

# A CLOSE POSITIVE ASSOCIATION BETWEEN OBESITY AND BLOOD PRESSURE IN RATS

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## ABSTRACT

The purpose of this study was to analyze the effect of an increase in Body Mass Index (BMI) on blood pressure (BP). The research design was a laboratory experiment with 52 non-obese and obese rats as subjects (non-obese,  $n = 14$  and obese,  $n = 38$ ). The rats consumed a high-fat, high-fructose diet for four weeks in order to induce obesity. The BMI used is based on the Lee Index with obesity indicators of  $>300$  g/cm. Data analysis used independent sample t-tests, simple linear regression tests, and Pearson correlation tests ( $P < 0.05$ ). The results concluded that BP in non-obese rats was lower than in obese rats ( $89.00 \pm 7.38$  vs  $190.11 \pm 4.42$ ;  $P = 0.001^*$ ); BMI was positively associated with BP ( $P = 0.001^*$ ); an increase in BMI will increase BP ( $P = 0.001^*$ ); and there is a strong correlation between BMI and BP ( $r = 0.977$ ;  $P = 0.001^*$ ). The regression equation ( $Y = 707.42 + 2.75 X$ ) indicates that every 1 g/cm increase in BMI will be followed by an increase in BP of 2.75 mmHg. The analysis of R-square = 0.972 shows that the accuracy of the linear equation model is 97.2%. In conclusion, BMI has a strong positive correlation with BP, meaning that an increase in BMI will likely increase BP and obesity induces high blood pressure in rats.

Key words: blood pressure, body mass index, hypertension, Lee index, obese

## ABSTRAK

Tujuan penelitian adalah menganalisis pengaruh peningkatan Indeks Massa Tubuh (IMT) terhadap peningkatan tekanan darah. Desain penelitian adalah eksperimen laboratorium dengan subjek tikus non-obesitas dan obesitas yang berjumlah 52 ekor (non-obesitas,  $n = 14$  dan obesitas,  $n = 38$ ). Tikus diinduksi obesitas menggunakan diet tinggi lemak tinggi fruktosa selama 4 minggu. IMT yang dimaksud adalah Indeks Lee dengan indikator obesitas jika  $>300$  g/cm. Analisis data menggunakan analisis independent sample t-test ( $P < 0,05$ ), uji regresi linier sederhana ( $P < 0,05$ ), dan uji korelasi Pearson ( $P < 0,05$ ). Hasilnya: tekanan darah pada kelompok tikus non-obesitas lebih rendah dari kelompok tikus obesitas ( $89,00 \pm 7,38$  vs  $190,11 \pm 4,42$ ;  $P = 0,001^*$ ), IMT berkorelasi positif dengan tekanan darah ( $P = 0.001^*$ ); peningkatan IMT akan mengakibatkan terjadinya peningkatan tekanan darah ( $P = 0.001^*$ ), terdapat korelasi kuat antara IMT dengan tekanan darah ( $r = 0,977$ ;  $P = 0,001^*$ ). Berdasarkan analisis dari persamaan regresi:  $Y = 707,42 + 2,75 X$ , mengindikasikan bahwa setiap kenaikan BMI sebesar 1 g/cm akan diikuti pula dengan kenaikan tekanan darah sebesar 2,75 mmHg. Analisis R-square = 0,972 menunjukkan bahwa akurasi model persamaan liniernya adalah 97,2%. Disimpulkan bahwa indeks massa tubuh berkorelasi positif kuat dengan tekanan darah. Peningkatan BMI akan meningkatkan tekanan darah pada tikus obesitas, dengan demikian obesitas menginduksi tekanan darah tinggi pada tikus.

Kata kunci: tekanan darah, indeks massa tubuh, hipertensi, indeks Lee, obesitas

## INTRODUCTION

Obesity is a critical public health problem because it increases morbidity and mortality due to cardiovascular diseases such as high blood pressure, endothelial dysfunction, hyperinsulinemia, and dyslipidemia (Dulskiene *et al.* 2014; Jiang *et al.* 2016; Gajalakshmi *et al.* 2018). Obesity is associated with various catastrophic diseases, including diabetes, dyslipidemia, and high blood pressure (Dua *et al.* 2014). Obesity is a predominant risk factor for hypertension in children and adults (Dulskiene *et al.* 2014; Jiang *et al.* 2016).

Recently, the prevalence of obesity in Indonesia has increased sharply. In 2013, the prevalence was only around 6.4%; in 2018, the number increased to more than three times to reach 21.8% (Harbuwono *et al.* 2018; Dewi *et al.* 2020). The increasing prevalence of obesity will increase the prevalence of hypertension (Bernabe-Ortiz *et al.* 2021). Hypertension significantly increases the risk of death and disability (Rahimi *et al.* 2015). In 2015, the prevalence of hypertension was reported to reach 1.13 billion and was responsible for a cause of death of 9.4 million people worldwide (Bernabe-Ortiz *et al.* 2021; Giles *et al.* 2016).

Indicators of obesity in humans and experimental animals are established based on Body Mass Index (BMI) values. A positive correlation between BMI and

blood pressure in humans has been reported for a long time (Friedrich 1982; Galhardi *et al.* 2007; Jorgens 2007; Dua *et al.* 2014). An excessive weight gain by approximately 65-75% will result in primary hypertension in humans (Hall *et al.* 2015). Obesity is a chronic health disorder and is also comorbid for hypertension and other chronic diseases and thus requires long-term treatment. Therefore, it is necessary to study how obesity can induce hypertension (Landi *et al.* 2018; Linderman *et al.* 2018).

The correlation between BMI with BP and hypertension has long been reported by scientists, but how strong the effect of a higher BMI has on BP needs to be analyzed to know to what degree obesity may induce high blood pressure. The results of this study will be used as a reference for the need for weight loss efforts as prevention of hypertension, as well as to reduce the incidence of obesity, whose prevalence continues to increase.

## MATERIALS AND METHODS

### Animals

The subjects were obese and non-obese rats, 2-3 months of age, male, of the Wistar strain, and with a body weight between 200-300 g. Obesity was induced on the rats by feeding them with a high-fat, high-fructose

diet for four weeks with the Lee Index indicator reaching  $>300$  g/cm. The non-obese populations were given standard feed. The Lee index is the most accurate indicator of obesity in rats (Malafaia *et al.* 2013). The high-fat, high-fructose diet is a high-calorie diet specifically for rats with a composition of 21.4% fat, 50% carbohydrate, 17.5% protein, 3.5% fiber, and 4.1% ash and added 25% fructose as a drink. The Research design was a laboratory experiment. A total of 52 rats were used: 14 non-obese rats (as the control group) and 38 obese rats (as the experimental group).

### Anthropometric and Blood Pressure Examination

The anthropometric values of rats measured were weight, length, and BMI. Weight was measured using a digital scale in grams (g) and length was measured from nose to anus using a length measuring device in centimeters (cm). BMI was assessed using the Lee Index, calculated by weight and length. The value of the Lee index is the cube root of body weight (grams) divided by

the length from nose to the anus (cm) (Galhardi *et al.* 2007). Systolic blood pressure was measured using a sphygmomanometer S-2 for rats (Figure 1).

Blood pressure measurement was carried out by measuring the tail arteries of rats using the non-invasive tail-cuff method (indirect technique) with the special tail-cuff for rats. Blood pressure measurements were carried out in a comfortable and quiet place to avoid stress in rats that would affect the blood pressure. Measurement of rat blood pressure was carried out by placing the cuff about 2 mm away from the base of the tail. Measurement of rat blood pressure was carried out by placing a cuff on the base of the tail with a distance of about 2 mm, then connecting the cuff and sensor to the monitor, and reading the measurement results. The rat should not move during the blood pressure recording process. The instrument only detects systolic blood pressure and cannot detect diastolic blood pressure. The illustrations of blood pressure measurement procedures as seen in Figure 2.



Figure 1. Sphygmomanometer S-2 for rats

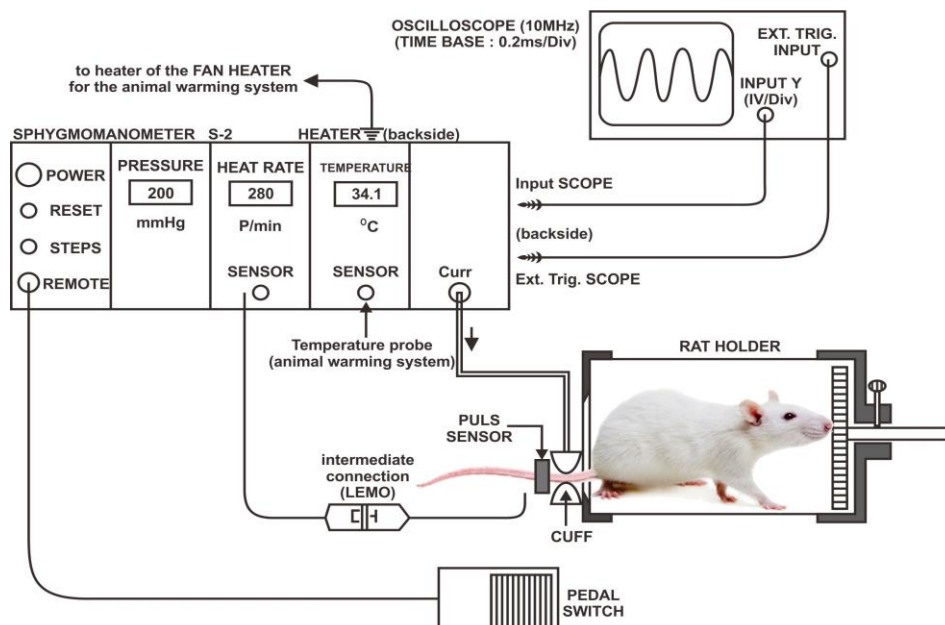


Figure 2. Illustrations of blood pressure measurement procedures using Sphygmomanometer S-2

### Ethical Approval and Statistical Analysis

This research has received ethical approval from Ethics Committee for Health Research, Faculty of Medicine, Universitas Syiah Kuala with the number 234/EA/FK-RSUDZA/2021. The data analysis included linear regression, Pearson correlation, and independent sample t-test with a 95% confidence interval. Linear regression was used to determine the correlation line between the independent variable (BMI) as the X-axis and the dependent variable (BP) as the Y-axis and obtained a correlation line. It would be positive correlation if the X variable has a positive effect on the Y variable (an increase in BMI will increase BP), whereas a negative correlation would be if an increase in BMI decreases BP. A Pearson correlation analysis was conducted to determine the strength of the relationship between BMI and BP and the results were: 0.80= very strong, 0.60-0.799= strong; 0.40-0.599= enough; 0.20-0.399 = weak and 0.00-0.199 = very weak. An independent sample t-test was conducted to see the difference in BP between normal and obese rats.

### RESULTS AND DISCUSSION

#### Differences in weight, length, Lee's index, and BP between non-obese and obese rats

The independent sample t-test analysis shows in Table 1 that weight, length, and BMI between groups of mice with non-obese and obese weight showed a significant difference ( $P=0.001^*$ ). The mean weight and Lee's index in the obese rat group were greater than that in the non-obese rat group. The mean length in the non-obese rat group was longer than that in the obese rat group. Likewise, the blood pressure between the non-obese group of rats and the obese rat group was significantly different ( $P=0.001^*$ ). Blood pressure in non-obese was lower than in the group of obese rats.

Data from the simple linear regression analysis shows a relationship between BMI and BP and can be seen in Figure 3. This figure shows that there was a significant positive association between BMI and BP ( $P=0.001^*$ ). This result explains that every increase in BMI will be followed by an increase in BP.

**Table 1.** Differences in weight, length, Lee Index, and blood pressure between groups of non-obese and obese rats

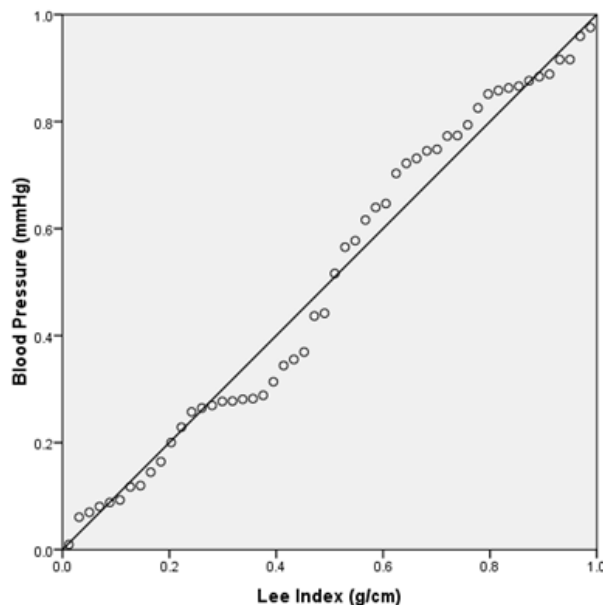
Data	Groups	n	Means	Minimum	Maximum	P-value
Weight (g)	Non-obese	14	209.14±12.91	193	225	0.04*
	Obese	38	213.95±3.79	201	229	
Length (cm)	Non-obese	14	20.15±0.37	19.87	20.62	0.001*
	Obese	38	18.31±0.13	18.11	18.72	
Lee Index (g/cm)	Non-obese	14	294.42±1.89	291.87	298.28	0.001*
	Obese	38	326.67±2.93	320.51	331.41	
BP (mmHg)	Non-obese	14	89.00±7.38	80	98	0.001*
	Obese	38	190.11±4.42	181	199	

\*= Significant at 5% error level ( $P<0.05$ )

**Table 2.** Pearson correlation analysis of the relationship between BMI and blood pressure in rats

Variable	n	Pearson correlation (r)	F	P-value
Correlation between weight and BP	52	0.428	4.81	0.031*
Correlation between BMI and BP	52	0.977	0.10	0.001*

\*= Significant at 5% error level ( $P<0.05$ ); Correlation (r): 0.80= Very strong, 0.60-0.799= Strong; 0.40-0.599= Medium; 0.20-0.399= Weak; 0.00-0.199= Very weak



**Figure 3.** Simple linear regression analysis: a positive correlation between BMI and BP in rat

The results of the Pearson correlation analysis, as shown in Table 2. There was a significant association between weight and BMI with BP ( $r=0.954$ ;  $P=0.001^*$ ) and ( $r=0.428$ ;  $P=0.031$ ). Based on the  $r$ -value, there was a very strong association between BMI and BP, while there was a moderate correlation between weight and BP. The results of this analysis indicate that if there is an increase in weight and BMI, it will also be followed by an increase in BP in rats.

The correlation gradient between BMI and BP can be analyzed using an equation as shown in Figure 4:  $Y = 707.42 + 2.75 X$ . These results illustrate that every increase in BMI of 1 g/cm will also be followed by an increase in BP of 2.75 mmHg. The results of the analysis show the value of the R-square = 0.972; this value indicates that the accuracy of the linear equation model is 97.2%. The correlation gradient between weight and BP can be seen in the equation:  $Y = 113.422 + 1.35 X$ . This equation shows that for every 1 g increase in body weight, the rat's BP will increase by 1.35 mmHg with an R-square value of 0.62.

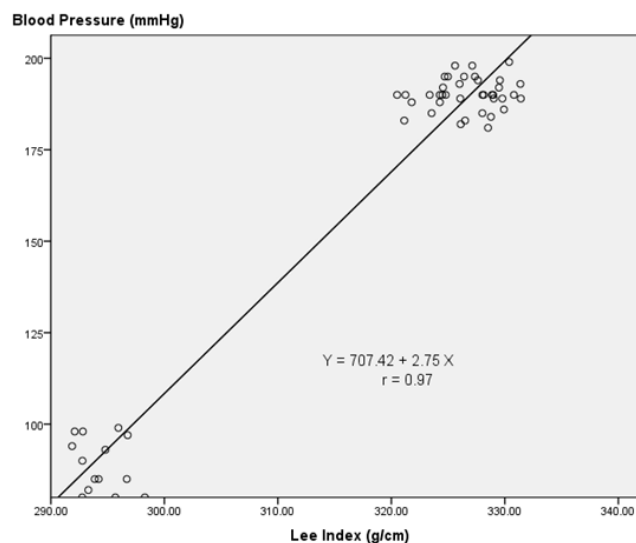
Obesity is not only a problem in high-economy countries but also a global problem for low- and middle-income countries, including Indonesia (Tsfaye *et al.* 2007). Obesity increases morbidity and mortality rates because it indirectly and positively increases the risk of disease: type II diabetes, cardiovascular disease, hypertension, and other chronic diseases (Tsfaye *et al.* 2007). Hypertension is the major risk factor for heart disease, myocardial infarction, and stroke (Kang 2021). The BMI is an indicator of determining obesity (Kang 2021). Our study found that weight and BMI have linearly and positively correlated with blood pressure in rats. One study reported that a positive and linear relationship between BMI and BP in various age groups has long been known (Hall *et al.* 2015; Tsfaye *et al.* 2007). It is estimated that between 78% and 65% of men and women with primary hypertension are associated with being overweight (Hall *et al.* 2015).

The association between obesity and hypertension has been studied by many scientists, while the mechanism of obesity-induced hypertension is still

unclear (Jiang *et al.* 2016). The mechanism of obesity in inducing hypertension occurs through several mechanisms such as hyperactivity of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system; sodium resistance which results in increased renal and proximal tubular sodium absorption; mineralocorticoid-releasing factors that affect intra-renal angiotensin-II and induce endothelial dysfunction (DeMarco *et al.* 2014; Ezequiel *et al.* 2016; Jiang *et al.* 2016). Sympathetic activation plays an important role in the pathogenesis of obesity-related hypertension (Kotsis *et al.* 2010; DeMarco *et al.* 2014). Obesity causes adipocyte dysfunction that result in sympathetic dysfunction and insulin resistance both vascularly and systemically (Kotsis *et al.* 2010; DeMarco *et al.* 2014). Insulin resistance is also caused by incretin signaling and is the beginning of the development of hypertension (DeMarco *et al.* 2014). Insulin resistance reduced bioavailability of Nitric Oxide (NO) due to interference from Metabolics signaling involving insulin receptor substrate-1 (IRS-1); NO is a vascular vasodilator (DeMarco *et al.* 2014).

In the early stages of obesity, increased renal tubular reabsorption increases sodium retention leading to intravascular hypervolemia, increased cardiac output (Kotsis *et al.* 2010; DeMarco *et al.* 2014). Increased activity of aldosterone, angiotensinogen, angiotensin II, and renin, inflammation, and insulin resistance affect vascular changes that cause hypertension (Kotsis *et al.* 2010). Changes in several hormones such as adiponectin, leptin, resistin, TNF, and IL-6 in obese patients induce hypertension and worsen cardiovascular disorders (DeMarco *et al.* 2014). Increased Reactive Oxygen Species (ROS) and oxidative stress cause endothelial dysfunction (Pardina *et al.* 2018).

This study shows that BMI has a very strong positive correlation with blood pressure, and an increase in BMI increases blood pressure in rats. The results of the 2010 study showed a strong correlation between BMI and BP (Oliveira *et al.*, 2010). Research on tens of thousands of populations shows a positive correlation between BMI and BP (Linderman *et al.* 2018). Changes in BMI



**Figure 4.** Simple linear regression equation functional relationship between BMI and BP in rats

directly affect blood pressure and are strongly correlated with the risk of hypertension and various other comorbidities (Landi *et al.* 2018; Pardina *et al.* 2018). An increase in BMI will increase the number of students with high blood pressure (Saeed *et al.* 2014). A high BMI has a strong chance for the development of hypertension in healthy and normotensive women even though they weigh within the normal range (Shuger *et al.* 2008). Hypertension is a critical risk factor in obese adults compared with ideal and normal-weight (Wang *et al.*, 2010).

## CONCLUSION

An increase in body weight and body mass index has a close positive association with blood pressure. An increase of 1 g of weight will increase by 1.35 mmHg of BP as well as an increase in BMI of 1 g/cm will increase BP by 2.75 mmHg. An increase in BMI will increase blood pressure. Therefore, obesity will increase the risk of high blood pressure in rats. Control of obesity is an important factor and changes its association with hypertension as a trigger of mortality due to other complications.

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