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Original article

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Association of Body Mass Index with Matrix Metalloproteinase-9, Tissue Inhibitor of Metalloproteinase-1, and Interleukin-6 Based on Blood Pressure

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Abstract

Background: A high body mass index (BMI) is known to be associated with high blood pressure. Levels of matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), and interleukin-6 (IL-6) are also increased in hypertensive patients. The aim of this study was to determine the correlation of BMI with MMP-9, TIMP-1, and IL-6 based on blood pressure.

Methods*:* The study design was cross-sectional with subjects aged >= 36 years, male and female and divided into 3 groups: group with normal blood pressure (NBP), group with controlled hypertension (CHT), and group with uncontrolled hypertension (UcHT). Height, weight, and blood pressure were measured, as well as serum levels of MMP-9, TIMP-1 and IL-6 using the ELISA method. The correlation was considered significant at p-value of < 0.05.

Results*:* The BMI in group UcHT was higher than in the other groups. There was a positive correlation between BMI and MMP-9; BMI and TIMP-1; and BMI and IL-6 (r=0.480, p=0.007; r=0.620; p=0.000; r=374, p=0.042 respectively) in group UcHT.

Conclusions*:* An increase in BMI is accompanied by an increase in levels of MMP-9, TIMP-1, and IL-6 in group UcHT, signifying that it is necessary to control BMI to maintain stable levels of MMP-9, TIMP-1, and IL-6, thereby keeping blood pressure under control.

Keywords: Body mass index (BMI), Blood pressure, Interleukin-6 (IL-6), Matrix metalloproteinase-9 (MMP-9), Tissue inhibitor of metalloproteinase-1 (TIMP-1).

Introduction

Hypertension is a cardiovascular disease and the most common non-communicable disease experienced by the public. About 46% of adults with hypertension are not aware that they have this condition (1). Hypertension is an important risk factor for cardiovascular disease, chronic kidney disease, and stroke (2). One of the risk factors for hypertension is obesity (3,4).

Being overweight will double the risk of cardiovascular disease, while being obese will triple the risk compared to underweight individuals (4).

Increased levels of matrix metalloproteinase-9 (MMP-9) in circulating blood are found in patients with systemic hypertension or isolated systolic hypertension (5). Research conducted by Ritter et al. on treatment-resistant hypertension patients found that the increase in MMP-9 levels was influenced by obesity (6). Likewise, research conducted by Boumiza et al. found a

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correlation of MMP-9 with several obesity-related parameters including BMI, waist circumference, blood pressure, and endothelium-dependent responses (7).

The relationship between MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1) in patients with essential hypertension has shown that after antihypertensive treatment, circulating levels of these molecules are significantly higher in subjects with hypertension than in normotensive controls. The dynamic balance between MMPs and TIMPs controls extracellular matrix turnover and maintains tissue homeostasis. Meanwhile, changes in the balance between MMPs and TIMPs are involved in the pathogenesis of cardiovascular disease (8). Research conducted by Boumiza et al. found an increase in TIMP-1 levels in obese patients (7).

IL-6 production is regulated by TIMP-1, which exerts its effects via activation of downstream signals and activator of transcription 3 (STAT3) signalling (9). IL-6 has been linked with impaired immune control in the adipose tissue of obese patients (10).

There have been no studies about the correlations between BMI and MMP-9, BMI and TIMP-1, BMI and IL-6 based on blood pressure. Therefore, the aim of this research was to determine the correlation between these parameters. Hopefully, the results of this research will increase our knowledge regarding the pathogenesis of hypertension so that better management of hypertension can be carried out.

Materials and Methods

Study Design and Subjects

The research design was cross-sectional with analytical observation. The research subjects were patients seeking treatment at Sumber Waras Hospital, Jakarta, Indonesia. The inclusion criteria were males and females, 36 years old or older, and willing to participate in the research study by signing an informed consent form. The exclusion criteria were patients with a history of chronic kidney failure, fever, infections, and inflammation. Sample collection was carried out by consecutive sampling resulting in a total of 80 subjects, who were divided into three groups, namely group NBP with normal blood pressure, group CHT with controlled hypertension, and group UcHT with uncontrolled hypertension. Hypertension was based on the 8th Joint National Committee (JNC 8) criteria namely systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg. Subjects with blood pressure <140/90 mmHg were grouped as NBP. Group CHT consisted of subjects with a history of hypertension who had received antihypertensive treatment for at least one month prior and had normal blood pressure when measured. Meanwhile, subjects with a history of hypertension who received antihypertensive treatment for at least one month prior but still had high blood pressure were assigned to group UcHT. The demographic data included age, gender, body weight, and height. The clinical data included blood pressure and serum levels of MMP-9, TIMP-1, and IL-6.

MMP-9, TIMP-1, and IL-6 measurement

Three milliliters of blood were taken from each subject, processed into serum and then stored at -20 °C until the samples were needed. Serum concentrations of MMP-9 (R&D, Minneapolis), TIMP-1 (R&D, Minneapolis, USA), and IL-6 (R&D, Minneapolis, USA) were measured using enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22.00 software. The normality of the data distribution was determined using the Kolmogorov-Smirnov test. he Kruskal-Wallis test was used to assess differences between the blood pressure groups UcHT, CHT, and NBP. Spearman's correlation test was used to determine the correlation of BMI with MMP-9, TIMP-1, and IL-6 levels in each blood pressure group. Statistical significance was set at $p<0.05$.

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Results

In this study, there were 30 subjects in group NBP, 20 subjects in group CHT, and 30 subjects in group UcHT. BMI, SBP, and DBP differed significantly between groups NBP, CHT and UcHT as shown in Table 1. Meanwhile, age, levels of MMP-9, TIMP-1, and IL-6 did not differ significantly between the three groups. The groups were not matched for gender and age.

In patients with normal blood pressure, a correlation study using Spearman's test between BMI and MMP-9 revealed no correlation between the two variables (r=0.277; p=0.138). Similar results were seen in patients with controlled hypertension (r=-0.191; p=0.420). However, a moderate positive correlation was found between BMI and MMP-9 in patients with uncontrolled hypertension (r=0.480; p=0.007) (Fig. 1).

Table 1. Comparison of subject characteristics and examination results by blood pressure group.

Variables	NBP	CHT	UcHT	P value
	Mean±SD (N=30)	Mean±SD (N=20)	Mean±SD (N=30)	
Age (years)	55.13±11.40	61.05±10.74	59.50±10.451	0.095
Gender				
Male	13 (43.3%)	11 (55%)	13 (43.3%)	0.667
Female	17 (56.7%)	9 (45%)	17 (56.7%)	
BMI	24.02±3.14	25.92±6.24	27.87±5.16	0.012*
SBP (mmHg)	120.90±10.57	128.90±8.82	160.07±14.17	0.000*
DBP (mmHg)	68.65±7.69	68.28±9.83	84.95±16.27	0.000*
MMP-9 (ng/mL)	1031.70±499.51	1236.10±521.21	1080.07±396.36	0.329
TIMP-1 (ng/mL)	222.69±93.92	217.95±64.24	218.75±39.21	0.366
IL-6 (pg/mL)	4.82±9.36	4.50±7.09	4.04±4.25	0.961

NBP: normal blood pressure; CHT: controlled hypertension; UcHT: uncontrolled hypertension; BMI: body mass index; SBP: systolic blood pressure; DPB: diastolic blood pressure; MMP-9: matrix metalloproteinase; TIMP-1: tissue inhibitor pf metalloproteinase; IL-6: Interleukin-6; p values with Kruskal Wallis test, significant value <0.05.

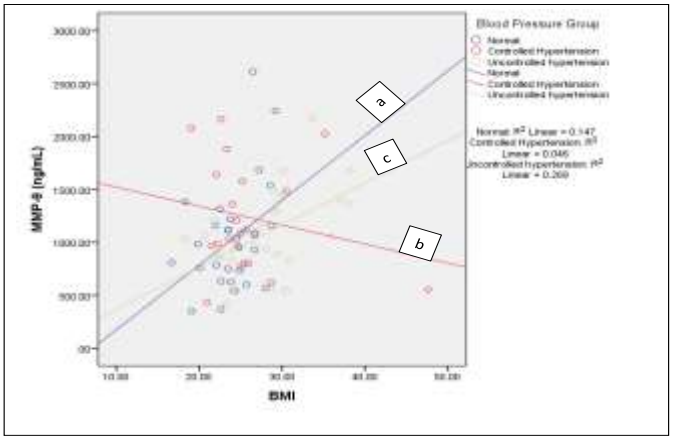

Fig. 1. Correlation between body mass index (BMI) and matrix metalloproteinase-9 (MMP-9). Normal blood pressure: r=0.277; p=0.138 (a). Controlled hypertension: r=-0.191; p=0.420 (b). Uncontrolled hypertension: r=0.480; p=0.007* (c).

The study analysis also revealed that there is no correlation between BMI and TIMP-1 in normal blood pressure patients (r=0.089; p=0.639) and in controlled hypertension patients (r=-0.059; p=0.806), whereas a moderately positive correlation was found in uncontrolled hypertension patients (r=0.620; p=0.000) (Fig. 2).

The correlation study between BMI and IL-6 also showed similar results, with no correlation in patients with normal blood pressure (r=0.028; p=0.882) and controlled hypertension (r=0.182; p=0.060). However, a weak positive correlation was found in patients with uncontrolled hypertension (r=0.374; p=0.042) (Fig. 3).

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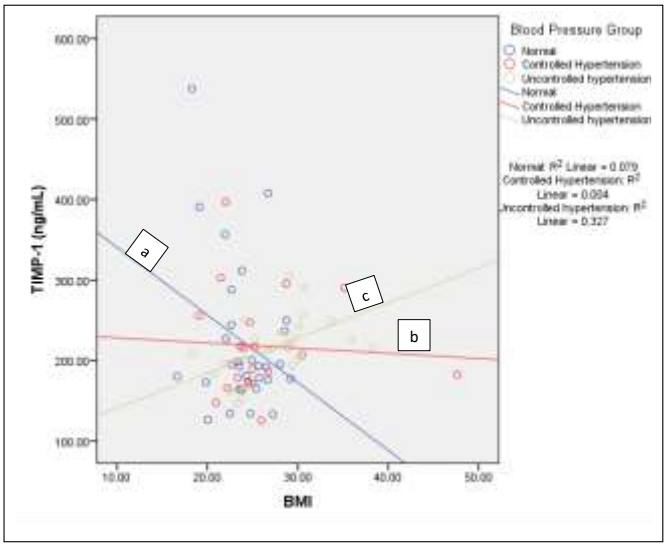

Fig. 2. Correlation between body mass index (BMI) and tissue inhibitor of metalloproteinase-1 (TIMP-1). Normal blood pressure: r=-0.089; p=0.639 (a). Controlled hypertension: r=-0.059; p=0.806 (b). Uncontrolled hypertension: r=0.620; p=0.000* (c).

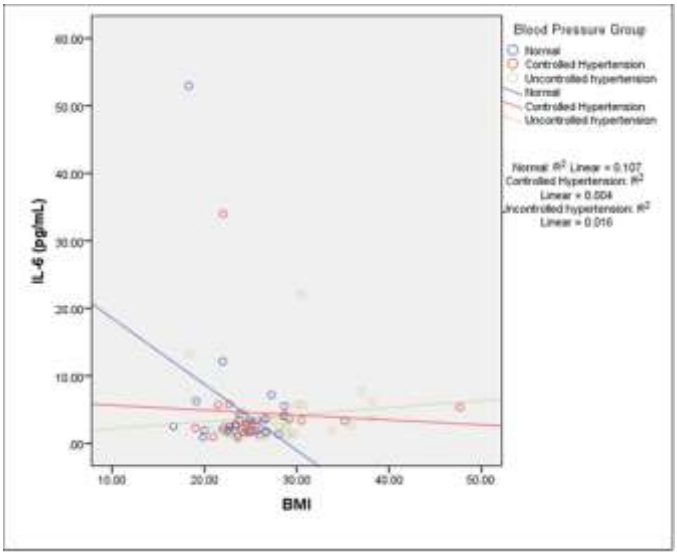

Fig. 3. Correlation between body mass index (BMI) and interleukin-6 (IL-6). Normal blood pressure: r=0.028; p=0.882(a). Controlled hypertension: r=0.182; p=0.060 (b). Uncontrolled hypertension: r=0.374; p=0.042* (c).

Discussion

In the present study, we found that there was a positive correlation between BMI and MMP-9, BMI and TIMP-1, and BMI and IL-6 in group UcHT, which showed an increase in BMI followed by an increase in MMP-9, TIMP-1 and IL-6 levels. However, there was no correlation between BMI and MMP-9, BMI and TIMP-1, and BMI and IL-6 in groups NBP and CHT. This showed that patients whose hypertension was not well controlled had increased BMI and were associated with increased levels of MMP-9, TIMP-1 and IL6**.** It is known that an increase in BMI results in an increase in blood pressure (4). A study conducted by Sushith et al. showed that BMI is higher in type 2 diabetics with hypertension than in healthy controls and type 2 diabetics without hypertension (11).

Meanwhile, increases in MMP-9, TIMP-1, and IL-6 play a role in cardiovascular disorders (12-15). Therefore, it is very important to control BMI. In this way, it is hoped that the

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levels of MMP-9, TIMP-1, and IL-6 will also be controlled.

The results of our study showed a positive correlation between BMI and MMP-9 in group UcHT. It is known that increasing MMP-9 will induce epithelial mesenchymal transition (EMT) which is a potentially significant stage in fibrosis (16). Fibrosis that occurs in blood vessels will cause vasoconstriction of arteries and venules, which can cause hypertension (17). In addition, other studies show that increased plasma MMP-9 levels correlate with increased cardiovascular risk, myocardial infarction mortality, cardiac dysfunction, and arterial wall remodeling (17,18).

Our study also showed a correlation between BMI and TIMP-1 in group UcHT. Research conducted by Glowinska-Olszewska and Urban found a correlation between MMP-9 and BMI (r=0.33, p=0.005) and between TIMP-1 and BMI (r=0.35, p=0.006) in obese children with coexisting hypertension (19). Likewise, in children with obesity and hypertension, a correlation was found between MMP-9 and BMI (r=0.41, p=0.001) and between TIMP-1 and BMI (r=0.33; p=0.025) (19). Our study found similar results in adults but further studies are still needed to obtain a clearer understanding regarding this issue. Kostov et al. state that high TIMP-1 leads to collagen accumulation in cardiovascular extracellular matrix and the development of pathological remodeling and fibrosis of the heart and arteries. Therefore, in order to control TIMP-1 levels properly, it is necessary to control the patient's BMI (20).

Finally, the results of this study reveal a correlation between BMI and IL-6 in group UcHT. IL-6 is a pleiotropic cytokine, with proinflammatory and anti-inflammatory effects and has many physiological roles (21,22). Approximately, thirty percent of circulating IL-6 originates in adipose tissue (22). That is why patients with high BMI will have increased production of IL-6 in adipose tissue and will increase circulatory IL-6. It is known that a high BMI, as in obesity, can cause adipose tissue dysfunction, which triggers the release of pro-inflammatory adipose tissue cytokines which can directly affect cardiovascular tissues and lead to disease (23). Expansion of adipose tissue accompanied by excessive adipocyte lipolysis and subsequent increase in free fatty acid levels will promote adipocyte IL-6 secretion (24). Comparable to obesity, the chronic proinflammatory state commonly found in old age is largely caused by a variety of factors including atherosclerosis, age-related pathological processes, and increased abdominal fat, all of which lead to increased circulating IL-6 levels (25,26). Research conducted by Tadi found that serum IL-6 was positively correlated with BMI, cholesterol, triglyceride, and sodium levels and negatively correlated with potassium levels in prehypertensive and hypertensive patients (27). Similarly, other studies show that there is no significant correlation between IL-6 and anthropometric parameters (BMI, SBP, DBP). However, IL-6 is found to increase in the presence of hypertension (25). Mohammadi et al. in their research found that patients with metabolic syndrome experienced increased IL-6. Metabolic syndrome is hypertension with abdominal obesity, hyperlipidemia, and insulin resistance (28).

The limitation of this study was that it did not include the types of antihypertensive drugs or other drugs consumed by the patients that might affect MMP-9, TIMP-1, and IL-6 levels.

In conclusion, this study shows that an increase in BMI is accompanied by an increase in levels of MMP-9, TIMP-1, and IL-6 in group UcHT. This means that it is necessary to control BMI so that it can maintain stable levels of MMP-9, TIMP-1, and IL-6 thereby keeping blood pressure under control. Further research is needed on BMI and the mechanisms of changes in MMP-9, TIMP-1 and IL-6 levels at the biomolecular level so that a clearer pathogenesis can be obtained in cases of hypertension.

Ethical clearance

Ethical clearance no.007/RSSW/KoM.EP/EC/IV/2022 was

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obtained from Sumber Waras Hospital, Jakarta, Indonesia. All participants signed written informed consent.

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Conflict of interest
The authors declare no conflict of interest

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