Reviews in Cardiovascular Medicine

Original Research

Serum endothelin-1 level positively correlates with waist and hip circumferences in stable coronary artery disease patients

Anggoro Budi Hartopo[1,*], Jajah Fachiroh[2], Ira Puspitawati[3], Fatwa Sari Tetra Dewi[4]

[1] *Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, 55281 Yogyakarta, Indonesia*

[2] *Department of Histology and Cell Biology, Faculty of Medicine, Public Health and Nursing - Biobank Development Team, Universitas Gadjah Mada, 55281 Yogyakarta, Indonesia*

[3] *Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada – Dr. Sardjito Hospital, 55281 Yogyakarta, Indonesia*

[4] *Department of Health Behavior, Environment and Social Medicine, Faculty of Medicine, Public Health and Nursing-Sleman Health and Demographic Surveillance System, Universitas Gadjah Mada, 55281 Yogyakarta, Indonesia*

*Correspondence: a_bhartopo@ugm.ac.id (Anggoro Budi Hartopo)

DOI:10.31083/j.rcm2203099

Submitted: 9 February 2021 Revised: 23 April 2021 Accepted: 23 June 2021 Published: 24 September 2021

Central obesity is associated with increased level and activity of endothelin-1. The waist and hip circumferences are simple indicators of central obesity. Waist circumference correlates with visceral adiposity, whereas hip circumference associates with gluteofemoral peripheral adiposity. Both measurements have independent and opposite correlation with coronary artery disease (CAD) risk factors. The relation between serum endothelin-1 in stable CAD and both parameters of central obesityneeds to be investigated. This study aims to examine the correlation between serum endothelin-1 level and waist and hip circumferences as parameters of central obesity in patients with stable CAD. This was a cross-sectional study. Consecutive subjects were enrolled among those who underwent elective coronary angiography with significant CAD. Serum endothelin-1 was measured from peripheral blood samples taken before coronary angiography procedure. The measurement of waist circumference, hip circumference, and ratio derived from them, was performed. Central obesity was determined by waist circumference cut-off for Indonesian population. The correlation analysis was performed with Pearson test. The multivariate analysis was performed with multiple linear regression test. The comparison of serum endothelin-1 level between groups was performed with Student *T* test. We enrolled 50 subjects. The majority of subjects was male (80.0%), hypertensive (86.0%), dyslipidemic (68%) and smoker (52%). Most subjects had history of acute coronary syndrome (64%). Mean waist circumference was 87.6 +/– SD cm, hip circumference was 95.3 cm +/– SD, mean waist-to-hip ratio was 0.92 +/– SD and mean waist-to-height ratio was 0.54 +/– SD. Central obesity occurred in 32% of subjects. Mean serum endothelin-1 level was 2.2 $\pm$ 0.7 pg/mL. Serum endothelin-1 level tended to be higher in subjects with central obesity as compared to those without. Serum endothelin-1 level was significantly correlated with age, hemoglobin level, waist circumference (coefficient of 0.311, *p* value = 0.023) and hip circumference (coefficient of 0.359, *p* value = 0.010). Multivariable analysis indicated that age (coefficient of –0.353, *p* value = 0.007) and hip circumference (coefficient of 0.335, *p* value = 0.011) were independently correlated with serum endothelin-1. For conclusion, in patients with stable CAD, serum endothelin-1 was positively correlated with both waist circumference and hip circumference. Hip circumference independently and positively correlated with serum endothelin-1 level.

Keywords

Endothelin-1; Central obesity; Waist circumference; Hip circumference; Stable coronary artery disease

1. Introduction

Cardiovascular disease (CVD) is one of the leading causes of death in many countries [1, 2]. Hypertension, diabetes mellitus, dyslipidemia, smoking behaviors and sedentary lifestyles are the established CVD risk factors for which prevalence are high and increasing in low- and middle-income countries [3]. In Indonesia, besides these risk factors, obesity, especially central obesity, continues to increase significantly and contributes meaningfully to CVD [4]. Individual with central obesity has an excess of visceral adiposity which is associated with sedentary lifestyle and metabolic diseases such as diabetes mellitus, hypertension, and dyslipidemia [5]. It adds multiple burdens of CVD risk factors. The increase in central obesity-related morbidity in Indonesia challenge CVD risk factor controls in a country which still struggles to implement CVD prevention program such as tobacco control policy, promotion of healthy diet and endorsement of healthy lifestyle [5].

Endothelin-1 is a main vasoconstrictor peptide in the circulation which operates in the peripheral, pulmonary, and coronary vascular beds through vascular smooth muscle cells contraction [6]. In a steady-state condition, it sustains the balanced vascular tones by stimulating the release of

a vasodilator, nitric-oxide [7]. In vascular dysfunction, the balance between endothelin-1 and nitric-oxide is disrupted which lead to profound increased of endothelin-1, malfunctioning vasodilation, and increased vasoconstrictor tone [8]. Vascular dysfunction, which is indicated by insulin resistance and hyperinsulinemia, frequently accompanies individual with central obesity [9, 10]. Excessive visceral adipocytes express endothelin-1 which inhibit their insulin-stimulated glucose uptake, stimulate their lipolysis, release their free fatty acids and induce their production of pro-inflammatory cytokines [11]. Previous study demonstrated the enhanced endothelin-1 activity and endothelin-1-mediated adiposity-related disruption ofvasodilationin overweight and obese individuals without CVD [12, 13].

Individual with excessive fat accumulation in the visceral adipose tissue has higher rate of obesity-related CVD events [14]. Visceral adiposity is associated with increased waist circumference, which is a parameter to determine central obesity [14]. Central obesity is considered as metabolically harmful obesity [8]. Hip circumference indicates the adiposity of lower-body gluteofemoral region, which possess opposite effect to visceral adipose tissue [8]. Increased-serum endothelin-1contributes to metabolic syndrome and higher CVD events in individual with central obesity without coronary artery disease (CAD) [8, 13]. In patients with stable CAD, endothelin-1 level in blood circulation is increasing [15, 16]. Our previous study indicated that patients survived from acute coronary syndrome (ACS) and who later developed stable CAD, the majority of them were overweight and obese individuals [17]. The association between serumendothelin-1 level and central obesity in individual with stable CAD has not been investigated.

To assess central obesity, waist circumference is a superior indicator and more strongly correlated with intra-abdominal visceral adipose content, whereas hip circumference is associated with gluteofemoral peripheral adipose mass [18]. Both measurements had independent and opposite correlation with atherogenic risk factors, glucose intolerance and lipid metabolism disturbances [18]. The relation between serum endothelin-1 in patients with angiographycally-proven stable CAD and parameters of central obesity, namely waist circumference, hip circumference and ratio derived from them needs to be investigated. This study aims to examine the correlation between serum endothelin-1 level and parameters of central obesity in Indonesian patients with stable CAD.

2. Methods

2.1 Subjects

This is a cross-sectional study. Subjects were patients diagnosed with stable CAD. The subjects were enrolled consecutively during the performance of coronary angiography (CAG) with/without stenting in Integrated Heart Center (*Pusat Jantung Terpadu*) Dr. Sardjito Hospital, Yogyakarta, Indonesia. The inclusion criteria were: (1) subjects underwent elective CAG, (2) subjects with age 30–75 years, (3) subjects with significant CAD (namely stenosis $\geq$50% in left main coronary artery or stenosis $\geq$70% in other main branches), and (4) subjects agreed to participate in the research by signing an informed consent form. The exclusion criteria were: (1) subjects with chronic heart failure reduced ejection fraction, (2) subjects with chronic kidney disease (MDRD $<$30 mL/min/1.73 m^2), (3) subjects with hepatic cirrhosis, (4) subjects with on-going treatment of malignancy, (5) subjects with history of previous coronary revascularisation (percutaneous coronary intervention (PCI) or coronary-artery bypass graft (CABG), and (6) subjects with coronary anatomy anomalies.

2.2 Procedures

Subjects were enrolled during hospitalization for CAG with/without PCI. The demographic and medical histories were collected by anamnesis. Clinical data were collected during day-1 hospitalization (before CAG procedure). The bodyweight (kg) and body height (m) were measured by standard body scale and height ruler respectively at day-1 hospitalization (before CAG procedure). The body mass index (BMI) was calculated as bodyweight/(body height)^2. Obesity based on BMI was determined as obese II (BMI $\geq$30), obese I (BMI 25–29.9), overweight (BMI 23–24.9) and normal (BMI $<$23) [19]. The waist circumference (cm) was measured by standard body tape to the closest 0.1 cm in the horizontal plane at middle-point between lowest rib and the iliac-crest. The hip circumference (cm) was measured at the maximum protrusion of hip by standard body tape to the closest 0.1 cm. Both measurements were performed during day-2 or day-3 hospitalization (after CAG procedure) by trained investigators in the morning (after 8 hours fasting). The waist-to-hip ratio was calculated from waist circumference (cm)/hip circumference (cm). The waist-to-height ratio was calculated from waist circumference (cm)/body height (cm). The central obesity was determined by criteria of male waist circumference $\geq$90 cm and female waist circumference $\geq$80 cm [19].

The elective CAG with/without PCI procedures and subsequent treatments for subjects were done at the discretion of attending cardiologists. The research procedure 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.

2.3 Laboratory tests

Peripheral blood samples were obtained from subjects while reclining in a supine position from antecubital venous access on day-1 (before CAG procedure). The blood samples were taken after at least 15 min of supine resting on vacutainer tubes; in each subject a first sample was prepared for routine and blood chemistry, whereas the second sample was prepared for endothelin-1 measurement. The blood samples were transferred into Vacutainer tubes (BD, USA) and left at a room temperature to form clotting at 20–30 min. The tubes

were sent to a hospital central laboratory for routine hematology and blood chemistry examinations. For endothelin-1 measurement, the tubes containing clotted blood samples were centrifuged at 200 g for 20 minutes and the supernatant was stored at –80 °C freezer until analysed. The procedures of measurement and quantification of endothelin-1 followed the manufacturer's instructions (Endothelin-1 immunoassay Quantikine® ELISA kit (R&D Systems, Minneapolis, MN, USA) without replication [20].

2.4 Statistical analysis

The normal distribution was tested with Kolmogorov-Smirnov test. The comparison between normally distributed continuous data was performed with Student's *t*-test, while Mann–Whitney test was used for not normally distributed continuous data. The bivariate correlation analysis was performed with Pearson correlation test or Spearman correlation test where applicable. A multivariate regression analysis was done to determine the strength of correlation among different independent co-variables. Co-variables were selected from bivariate analysis which had p value < 0.05. A p value ≤ 0.05 was considered statistically significant.

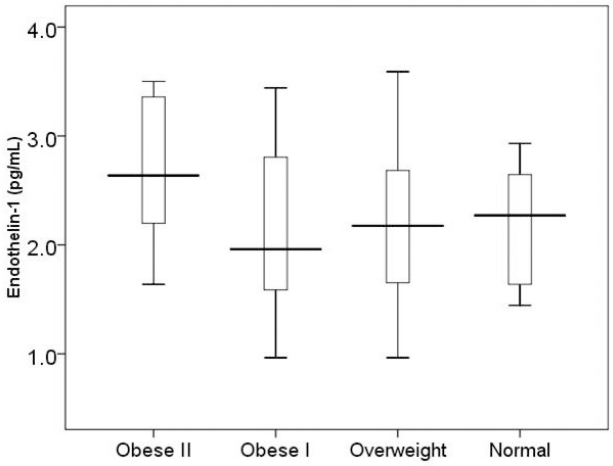

Fig. 1. Comparison of endothelin-1 level among obese, overweight and normal subjects. There was no significant difference in endothelin-1 level among four groups of subjects (obese II: 2.7 ± 0.8 pg/mL (n = 5), obese I: 2.1 ± 0.7 pg/mL (n = 16), overweight: 2.2 ± 0.8 pg/mL (n = 16) and normal: 2.2 ± 0.5 pg/mL (n = 13), p value = 0.503). There was a trend that highest mean level of endothelin-1 was in subjects with obese II.

3. Results

Table 1 shows the characteristics of research subjects. Fifty-consecutive subjects were enrolled in this study. Mean endothelin-1 level in all subjects was 2.2 ± 0.7 pg/mL. Majority of subjects were males (80.0%) with mean age of 58.8 ± 8.5 years old. Most of subjects were with hypertension (86.0%), dyslipidemia (68%) and smokers (52%). Only minority of patients had diabetes mellitus (28.0%). Additionally, most subjects had history of ACS (64%) within previous 1 year.

Table 1. The characteristics of subjects with angiographycally-proven stable CAD.

Characteristics	All subjects
	n = 50
Demography	
Males, n (%)	40 (80.0)
Age (year), mean ± SD	58.8 ± 8.5
CVD risk factors	
Diabetes mellitus, n (%)	14 (28.0)
Hypertension, n (%)	43 (86.0)
Dyslipidemia, n (%)	34 (68.0)
Smoking, n (%)	26 (52.0)
History of ACS, n (%)	32 (64.0)
Clinical parameters, mean ± SD	
Systolic pressure (mmHg)	129.9 ± 16.5
Diastolic pressure (mmHg)	76.3 ± 10.5
Heart rate (bpm)	73.9 ± 10.0
Anthropometric parameters, mean ± SD	
Bodyweight (kg)	66.3 ± 11.5
Body height (m)	1.62 ± 0.07
Body mass index	25.1 ± 3.5
Waist circumference (cm)	87.6 ± 11.4
Hip circumference (cm)	95.3 ± 10.5
Waist-to-hip ratio	0.92 ± 0.06
Waist-to-height ratio	0.54 ± 0.07
Obesity categories	
Obesity by BMI	
Obese II	5 (10.0)
Obese I	16 (32.0)
Overweight	16 (32.0)
Normal	13 (26.0)
Central obesity	16 (32.0)
Laboratory, mean ± SD	
Hemoglobin (g/dL)	12.8 ± 1.9
Leucocytes (×10^3/mm^3)	7.8 ± 1.9
Platelets (×10^3/mm^3)	269.7 ± 82.5
Creatinine (mg/dL)	1.2 ± 0.4
Glucose (mg/dL)	140.3 ± 69.3
Endothelin-1 level (pg/mL)	2.2 ± 0.7

CAD, coronary artery disease; CVD, cardiovascular disease; ACS, acute coronary syndrome; BMI, body mass index.

Anthropometric parameters indicated that mean bodyweight was 66.3 ± 11.5 kg, mean body height was 1.62 ± 0.07 m, and mean BMI was 25.1 ± 3.5. Based on different obesity groups by BMI parameters, there was a trend that the highest level of endothelin-1 was in obese II subjects (as shown in Fig. 1).

The circumference measurements indicated that mean waist circumference was 87.6 ± 11.4 cm, hip circumference was 95.3 ± 10.5 cm, mean waist-to-hip ratio was 0.92 ± 0.06, and mean waist-to-height ratio was 0.54 ± 0.07. Based on waist circumference, central obesity occurred in 32% of subjects, as shown in Table 1. Serum endothelin-1 level tended to be higher in subjects with central obesity as compared to those without central obesity (as shown in Fig. 2).

Table 2. The level of endothelin-1 based on the CVD risk factors.

Demography and CVD risk factors	Mean ± SD	*p* value
Male (n = 40)	2.3 ± 0.7	0.203
Female (n = 10)	1.9 ± 0.7	
Diabetes mellitus (n = 14)	2.3 ± 0.8	0.621
No diabetes mellitus (n = 36)	2.2 ± 0.6	
Hypertension (n = 43)	2.2 ± 0.7	0.661
No hypertension (n = 7)	2.3 ± 0.8	
Dyslipidemia (n = 34)	2.3 ± 0.7	0.181
No dyslipidemia (n = 16)	2.0 ± 0.6	
Smoking (n = 26)	2.2 ± 0.7	0.881
No smoking (n = 23)	2.2 ± 0.7	
History of ACS (n = 32)	2.2 ± 0.7	0.887
No history of ACS (n = 18)	2.3 ± 0.7	

ACS, acute coronary syndrome.

Serum endothelin-1 did not significantly differ based on demographic and CVD risk factors variables (Table 2).

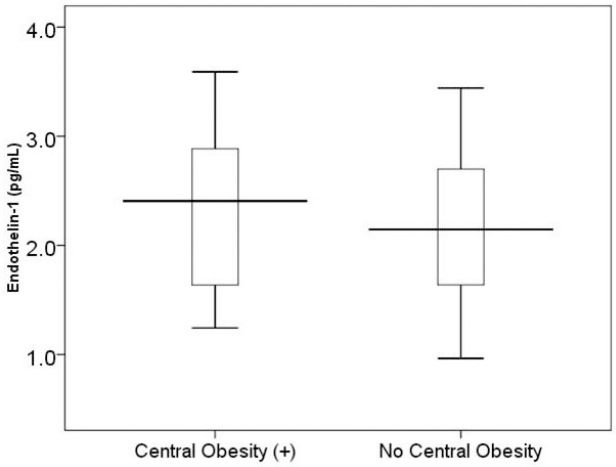

Fig. 2. Comparison of endothelin-1 level between subjects with central obesity (n = 16) and no central obesity (n = 34). There was no significant difference in endothelin-1 level between two groups (mean ± SD: 2.4 ± 0.8 pg/mL vs. 2.2 ± 0.7 pg/mL, *p* value = 0.425). There was a trend that higher mean level of endothelin-1 was in subjects with central obesity.

Table 3 shows result of correlation analysis between serum endothelin-1 level and other continuous variables. Among clinical, anthropometric and laboratory variables, serum endothelin-1 level was significantly correlated with age in years (correlation coefficient of –0.376, *p* value = 0.007) and hemoglobin level (correlation coefficient of 0.316, *p* value 0.026). Serum endothelin-1 was significantly correlated with parameters of central obesity, namely waist circumference (correlation coefficient of 0.311, *p* value = 0.023) and hip circumference (correlation coefficient of 0.359, *p* value = 0.010). Other variables, i.e., age, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, hemoglobin level, leucocytes count, platelet count, glucose level and creatinine level, were not significantly correlated with serum endothelin-1 level.

Table 3. The bivariate analysis by correlation test between endothelin-1 andother continuous variables.

Variables	Coefficient correlation	*p* value
Age (years)	–0.376	0.007
Systolic blood pressure (mmHg)	0.061	0.676
Diastolic blood pressure (mmHg)	0.251	0.079
Heart rate (beat/min)	0.234	0.102
Bodyweight (kg)	0.252	0.078
Bodyheight (m)	0.241	0.092
Bodymass index	0.172	0.233
Waist circumference (cm)	0.311	0.023
Hip circumference (cm)	0.359	0.010
Waist-to-hip ratio	0.017	0.907
Waist-to-height ratio	0.256	0.073
Hemoglobin (g/dL)	0.316	0.026
Leucocytes ($\times 10^3/mm^3$)	0.035	0.807
Platelets ($\times 10^3/mm^3$)	0.085	0.556
Creatinine (mg/dL)	0.058	0.690
Glucose (mg/dL)	–0.027	0.853

Table 4. The multivariable analysis by amultivariate regression test between endothelin-1 and co-variables: age, waist circumference, hip circumference, and hemoglobin.

Co-variables	Standardized Coefficient (Beta)	*p* value
Age (years)	–0.353	0.007
Waist circumference (cm)	–0.020	0.893
Hip circumference (cm)	0.335	0.011
Hemoglobin (g/dL)	0.115	0.435

Table 4 shows the result of multivariate regression analysis. Multivariable analysis were included age, hemoglobin, waist circumference and hip circumference as covariates and endothelin-1 as the dependent variable. Correlation were observed inage (coefficient of –0.353, *p* value = 0.007) and hip circumference (coefficient of 0.335, *p* value = 0.011) with endothelin-1 level. Waist circumference did not significantly correlate independently with serum endothelin-1 level.

4. Discussion

Results of our study indicated that in patients with angiographycally-proven stable CAD, serum endothelin-1 level was positively correlated with both waist circumference and hip circumference. The independent correlation was significantly observed in age (inverse correlation) and hip circumference (positive correlation). Serum endothelin-1 tended to be higher in stable CAD patients with central obesity and patients with BMI-derived obesity compared to their counterparts. The measurement of serum endothelin-1 as a prognostic indicator in stable CAD patients with central obesity needs to be corroborated by larger and more extensive research.

Previous study indicated that obese individuals (BMI $\geq$30.5 males and BMI $\geq$27.3) had significantly higher levels of serum endothelin-1 as compared to lean individual (BMI $<$25 for males and BMI $<$24.7 for females). Obese subjects with hypertension had the highest endothelin-1 level [21]. This study also indicated that obese individuals had higher waist-to-hip ratio [21]. Activity of endothelin-1-mediated vasoconstriction in vascular tone is elevated in obese individual with waist circumference $>$100 cm [13]. Its enhanced activity contributes to the adiposity-related impairment in endothelium-dependent vasodilation, which is prevalent in obese individuals [13]. It was postulated that increased endothelin-1 level and enhanced activity in obese patients are due to an insulin resistance mechanism [13]. However, these studies had excluded subjects with established CAD.

An important mechanism by which obesity leads to the development of vascular diseases is the development of insulin resistance and inflammation [8]. Furthermore, in patients with stable CAD, within a spectrum of advanced atherosclerosis, insulin resistance and inflammation may have developed for long time before any stable CAD events. Evidence indicates that endothelin-1 contributes to insulin resistance and inflammation through numerous mechanisms, including impairment of insulin signaling in endothelial cells as a precursor of early atherosclerosis [22, 23]. Atherosclerosis itself is associated with excess endothelin-1, which is by several mechanisms known to enhance the atheroma formation and atherosclerotic disease progression [24, 25]. Furthermore, excess endothelin-1 inhibits insulin-stimulated glucose uptake in adipocytes and skeletal muscle cells, as well as enhancing lipolysis, release free fatty acids and pro-inflammatory cytokines in adipocytes [11]. In obese patients with stable CAD, all factors that contribute to increased serum endothelin-1 levels were found. Hypertension, which predominates in our study subjects, also contribute to elevated level of serum endothelin-1 [26].

Our study indicated positive correlation between serum endothelin-1 level with both waist and hip circumferences, but not with other obesity and central parameters. As an individual measure, waist circumference is a measure of visceral and subcutaneous adipose tissue in the abdominal region, whereas hip circumference is a measure of adipose tissue and also muscle mass in the lower body part [27]. After adjustment with covariables, unexpectedly, hip circumference independently correlated positively with serum endothelin-1. From this current observation, we speculate that increased hip circumference reflects increased subcutaneous adipose storage and muscle mass of the gluteofemoral region which had specific lipid storage and secretion of adipose tissue-related proteins [27]. Adipose tissue in the gluteofemoral region had active role in the removal of circulating nonesterified fatty acids which could limit the development of insulin resistance [28]. Similarly, thigh subcutaneous adipocytesc correlated with greater insulin sensitivity [28]. Both adipocytes and skeletal muscle cells express endothelin-1 and its receptors [11]. Whether the activity of gluteofemoral adipose tissue is mediated by endothelin-1 needed further research.

This study had several limitations. The major limitation was the small number of subjects enrolled in the analysis. Further study with larger sample size is needed to be performed to confirm our findings. Another limitation was laboratory parameters of various metabolic disturbances were not measured in this research. Further study with measurements of parameters of metabolic disturbances as additional confounding variables needs to be performed in patients with angiographycally-proven stable CAD.

In conclusion, serum endothelin-1 level was significantly positively correlated with waist circumference and hip circumference, as parameters of central obesity among Indonesian patients with angiographycally-proven stable CAD. The independent positive correlation was found between serum endothelin-1 level and hip circumference.

Author contributions

ABH designed the study, performed subject's enrollment, data collection, statistical analysis and manuscript writing. JF performed data collection, laboratory analysis and manuscript writing. IP performed subjects enrollment, data collection, and statistical analysis. FSTD contributed to data collection, data analysis and manuscript writing. All authors gave final approval of the manuscript.

Ethics approval and consent to participate

Ethics approval for this research had been granted by The Medical and Health Research Ethic Commitee of Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada – Dr. Sardjito Hospital, Yogyakarta, Indonesia.

Acknowledgment

Authors expressed gratitude to Ms. F. Linda Tri Pramatasari and Dr. Ahmad Musthafa from the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta for their technical assistance on blood sample biobanking and analysis of endothelin-1. Authors expressed gratitude to Dr. Adysti Dhian Rizky Paramytha, Dr. Aras Amilla Husna and Dr. Brilliant Winona Jhundy for performing data collection of stable CAD subjects.

Funding

This research received funding from *Deputi Bidang Penguatan Riset dan Pengembangan*, Ministry of Research and Technology/National Research and Innovation Agency of Republic of Indonesia via Universitas Gadjah Mada with contract number: 2750/UN1.DITLIT/DIT-LIT/PT/2020 and Research Grant of Dr. Sardjito Hospital with grant number: HK.02.03/XI.2/17234/2019; both are granted to Anggoro Budi Hartopo as Principal Investigator.

Conflict of interest

The authors declare no conflict of interest.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

References

[1] Nguyen HN, Fujiyoshi A, Abbott RD, Miura K. Epidemiology of cardiovascular risk factors in Asian countries. Circulation Journal. 2013; 77: 2851–2859.

[2] GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specifc mortality for 264 causes of death, 1980-2016: a systematic analysis for the global burden of disease study 2016. Lancet. 2017; 390: 1151–1210.

[3] GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet. 2017; 390: 1345–1422.

[4] Kusuma D, Kusumawardani N, Ahsan A, K. Sebayang S, Amir V, Ng N. On the verge of a chronic disease epidemic: comprehensive policies and actions are needed in Indonesia. International Health. 2019; 11: 422–424.

[5] Adisasmito W, Amir V, Atin A, Megraini A, Kusuma D. Geographic and socioeconomic disparity in cardiovascular risk factors in Indonesia: analysis of the Basic Health Research 2018. BMC Public Health. 2020; 20: 1004.

[6] Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, *et al.* A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature. 1988; 332: 411–415.

[7] Kinlay S, Behrendt D, Wainstein M, Beltrame J, Fang JC, Creager MA, *et al.* Role of Endothelin-1 in the active constriction of human atherosclerotic coronary arteries. Circulation. 2001; 104: 1114–1118.

[8] Schinzari F, Cardillo C. Intricacies of the endothelin system in human obesity: role in the development of complications and potential as a therapeutic target. Canadian Journal of Physiology and Pharmacology. 2020; 98: 563–569.

[9] Muniyappa R, Iantorno M, Quon MJ. An integrated view of insulin resistance and endothelial dysfunction. Endocrinology and Metabolism Clinics of North America. 2008; 37: 685–711.

[10] Kim J, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation. 2006; 113: 1888–1904.

[11] Pernow J, Shemyakin A, Böhm F. New perspectives on endothelin-1 in atherosclerosis and diabetes mellitus. Life Sciences. 2012; 91: 507–516.

[12] Cardillo C, Campia U, Iantorno M, Panza JA. Enhanced vascular activity of endogenous endothelin-1 in obese hypertensive patients. Hypertension. 2004; 43: 36–40.

[13] Weil BR, Westby CM, Van Guilder GP, Greiner JJ, Stauffer BL, DeSouza CA. Enhanced endothelin-1 system activity with overweight and obesity. American Journal of Physiology Heart and Circulatory Physiology. 2011; 301: H689–H695.

[14] Britton KA, Massaro JM, Murabito JM, Kreger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, cancer, and all-cause mortality. Journal of the American College of Cardiology. 2013; 62: 921–925.

[15] Wieczorek I, Haynes WG, Webb DJ, Ludlam CA, Fox KA. Raised plasma endothelin in unstable angina and non-Q wave myocardial infarction: relation to cardiovascular outcome. British Heart Journal. 1994; 72: 436–441.

[16] Qiu S, Théroux P, Marcil M, Solymoss BC. Plasma endothelin-1 levels in stable and unstable angina. Cardiology. 1993; 82: 12–19.

[17] Hartopo AB, Susanti VY, Setianto BY. The prevalence and impact of body mass index category in patients with acute myocardial infarction. Acta Cardiologia Indonesiana. 2016; 2: 61–68.

[18] Rocha PM, Barata JT, Teixeira PJ, Ross R, Sardinha LB. Independent and opposite associations of hip and waist circumference with metabolic syndrome components and with inflammatory and atherothrombotic risk factors in overweight and obese women. Metabolism: Clinical and Experimental. 2008; 57: 1315–1322.

[19] Kurniati N. Obesity and central obesity. Medical Journal of Indonesia. 2018; 27: 69–70.

[20] Hartopo AB, Sukmasari I, Puspitawati I, Setianto BY. Serum endothelin-1 correlates with myocardial injury and independently predicts adverse cardiac events in non-ST-elevation acute myocardial infarction. International Journal of Vascular Medicine. 2020; 2020: 1–6.

[21] Parrinello G, Scaglione R, Pinto A, Corrao S, Cecala M, Di Silvestre G, *et al.* Central obesity and hypertension: the role of plasma endothelin. American Journal of Hypertension. 1996; 9: 1186–1191.

[22] Prieto D, Contreras C, Sánchez A. Endothelial dysfunction, obesity and insulin resistance. Current Vascular Pharmacology. 2014; 12: 412–426.

[23] Ishibashi KI, Imamura T, Sharma PM, Huang J, Ugi S, Olefsky JM. Chronic endothelin-1 treatment leads to heterologous desensitization of insulin signaling in 3T3-L1 adipocytes. The Journal of Clinical Investigation. 2001; 107: 1193–1202.

[24] Gupta RM, Libby P, Barton M. Linking regulation of nitric oxide to endothelin-1: the Yin and Yang of vascular tone in the atherosclerotic plaque. Atherosclerosis. 2020; 292: 201–203.

[25] Campia U, Tesauro M, Di Daniele N, Cardillo C. The vascular endothelin system in obesity and type 2 diabetes: pathophysiology and therapeutic implications. Life Sciences. 2014; 118: 149–155.

[26] Moroni C, Tolone S, Bondanini F, Schillaci O, Affricano C, Cassone R, *et al.* Endothelin-1 in hypertensive patients with ischemic heart disease. Internal and Emergency Medicine. 2019; 14: 1119–1124.

[27] Cameron AJ, Romaniuk H, Orellana L, Dallongeville J, Dobson AJ, Drygas W, *et al.* Combined influence of waist and hip circumference on risk of death in a large cohort of European and Australian adults. Journal of the American Heart Association. 2020; 9: e015189.

[28] Katz EG, Stevens J, Truesdale KP, Cai J, Adair LS, North KE. Hip circumference and incident metabolic risk factors in Chinese men and women: the People's Republic of China study. Metabolic Syndrome and Related Disorders. 2011; 9: 55–62.