone and may further induce the risk of insulin resistance.

The leptin to adiponectin ratio was higher in obese participants. However, the ratio found in this study is much higher compared to previous report.[52] The higher ratio results from lower plasma adiponectin found in this study. The lack of sex difference in leptin to adiponectin ratio suggests that the increase plasma leptin and decrease plasma adiponectin in both sex is at the similar proportion. However, the leptin to adiponectin ratio is only correlated with insulin resistance in boys.

Obesity is a chronic inflammatory state, and inflammation may induce insulin resistance.[53] In this study, no significant differences were observed in the plasma IL-17 in the obese–overweight group compared with the non-obese group. Recently, an increased serum IL-17 level was reported in obese children and adults, and it correlated with a higher number of mucosal invariant T lymphocytes.[54] However, our data do not confirm this observation. Contrastingly, studies have reported that plasma IL-17 is negatively correlated with obesity in adults[14] and overweight adolescents.[55] The plasma IL-17 may be influenced by other modifying factors because we could not objectively exclude participants with other conditions that may affect the plasma IL-17, such as acute infection and trauma. Because a high level of inflammation may induce endothelial tissue damage and vascular injury,[56] the plasma IL-17 may be more correlated with cardiovascular disorders.

In this study, we demonstrated the existence of sexual dimorphism in IL-17 in adolescents. Sexual dimorphism in the blood cytokine was previously reported.[57] However, studies have yet to report on the plasma IL-17. Herein, we report the existence of such sexual dimorphism in the plasma IL-17. IL-17 was lower in girls, possibly because of oestrogen signalling. Oestradiol administration was reported to reduce the pro-inflammatory cytokine concentration in obese female participants.[58] In an animal model, oestrogen was reported to inhibit insulin resistance through its anti-inflammatory effects in adipose tissue.[59] Moreover, testosterone was reported to prevent

inflammatory effects by reducing IL-17 secretion in an animal model.[60] However, other factors such as differential fat distribution might reduce the anti-inflammatory effects of testosterone.

The larger visceral adipose tissue in male participants may contribute to higher plasma IL-17. IL-17 mRNA expression was reportedly higher in the visceral fat of obese individuals than in subcutaneous adipose as well as adipose tissue of non-obese participants.[61] However, central obesity, as indicated by the WHtR in this study, did not significantly vary in both sex. Other factors such as lower adiponectin and probably lower leptin sensitivity might become stronger factors in inducing insulin resistance in boys. Because plasma leptin and adiponectin are higher in girls and the plasma IL-17 is higher in boys, we determined that plasma leptin and adiponectin were inversely associated with the plasma IL-17. A higher plasma adiponectin in female participants might contribute to their lower plasma IL-17, because adiponectin was reported to be a predictor of IĸB expression, the inhibitor of the pro-inflammatory transcription factor nuclear factor-ĸB.[62]

The present study had several limitations. First, since cross-sectional design is used, this study lacks information about the causal relationship between variables. The subjects are resident of Yogyakarta and surrounding area, but there is no data of their ethnicity. Considering the variation between ethnicity in Indonesia, the results may not be generalized for the whole Indonesian population.

In conclusion, our data reveals the existence of sexual dimorphism in plasma IL-17 as well as adiponectin and leptin in adolescents. Obesity status plus leptin concentration is the strongest predictor of insulin resistance, whereas the plasma IL-17 cannot predict insulin resistance status. Additional studies are required to elaborate the correlation between sex hormones and adipocytokines and pro-inflammatory cytokines in association with insulin resistance status. Appropriate interventions for obese adolescents are required for preventing cardiovascular and metabolic diseases in adulthood. Because sex differences exist in plasma adipocytokines and cytokines as well as sex hormones concentration, an effective clinical management of obese adolescents should be designed and developed, more specifically for both sex.

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AUTHOR DISCLOSURES

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