Serum endothelin-1 level among adult Indonesian females with obesity: a nested cross-sectional study from Universitas Gadjah Mada Health and Demographic Surveillance System, Sleman, Indonesia

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ORIGINAL ARTICLE

Serum Endothelin-1 Level Among Adult Indonesian Females With Obesity: A Nested Cross-Sectional Study From Universitas Gadjah Mada Health and Demographic Surveillance System, Sleman, Indonesia

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Abstract

Background: The increased obesity prevalence is seen among adult Indonesian females. Obesity is linked to increased endothelin-1 levels, which contribute to endothelial dysfunction, inflammation and insulin resistance. This study aimed to investigate the association between serum endothelin-1 levels with obesity among Indonesian females.

Methods: This was a cross-sectional study. The subjects were from the population of Universitas Gadjah Mada Health and Demographic Surveillance System (HDSS) in Sleman, Indonesia. We collected venous blood, measured obesity parameters and performed the standardized questionnaire for 124 males and females. Endothelin-1 level was measured from serum by ELISA-method. Endothelin-1 level was compared between subjects according to obesity category and correlated with parameters of obesity.

Results: There were 124 subjects enrolled, consisting of 70 females and 54 males. Endothelin-1 level was comparable between both sexes. Females had significantly higher proportion of central obesity compared to males (70.0% vs. 33.3%, p < 0.001). Females with central obesity and increased waist-to-height ratio had a tendency to have higher endothelin-1 levels. Females with body-mass index (BMI)-derived obese class II had the highest level of endothelin-1 (1.98 ± 1.09 pg/mL), which was significantly higher compared to obese class I females (1.48 ± 0.35 pg/mL, p = 0.026) and normoweight females (1.53 ± 0.41 pg/mL, p = 0.030). Furthermore, in females, endothelin-1 level was significantly correlated with waist circumference (r = 0.331, p = 0.005), hip circumference (r = 0.237, p = 0.048), waist-to-hip ratio (r = 0.246, p = 0.040), waist-to-height ratio (r = 0.354, p = 0.003), BMI (r = 0.248, p = 0.038) and body adiposity index (BAI) (r = 0.277, p = 0.020). This correlation was not found among males.

Conclusion: Serum endothelin-1 level was significantly correlated with the parameters of obesity among adult Indonesian females.

Keywords: Obesity, Central obesity, Endothelin-1, Females

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Introduction

The prevalence of overweight and obesity has strikingly spiked over the past decades in developing countries, including Indonesia, involving all age groups in the general population [1]. The higher increase in overweight and obesity prevalence is especially seen, among adults, in Indonesian females compared to males [1]. Compared with global data, the prevalence of overweight and obesity in Indonesian females has almost doubled [1]. Increased prevalence of overweight and obesity in Indonesia are associated with living in urban parts, wealthier living conditions, higher educational level, and more intake of ultra-processed foods [2]. Sedentary lifestyle and easy access to unhealthy fast food among females are the most responsible factors for this condition, as compared to males which have more active lifestyle [2]. Increased body adiposity, typically seen in obese females, is associated with increased risk of cardiovascular disease, especially for developing heart failure with preserved ejection fraction and ischemic heart disease [3].

Endothelin-1 is a powerful vasoactive peptide generated mostly by endothelial cells and works mostly in a paracrine manner causing vascular smooth muscle cells to vasoconstrict [4]. In addition to endothelial cells, adipocytes also contribute to producing endothelin-1 and releasing it in circulation [5]. Obesity is linked to increased levels of endothelin-1, which contribute to unhealthy consequences such as endothelial dysfunction, inflammation and insulin resistance [6]. Our previous studies indicated that, among the Indonesian population, coronary artery disease was associated with increased serum endothelin-1 level and its higher level was correlated with parameters of central obesity [7,8]. Whether sex differences associated with serum endothelin-1 level especially among obese individuals is not yet confirmed, at least among Indonesian. Therefore, in this study, we aimed to investigate serum endothelin-1 level in the apparently-healthy individuals, both males and females, in an Indonesian populational study and identify any associations with the parameters of obesity based on anthropometric measurements.

Methods

Subjects

This was a cross-sectional study performed in the regional populational survey conducted by Universitas Gadjah Mada (UGM) in Sleman District, Province of Special Region of Yogyakarta, dubbed UGM Health Demographic and Surveillance System (HDSS) Sleman. The UGM HDSS Sleman is a longitudinal and population-based survey (https://hdss.fk.ugm.ac.id/) [9]. This current study involved a nested community survey with collection of medical history, anthropometric measurement, venous blood samples, and resting 12-lead electrocardiograms, among respondents of the 2019 UGM HDSS Sleman survey [7]. Based on the medical history and resting 12-lead electrocardiograms, respondents with signs of cardiovascular diseases were excluded from this study. The respondents without cardiovascular diseases were included in this study as subjects. This study was approved by The Medical and Health Research Ethics Committee Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada and Dr Sardjito Hospital Yogyakarta, Indonesia (Ref: KE/FK/0526/EC/2019; KE/FK/0551/EC/2021).

Data collection

The data regarding the history of diabetes mellitus, hypertension, dyslipidemia, and smoking were collected by direct interview. The anthropometric measurements were performed as previously described [7,8]. Standard body scale and height measuring device were used to measure body weight and height. Body mass index (BMI) was calculated as body weight/(body height)² and BMI-derived obesity was defined based on the Asian classification [10]. Obese class I is defined as a BMI of 30-34.9kg/m² and obese class II is defined as a BMI of 35-39.9kg/m². Standard body tape was used to perform a standardized procedure for waist and hip circumference measurements [8]. Accordingly, central obesity was determined as waist circumference of ≥90 cm for males and ≥80 cm for females [11]. Waist-to-hip ratio and waist-to-height ratio were calculated accordingly. Increased waist-to-hip ratio was defined as more than 0.5 [12]. Body adiposity index (BAI) was derived from previously described formulae [13]. Obesity criteria by excess BAI were defined as previously described based on sex and age [14].

Laboratory examination

For laboratory examination, venous blood samples were obtained on BD Vacutainer tubes (Becton Dickinson, U.S.A) and placed at room temperature for 20–30 minutes. The glucose level was measured by standard chemical procedure. For endothelin-1 level measurement from serum, the tubes were
centrifuged at 200 g for 20 minutes, and the supernatant was kept in a freezer (−80 °C). The frozen supernatant samples were thawed for endothelin-1 measurement using immunoassay Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA) by trained laboratory technicians, as described previously [7].

**Statistical analysis**

For statistical analysis of normality data, the Kolmogorov–Smirnov test and log transformation was performed for all continuous data before each analysis. The non-parametric test was conducted on non-normally distributed data. The group comparison of endothelin-1 level was performed with Student’s T or Mann–Whitney tests and one-way ANOVA or Fisher exact tests which ever suitable. The correlation test was performed with Pearson or Spearman test whichever appropriate. A statistical significance was defined with a p-value <0.05.

**Results**

As many as 124 subjects were eligible to be enrolled in this study. There were 70 females and 54 males. Serum endothelin-1 level was comparable between males and females, (mean ± standard deviation (SD): 1.96 ± 1.07 pg/mL vs. 1.61 ± 0.54 pg/mL, p = 0.310). The proportion of hypertension was higher in females as compared with males (51.4% vs. 24.1%, p = 0.002). Mean systolic and diastolic blood pressures were significantly higher in females than males (146.6 ± 25.5 mmHg vs. 134.6 ± 19.2 mmHg, p = 0.005 and 86.8 ± 12.0 mmHg vs. 81.2 ± 11.7 mmHg, p = 0.011, respectively). Females had significantly higher proportion of central obesity compared with males (70.0% vs. 33.3%, p < 0.001). Mean BAI value was higher in females compared with males (34.6 ± 6.5 vs. 28.6 ± 3.9, p < 0.001). Table 1 depicts the characteristics of subjects.

Females with central obesity tended to have higher mean serum endothelin-1 levels (1.67 ± 0.59 vs. 1.47 ± 0.41 pg/mL, p = 0.085, Fig. 1). Females with increased waist-to-height ratio also tended to have higher mean serum endothelin-1 levels (1.65 ± 0.57 pg/mL vs. 1.41 ± 0.40 pg/mL, p = 0.071, Fig. 2). Females in obese class II had the highest mean levels of serum endothelin-1 (1.98 ± 1.09 pg/mL), which were significantly higher compared with females in obese class I (1.48 ± 0.35 pg/mL, p = 0.026) and normoweight females (1.53 ± 0.41 pg/mL, p = 0.030) (Fig. 3).

In females, serum endothelin-1 level was significantly correlated with waist circumference (r = 0.331, p = 0.005), hip circumference (r = 0.237, p = 0.048), waist-to-hip ratio (r = 0.246, p = 0.040), waist-to-height ratio (r = 0.354, p = 0.003), BMI (r = 0.248, p = 0.038) and BAI (r = 0.277, p = 0.020) (Table 2).

In males, there was no significant difference in mean serum endothelin-1 levels based on central obesity (1.96 ± 0.96 pg/mL vs. 1.96 ± 1.14 pg/mL, p = 0.988), BMI-derived obese categories, and excess BAI (1.89 ± 1.28 pg/mL vs. 1.96 ± 0.99 pg/mL, p = 0.197). Females with central obesity had significantly higher mean serum endothelin-1 levels (1.67 ± 0.59 vs. 1.47 ± 0.41 pg/mL, p = 0.085, Fig. 1). Females with increased waist-to-height ratio also tended to have higher mean serum endothelin-1 levels (1.65 ± 0.57 pg/mL vs. 1.41 ± 0.40 pg/mL, p = 0.071, Fig. 2). Females in obese class II had the highest mean levels of serum endothelin-1 (1.98 ± 1.09 pg/mL), which were significantly higher compared with females in obese class I (1.48 ± 0.35 pg/mL, p = 0.026) and normoweight females (1.53 ± 0.41 pg/mL, p = 0.030) (Fig. 3).

In females, serum endothelin-1 level was significantly correlated with waist circumference (r = 0.331, p = 0.005), hip circumference (r = 0.237, p = 0.048), waist-to-hip ratio (r = 0.246, p = 0.040), waist-to-height ratio (r = 0.354, p = 0.003), BMI (r = 0.248, p = 0.038) and BAI (r = 0.277, p = 0.020) (Table 2).

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**Table 1. The characteristics of subjects and their comparison based on sex**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 124)</th>
<th>Males (n = 54)</th>
<th>Females (n = 70)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (years)</td>
<td>60.2 ± 9.9</td>
<td>61.3 ± 9.7</td>
<td>59.4 ± 10.1</td>
<td>0.708</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (8.1)</td>
<td>3 (5.6)</td>
<td>7 (10.0)</td>
<td>0.289*</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>49 (39.5)</td>
<td>13 (24.1)</td>
<td>36 (51.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>24 (19.4)</td>
<td>11 (20.4)</td>
<td>13 (18.6)</td>
<td>0.802</td>
</tr>
<tr>
<td>Current/ex-smokers, n (%)</td>
<td>50 (40.3)</td>
<td>48 (88.9)</td>
<td>2 (2.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>141.4 ± 23.6</td>
<td>134.6 ± 19.2</td>
<td>146.6 ± 25.5</td>
<td>0.005</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84.4 ± 12.2</td>
<td>81.2 ± 11.7</td>
<td>86.8 ± 12.0</td>
<td>0.011</td>
</tr>
<tr>
<td>Fasting glucose (g/dL)</td>
<td>119.9 ± 37.2</td>
<td>112.1 ± 29.4</td>
<td>125.4 ± 41.1</td>
<td>0.059</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>85.9 ± 11.7</td>
<td>85.1 ± 10.9</td>
<td>86.6 ± 12.3</td>
<td>0.486</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>95.5 ± 10.2</td>
<td>94.7 ± 8.8</td>
<td>96.1 ± 11.2</td>
<td>0.475</td>
</tr>
<tr>
<td>Waist-to-hip circumference ratio</td>
<td>0.89 ± 0.07</td>
<td>0.89 ± 0.07</td>
<td>0.90 ± 0.07</td>
<td>0.780</td>
</tr>
<tr>
<td>Central obesity, n (%)</td>
<td>67 (54.0)</td>
<td>18 (33.3)</td>
<td>49 (70.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>23.8 ± 4.6</td>
<td>23.1 ± 4.1</td>
<td>24.3 ± 4.9</td>
<td>0.167</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>39 (31.5)</td>
<td>14 (26.4)</td>
<td>25 (35.7)</td>
<td>0.272</td>
</tr>
<tr>
<td>Body-adiposity index</td>
<td>32.0 ± 6.3</td>
<td>28.6 ± 3.9</td>
<td>34.6 ± 6.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Endothelin-1 level (pg/mL)</td>
<td>1.76 ± 0.83</td>
<td>1.96 ± 1.07</td>
<td>1.61 ± 0.54</td>
<td>0.310*</td>
</tr>
</tbody>
</table>

SD: standard deviation; BP: blood pressure.
Continuous data presented in mean ± standard deviation.

* Fisher exact test.

** Mann–Whitney test.

* Body-mass index ≥25.
There was a tendency towards higher mean serum endothelin-1 levels in males with increased waist-to-hip ratio (2.21 ± 0.97 pg/mL vs. 1.73 ± 1.13 pg/mL, p = 0.050) and waist-to-height ratio (2.07 ± 1.13 pg/mL vs. 1.65 ± 0.90 pg/mL, p = 0.098). Furthermore, there were no significant correlations between serum endothelin-1 levels and anthropometric parameters (Table 3).

### Discussion

In this study, the association between serum endothelin-1 and obesity was apparent in females, but not in males. Obese females tended to have higher serum endothelin-1. There were significant positive correlations between serum endothelin-1 and parameters of obesity, namely higher waist and hip circumferences, elevated waist-to-hip ratio, increased waist-to-height ratio, higher body-mass index, and increased body-adiposity index in females and these were not observed in males.

Individuals with overweight and obesity have weakened endothelium-dependent vasodilation, a sign of endothelial dysfunction [15]. Obese individuals and those with increased adiposity have shown an elevated level of endothelin-1 [15]. Taken together, this combination increases the risk of cardiovascular disease because of elevated endothelin-1-mediated vasoconstrictor tone and vaso-motor dysfunction in obesity [16]. An experimental
study indicated that endothelin-1-mediated vasoconstrictor tone is escalated in overweight and obese individuals [17]. This affects the adiposity-related impairment in endothelium-dependent vasodilation, which is an important parameter of vascular tone homeostasis that protects from vascular dysfunction [17]. In our study, only in females, but not males, was an increased level of endothelin-1 associated with parameters of obesity and increased adiposity.

Previous populational study in apparently-healthy females of South Asian population showed that increased endothelin-1 level was not associated with the parameters of obesity, namely BMI and waist circumference [18]. Among Arabian subjects, endothelin-1 level was higher in healthy females than males, which is in contrary to our finding [19]. African black females had similar levels of endothelin-1 as male counterparts, but it had a protective effect on increased oxidative stress only in females [20]. The endothelin-1 signaling pathway varies between males and females in terms of circulating peptide levels, tissue concentrations, receptor expression, receptor function, and downstream signaling [21]. In experimental study, the response of endothelin-1 release at basal state and upon stimulation was different between endothelial cells from males and females [22]. The role of estradiol in endothelin-1 has been clarified in experimental models, as it can attenuate the production, secretion, and constrictor effects of endothelin-1 [23]. In obese females, increased estrogen activity is associated with endothelial stiffness which is probably mediated by endothelin-1 [24]. In our study, the level of serum endothelin-1 was comparable between females and males, with slightly

### Table 2. Correlation between serum endothelin-1 level and other variables in females

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient correlation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (years)</td>
<td>–0.001</td>
<td>0.992</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>–0.0078</td>
<td>0.524</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>0.052</td>
<td>0.671</td>
</tr>
<tr>
<td>Fasting glucose (g/dL)</td>
<td>0.024</td>
<td>0.845</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.331</td>
<td>0.005</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>0.237</td>
<td>0.048</td>
</tr>
<tr>
<td>Waist-to-hip circumference ratio</td>
<td>0.246</td>
<td>0.040</td>
</tr>
<tr>
<td>Waist-to-height ratio</td>
<td>0.354</td>
<td>0.003</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>0.248</td>
<td>0.038</td>
</tr>
<tr>
<td>Body-adiposity index</td>
<td>0.277</td>
<td>0.020</td>
</tr>
</tbody>
</table>

BP: blood pressure.

### Table 3. Correlation between serum endothelin-1 level and other variables in males

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient correlation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages (years)</td>
<td>–0.071</td>
<td>0.611</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>–0.140</td>
<td>0.316</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>0.022</td>
<td>0.875</td>
</tr>
<tr>
<td>Fasting glucose (g/dL)</td>
<td>–0.182</td>
<td>0.221</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>0.101</td>
<td>0.468</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>–0.028</td>
<td>0.842</td>
</tr>
<tr>
<td>Waist-to-hip circumference ratio</td>
<td>0.211</td>
<td>0.125</td>
</tr>
<tr>
<td>Waist-to-height ratio</td>
<td>0.135</td>
<td>0.336</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>0.027</td>
<td>0.845</td>
</tr>
<tr>
<td>Body-adiposity index</td>
<td>0.035</td>
<td>0.803</td>
</tr>
</tbody>
</table>

BP: blood pressure.

Fig. 3. Females in obesity class II had the highest levels of endothelin-1 (1.98 ± 1.09 pg/mL), which were significantly higher compared with females in obesity class I (1.48 ± 0.35 pg/mL, p = 0.026) and normoweight females (1.53 ± 0.41 pg/mL, p = 0.030).
Subjects. There was a significant positive correlation between obesity parameters and endothelin-1 level only in females.

Obesity defined by BMI cut-off points correlates with abdominal obesity defined by waist circumference [25]. Waist circumference is an indicator of abdominal body fat and, along with BMI, provides a marker of body composition and is associated with cardiometabolic disease and risk of cardiovascular disease [25]. Another anthropometric parameter of visceral obesity, namely waist-to-hip circumference ratio, has been shown to predict cardiovascular mortality independent of BMI [26]. There are recommendations to include visceral adiposity measurements as part of clinical examinations as a marker of cardiovascular disease risk [25]. The BAI is derived from hip circumference and height, which showed a high correlation with percentage of body fat [12]. This index was also associated with cardiovascular disease risk in several populations [27]. Our study indicated that females had higher proportion of central obesity and excess values of obesity parameters, as compared with males. Furthermore, only in females, endothelin-1 level was significantly correlated with obesity parameters.

Further research is needed to corroborate the findings in our study. Limitations of our study include the small sample size and selection bias of subjects.

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Conflicts of interest

Authors declare that there is no conflict of interest on this manuscript.

Ethical Information

This study was approved by the Medical and Health Research Ethics Committee Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada and Dr Sardjito Hospital Yogyakarta, Indonesia (Ref: KE/FK/0526/EC/2019; KE/FK/0551/EC/2021).

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