ANALYSIS OF URINARY ENDOTHELIN-I LEVELS IN OBESE LATE ADOLESCENTS

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ABSTRACT

Obesity is a health problem that often occurs in late adolescents and early adults. It is characterized by an increase in body weight which results in excess body fat accumulation, leading to endothelial damage. Endothelial damage that occurs in obese people can cause increased production of endothelin-1. This study compares urinary endothelin-1 levels in the obese and normal groups. This study used analytical research methods with a quantitative approach to collect and measure data in numbers. The study design was cross-sectional by comparing endothelin-1 levels in normal and obese adolescent groups. This research was conducted in Makassar City for three months, from April to June 2022. The study population was obese and non-obese people in their late teens and early adulthood. The sample collection technique used in this study is a purposive sampling technique, which is a non-random sampling technique. The number of samples in the study for the Obese group was 26, while in the Normal group was 26. The analysis used to test differences in endothelin-1 levels based on the obese group and the normal group is the Independent Sample T Test statistical test. The results showed that the average urinary endothelin I level in the obese group was 40,930 ng/l, and in the normal group, 55,547 ng/l. Which shows a significant difference in average endothelin I levels ($p<0.05$) between the obese and normal groups.

Keywords: Obesity; Endothelin-1; Urine

INTRODUCTION

Obesity has become a worldwide problem and a serious health problem in developing countries. It is experiencing an alarming increase in new cases.[1] More than 1.9 billion cases of overweight people aged over 18 years in 2016, 650 million of whom were obese, and 340 million of whom were children and adolescents. The prevalence of overweight and obesity seems to increased dramatically in children and adolescents; 4% in 1975, while in 2016 increased to more than 18%.[2]

Obesity is caused by excessive fat accumulation and is considered a factor underlying the pathogenesis of several diseases. It was reported that children and adolescents with obesity have a higher tendency to become obese than adults. Marseglia et al. (2015) reported that obesity has a relationship with the occurrence of low-grade chronic inflammation in adipose tissue. This condition induces the infiltration of immune cells in adipose tissue, which increases pro-inflammatory status, endothelial damage, and oxidative stress.[3]

Endothelial damage that occurs in obesity can lead to increased production of endothelin-I [(4).] Endothelin-I (ET-I) is a substance with 21 amino acids. Endothelin-I is the most powerful vasoconstrictor peptide produced by endothelial cells, which plays a role in the regulation of vascular tone and atherosclerotic etiology.[5,6] Endothelium consists of endothelin-1, endothelin-2, and

endothelin-3. There are two receptors in mammals; ET_A (*Endothelin Receptor type A*) and ET_B (*Endothelin Receptor type B*) receptors. The interaction between ET-I and its receptors can induce a constricting effect [7]. An increase in the ET-I system is associated with the development of pathological processes of vascular disease such as adiposity, including hypertension, type-2 diabetes mellitus, coronary artery disease, and chronic heart failure[8]. Several previous studies have explained that there is an increase in ET-I levels in obese rats. It is known that the Wistar rat is an experimental animal that has structural similarities to humans [9].

Examination of urine in the case of obesity, metabolic disease, and type-2 diabetes mellitus has a significant correlation with kidney disease and vascular damage in an adult population. Adolescents and young adults are representatives of groups where non-invasive screening is more desirable since the low level of awareness about health screening and invasive procedures can affect decision-making[10] Singh et al. (2017) reported that there was an increase in urinary ET-I levels in the obese group. Another study by Selvaraju et al. (2019) found that there was a significant increase in ET-I and 8-OHdG levels in the overweight and obese group. [11] We perform this study to analyze ET-I levels in urine in obesity.

MATERIAL AND METHODS

The study used analytical research methods with a quantitative approach using numeric variables. This cross-sectional study was done in late adolescent patients (aged 18-20 years), comparing ET-I in obese and normal body mass index (BMI). It was conducted in Makassar within three months of study, between April 2022 and June 2022.

The study populations were late adolescents and early adults with obesity and normal BMI. We used a purposive non-randomized sampling technique to collect the samples, in which we determined specific characteristics according to the research objectives. Subjects were assigned to two groups; obese and normal (non-obese) groups, with 26 subjects in each group. There were a total of 52 subjects included in this study. We prepared letters and permits and made observations prior to data collection. The research-related questions were formulated and poured into the problem formulation. Consequently, we determined the population and research sample before entering the research implementation phase. We collect data from primary and secondary data. Primary data was obtained from the results of questionnaires, while secondary data was obtained by collecting data on obese people in Makassar.

Collected data were analyzed using *the Statistical Product and Service Solution* (SPSS). The statistical result was described in narrative form and provided with tables or graphs containing the variables examined. The analysis of differences in urinary ET-I levels in obese and normal groups was done using an independent sample t-test. Results were considered statistically significant if $p<0.05$.

As ethical protection for researchers, this study has fulfilled various ethical considerations and passed an ethical-clearance process No.136/ UN4.6.4.5.31/ PP36/ 2022.

RESULT

Fifty-two samples were included in this study, assigned in two groups; obese group (n=26) and normal group (n=26). Mean age of both groups was 19 years. Average body mass index (BMI) in the obese group was 33.69 kg/m^2 while the normal group had an average BMI of 20.58 kg/m^2. Mean duration of obesity was 7 years (Table 1).

There was significant mean difference of urinary endothelin-I in obese and normal group, based on the age group 18-20 years (late adolescent), as shown in Table 2. The average urinary endothelin-I level in obese group was higher compared to normal group (40.930 ng/l vs 55.547 ng/L), as shown in Figure 1.

Table 1. Sample characteristics.

Parameter	Obese (n=26)	Normal (n=26)
[a] Age (years)	19.10 ±16.56	19.19±7.69
[b] Sex		
Male	18 (69.2)	12 (46.2)
Female	8 (30.8)	14 (53.8)
[a] Body weight (kg)	94.10 ± 16.56	54.19± 7.49
[a] Body height (cm)	166.73±6.29	161.85 ± 7.24
[a] Body mass index (kg/m^2)	33.69±4.53	20.58 ± 1.44
[a] Systolic blood pressure (mmHg)	127.07±10.15	111.57±9.37
[a] Diastolic blood pressure (mmHg)	84.73±7.30	74.96±6.390
[a] Duration of obesity	7.00±4.363	-
[b] Family history of obesity		
Yes	8 (30.8)	4 (15.4)
No	18 (69.2)	22 (84.6)

n = number of samples
[a] = parameter of numeric variable (mean ± standard deviation)
[b] = parameter of categoric variable (%)

Table 2. Urinary endothelin-I levels between obese and normal groups based on the age group 18-20 years (late adolescents).

Groups	N	Mean endothelin-1 level (ng/L) ± SD	*p
Normal	26	40.930 ± 21.381	0.012
Obese	26	55.547 ± 19.134	

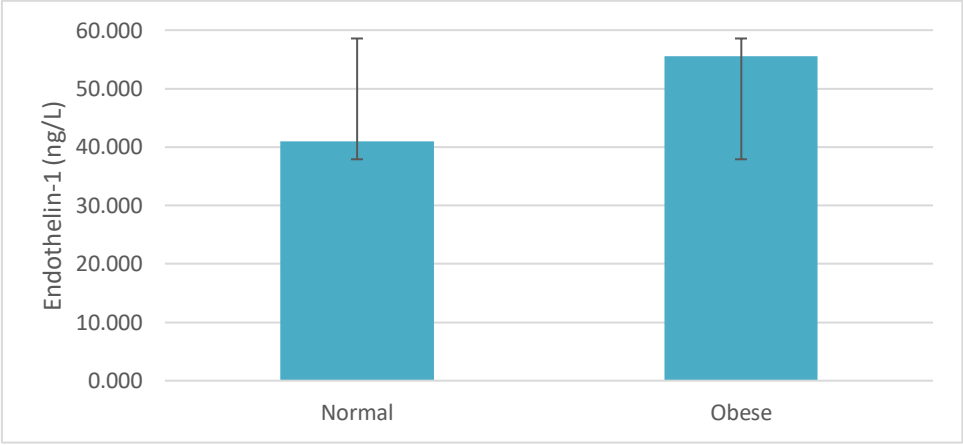

Figure 1. Difference of urinary endothelin-I levels between obese and normal groups in late adolescent.

DISCUSSION

Our study's results showed significant differences in urinary ET-I levels between the obese and normal groups based on the age group 18-20 years, with 40.930 ng/L in the obese group compared to 55.547 ng/L in the normal group. The results of this study showed that obesity is associated with damage to the blood vessels and kidneys. This result is similar to a study by Shin et al. [12,] which states that increased urinary endothelin-I levels may reflect damage to the kidneys. Obesity results in insulin resistance; ET-I levels may increase in conditions related to insulin resistance [(13)]. Furthermore, this study is similar to the previous study by stating that there is a link between obesity and inflammation, oxidative stress, and endothelial dysfunction. Endothelin can be synthesized in the glomerular epithelial cells of the kidney. Studies conducted on obese patients showed that obesity is characterized by abnormal endothelial cells. [14,15] These changes result in an imbalance between ET-I and nitrite oxide, which causes excessive activation by the endogenous ET-I system 1 [16]

Obesity has a strong correlation with body fat. Fat distribution, along with the amount of fat, determines the risk associated with obesity. Abdominal and visceral fat is associated with an increased risk of cardiovascular disease.[17] Circulatory pro-inflammatory mediator cytokine or leptin levels increased in obese patients. Endothelin-I acts as paracrine or autocrine at two receptors, namely ET_A and ET_B, on endothelial cells and smooth muscle tissue. Endothelin-1 is the only type of endothelin produced by endothelial cells and vascular smooth muscle cells. Stimulation of receptors ET_A and ET_B in smooth muscle tissue results in contraction and stimulates cell proliferation and hypertrophy.[18]

Endothelin-I is important for maintaining renal perfusion and affects vascular tone and hemodynamics of glomerular arterioles. Endogenous renal ET-I also serves as an integral part of fluid and sodium homeostasis. The final effects of ET-I can be opposite and are mediated by homologous receptor binding. Endothelin-I binding of ET_A in the renal cortex induces afferent vasoconstriction that reduces renal blood flow and glomerular filtration rate (GFR). In addition, the binding of ET-I to ET_A has pro-inflammatory and sclerotic effects on the kidney, and studies have shown that increased expression of the ET-I transgene in mice leads to renal scarring, interstitial fibrosis, and glomerulosclerosis [7,19].

Endothelin-I has an effect on the glomerular filtration barrier; the glomerulus has 3 layers of capillary walls consisting of: 1. the inner layer of endothelial cells, 2. the middle layer, which is the outer layer of the glomerular basement membrane, and 3. the outer layer of epithelial cells, also called podocytes. Podocytes with complex cytoarchitecture are essential determinants of the glomerular filtration barrier, and their damage can lead to proteinuria. Podocytes produce, secrete, and bind ET-I, therefore, function as an autocrine target. The ET-I autocrine and/or paracrine signaling is thought to be important in contributing to the development of albuminuria. In addition, podocytes produce vascular endothelial cell factor (VEGF), which acts on podocytes and endothelial cells and maintains the endothelial cells. Loss of VEGF function results in endothelial dysfunction and proteinuria. In particular, loss of VEGF causes cytoskeleton actin disruption and podocyte damage by stimulating ET-1 release, resulting in severe proteinuria.[20] In addition to the glomerulus, ET-1 also plays a role in the kidney tubules. Based on research by Arfian et al that ET-1 originating from the vascular endothelium has an important role in causing damage to the proximal tubule.

CONCLUSION

The endothelin-1 level is higher in the obese patient compared to those with normal body mass. It means that increased endothelin 1 levels in the obese late adolescent group indicate the possibility of renal damage. The potential use of urinary ET-1 as an early marker for renal damage needs further investigation.

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