The Correlation Between Angiotensin II Levels and Homeostatic Model Assessment of Insulin Resistance in Normotensive Young Adults with a Family History of Essential Hypertension

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ABSTRACT

Background: *A family history of hypertension increases the risk of renin–angiotensin–aldosterone system activation, insulin resistance, and vascular inflammation, contributing to cardiovascular disease. Early vascular disturbances, marked by angiotensin II and insulin resistance assessed through the homeostatic model assessment of insulin resistance (HOMA-IR), play crucial roles in hypertension development. This study aims to determine the comparison and correlation between Ang II levels and HOMA-IR in normotensive young adults with or without offspring hypertension.* ***Methods:*** *This observational analytical cross-sectional study was conducted on fifty normotensive subjects, who were categorized into two groups: normotensive young adults who are offspring of parents with essential hypertension (case) and those who are not (control). The serum Ang II and HOMA-IR were measured. The comparative analysis was conducted using the Mann-Whitney test, and correlations were evaluated using Spearman's test.* ***Results:*** *Among the 50 subjects (25 cases and 25 controls), a significant difference emerged in Ang II levels ($p = 0.010$), whereas HOMA-IR ($p = 0.206$) showed no notable difference between case and control. Notably, a positive correlation between Ang II and HOMA-IR ($r = 0.554$; $p = 0.004$) surfaced in the case group, while the control group exhibited an insignificant correlation ($r = –0.089$; $p = 0.671$).* ***Conclusion:*** *There are notable differences in Ang II levels between normotensive young adults with a family history of essential hypertension and those without such a history. Additionally, a significant correlation was found between Ang II and HOMA-IR in normotensive young adults who have a family history of essential hypertension.*

Keywords: *Normotensive, offspring essential hypertension, angiotensin II, HOMA-IR.*

INTRODUCTION

Hypertension is the leading contributor to cardiovascular disease (CVD) mortality worldwide. Annually, hypertension causes approximately 9.4 million deaths globally, with projections indicating an increase to 23.6 million by 2030 if the current trend persists.[1]

Numerous factors play a role in the development of hypertension and CVD. These factors can be classified into modifiable elements such as inadequate physical activity, an unhealthy diet, stress, smoking, alcohol

consumption, and the presence of metabolic comorbidities, including diabetes mellitus or obesity. Non-modifiable risk factors encompass family history, age, and gender.[2] Hypertension is a complex genetic disorder. Individuals with a family history of hypertension have a twofold higher risk of developing hypertension, increasing the likelihood of future cardiovascular complications.[3,4]

Normotensive individuals with offspring of essential hypertension experience increased activity in the renin-angiotensin-aldosterone system (RAAS). Renin activation within the RAAS leads to elevated levels of angiotensin II (Ang II), a key effector that plays a crucial role in blood pressure regulation.[5–7] It is also involved in arterial wall remodeling and contributes to insulin resistance.[8–10] Insulin resistance is assessed using the homeostatic model assessment of insulin resistance (HOMA-IR) based on basal glucose and insulin levels.[11] Activation of the RAAS can induce early vascular disturbances and CVD by causing vascular inflammation, which involves endothelial activation and dysfunction.[9] Vascular inflammation is preceded by increased blood vessel permeability, leukocyte recruitment, and activation of tissue repair processes, in which Ang II influences the entire process.[12]

Angiotensin II is directly involved in the RAAS pathway and has a direct vasoconstrictor effect.[10] Thus making it a more sensitive indicator of RAAS dysregulation than aldosterone. Angiotensin II is also associated with some risk factors of hypertension, such as insulin resistance and inflammation. Besides, aldosterone levels are influenced by Ang II, which makes it a suitable marker for predicting early hypertension.

To the best of the author's knowledge, limited research has explored early predictors causing vascular dysfunction in descendants of offspring of essential hypertension. Consequently, this study aims to assess the mean difference between Ang II and HOMA-IR levels among normotensive young adults with or without hypertensive parents. In addition, the investigation seeks to analyze the correlation between Ang II and HOMA-IR in normotensive young adults with a familial predisposition to essential hypertension.

METHODS

This study is an analytical observational research employing a cross-sectional study design conducted at the Department of Internal Medicine and Nephrology-Hypertension Clinic of Prof. Dr. R. D. Kandou Manado Hospital from March to September 2019. The study targeted individuals aged 18–35 years with normal blood pressure, categorized into two groups: normotensive young adults who are the offspring of essential hypertension (case group) and those without offspring hypertension (control group).

The sample size was calculated using. the sample size calculation for comparing two means in a two-sample (independent groups) study design formula, using $Z\alpha=1.96$ and $Z\beta=1.64$. Based on the calculation, the sample size for both the case and control groups is 25 samples each.

Samples were consecutively collected from the nephrology and hypertension clinic outpatients until the desired number was achieved. Inclusion criteria involved individuals aged 18–35 years with normal blood pressure and voluntary participation. Exclusion criteria were applied to individuals presenting specific conditions such as diabetes, infections, acute inflammation, and autoimmune diseases or using medications that could potentially affect inflammation status, including antihypertensive drugs (ACE inhibitors, ARBs, calcium antagonists, diuretics, β-blockers), antidiabetic drugs (oral hypoglycemics, insulin), anti-inflammatory drugs (aspirin, steroids, nonsteroids, analgesics), and antioxidants (flavonoids, α-tocopherol, ubiquinone).

The blood pressure was measured using a digital manometer, and venous blood samples were taken for fasting blood glucose and Ang II levels. *Enzyme-linked immunosorbent assay* (ELISA) was used to determine serum Ang II, and the HOMA-IR formula: (fasting insulin (μU/ml) x fasting blood glucose (mmol/L) / 22.5) was used to identify the insulin resistance. Data were analyzed using SPSS version 25.0. Statistical methods included univariate descriptive analysis for variable overview and independent t-tests and Mann–Whitney tests to evaluate differences between the two research groups. The relationship between Ang II and HOMA-IR levels was analyzed using Spearman's test.

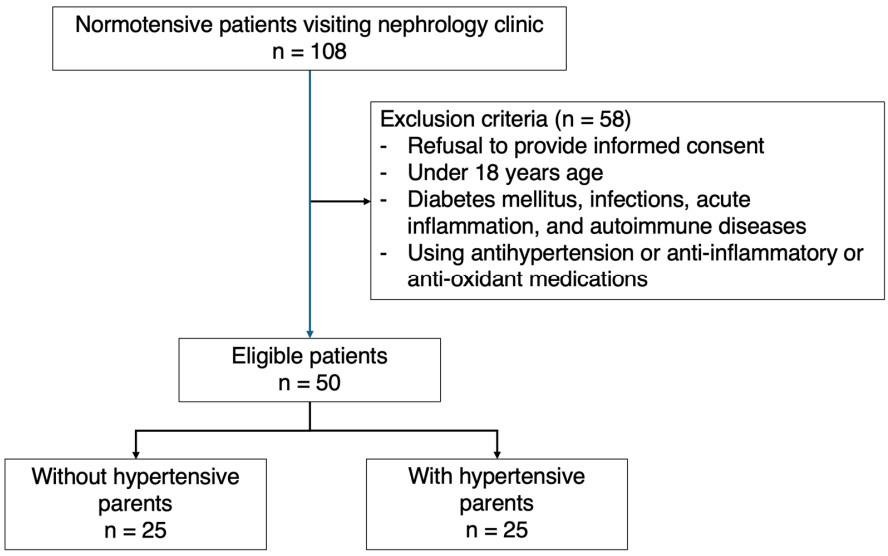

Figure 1. Flow chart of the study

RESULTS

This research was conducted at Prof. Dr. R. D. Kandou Manado Teaching Hospital over six months, from March to September 2019. The study involved 50 research subjects, comprising 25 cases and 25 controls. Detailed characteristics of the research subjects are presented in **Table 1**.

Within the case group, there were 15 male and 10 female subjects, while the control group comprised 12 male and 13 female subjects. Comprehensive characteristics of the study variables are presented in **Table 2**. The outcomes of the descriptive analysis of the study variables, utilizing the one-sample Kolmogorov and Smirnov test, expound upon the minimum, maximum, mean, and SD values.

The difference in Ang II and HOMA-IR levels between the control and case groups was assessed using the Mann–Whitney test.

Table 1. Characteristics of Research Subjects

Variables	Case (n = 25)		Control (n = 25)	
	Mean± SD	Median (IQR)	Mean± SD	Median (IQR)
Age (year)		28.00 (25.00-31.00)		30.00 (27.00-32.00).
BMI (kg/m^2)	23.96 ±3.11		22.67 ±15.90	
LDL (mg/dL)	124.84±29.32		118.28±24.22	
HDL (mg/dL)	49.76±10.40		54.56±11.49	
FBS (mg/dL)	86.56±5.97		86.32±7.32	
HbA1C (%)		5.40 (5.20-5.40)	5.33±0.31	
Fasting Insulin Levels (µU/mL)		3.70 (2.40-5.60)		4.40 (3.10-7.10)
Waist circumference (cm)		90.00 (83.00-95.00)		84.00 (78.50 - 93.00)

n = number of samples, SD = standard deviation, FBS = fasting blood sugar, BMI = body mass index, LDL = low density lipoprotein, HDL = high density lipoprotein

Table 2. Characteristics of Study Variables

Variables	n	Median (IQR)	
		Case	Control
Ang II (pg/mL)	25	3.10 (2.54-4.00)	2.04 (1.26-3.32)
HOMA-IR	25	0.69 (0.48-1.12)	1.06 (0.62-1.54)

n = number of samples, SD = standard deviation, Ang II = angiotensin II, HOMA-IR = homeostatic model assessment for insulin resistance

Table 3. The Difference in Ang II Levels Between Case and Control Groups

Variables	Median (IQR)		P values
	Case	Control	
Ang II (pg/mL)	3.10 (2.54-4.00)	2.04 (1.26-3.32)	0.010*
HOMA-IR	0.69 (0.48-1.12)	1.06 (0.62-1.54)	0.260

*significance

Table 4. The Relationship Between Angiotensin II Levels and HOMA-IR Values in the Case and Control Groups

Variables Relationship	Case (n = 25)	Control (n = 25)
Ang II Levels and HOMA-IR Values	r = 0.554 (p = 0.004)*	r = –0.089 (p = 0.671)

r = correlation coefficient, p = level of significance, *significance

The difference in Ang II levels between the control and case groups was assessed using the Mann–Whitney test, with a p-value of 0.010, indicating a statistically significant difference. Meanwhile, the difference in HOMA-IR values, evaluated through the Mann–Whitney test, resulted in a p-value of 0.260, suggesting no statistically significant difference.

The correlation between Ang II levels and HOMA-IR values in the control and case groups was analyzed using Spearman's test.

The correlation between Ang II levels and HOMA-IR values in the case group yielded a correlation coefficient of 0.554 and a p-value of 0.004, indicating a statistically significant positive correlation. Meanwhile, the relationship between Ang II levels and HOMA-IR values in the control group resulted in an r-value of –0.089 and a p-value of 0.671. These results suggest no statistically significant correlation in this group.

DISCUSSION

The mean age for the case group was 28.88 ± 3.59 years, while for the control group, it was 28.92 ± 3.87 years. These results suggest comparable mean ages in both groups. The selection of the age range in this study aimed to avoid bias related to age, body mass index (BMI), fasting blood glucose, and other baseline characteristics. The mean BMI in the case group was 23.96 ± 3.11 kg/m^{2,} and in the control group was 22.67 ± 2.16 kg/m^2. Similar findings were reported by Motta et al., showing a higher BMI in the case group (28.8 ± 4.6 kg/m^2) compared with the control group (25.5 ± 4.3 kg/m^2). However, similar to this study, the difference was not statistically significant in both research groups.[13,14] The baseline data variables in this study also indicate no significant differences between the case and control groups.

The study results revealed a statistically significant difference in Ang II levels between the two groups, with a p-value of 0.010. Angiotensin II, a crucial component of the RAAS, exhibits vasoconstrictor properties, leading to vascular dysfunction. The pathological effects of Ang II result from its interaction with AT1R, causing sodium retention, aldosterone secretion, fibrosis, cellular proliferation, vasoconstriction, superoxide formation, inflammation, and thrombosis.[15] The significant increase in Ang II levels among individuals who are offspring of essential hypertension implies an early predisposition, rendering them at a higher risk of developing hypertension later in life. This also suggests that Ang II can serve as an early marker for vascular damage occurring in early adulthood, even before clinical manifestations of hypertension. There is a lack of previous research specifically measuring Ang II levels in normotensive young adults who are the offspring of hypertensive parents. However, the long-established evidence of higher Ang II levels in hypertensive patients compared with normotensive subjects supports the findings of this study.[16] Subsequent research has also documented a significant elevation of

blood pressure in response to the intravenous administration of Ang II in human subjects.[17]

The HOMA-IR is higher in the control group compared to the case group due to several factors. Higher fasting blood glucose levels in the control group resulted in higher HOMA-IR calculation. Genetics[18], physical activity[19], and physiological stress[20] are known to affect blood glucose and insulin resistance; therefore, the HOMA-IR value may vary. However, statistical analysis found no significant difference in HOMA-IR values between the control and case groups.

Similar findings were reported by Rice et al. in a study involving 979 children with or without offspring hypertension, revealing no significant difference in insulin resistance levels between the two groups.[21] By contrast, Montagnani et al. reported an association between insulin resistance and early vascular dysfunction in individuals with offspring of essential hypertension. This association was linked to the formation of pro-atherogenic lipids, increased release of proinflammatory mediators, and reduced nitric oxide (NO) release.[22] There are discrepancies between these findings and our study. Currently, there is still an ongoing debate regarding insulin resistance in normotensive individuals with or without offspring hypertension.

This study suggests a significant positive correlation between Ang II levels and HOMA-IR values in the case group, while no significant correlation was observed in the control group. Ang II can induce insulin resistance, and conversely, insulin resistance increases Ang II levels. Hypertension is often associated with hyperinsulinemia and glucose intolerance. Elevated Ang II expression can trigger insulin resistance through the mTOR–S6K1 signaling pathway, leading to oxidative stress and disruption in the insulin–PI3K signaling pathway. Conversely, insulin resistance can increase the release of proinflammatory cytokines and decrease NO production, resulting in endothelial dysfunction and an increased risk of hypertension. Insulin resistance can also trigger hyperactivity in the sympathetic nervous system and the RAAS.[12,23,24]

For young individuals with offspring of essential hypertension, early education is recommended to prevent future CVDs. The limitation of this study lies in its cross-sectional design, preventing a definitive assessment of cause-and-effect relationships due to data collection at a specific point in time without evaluating the change of Ang II and HOMA-IR over time. In addition, the small sample size (50 subjects), though sufficient for detecting moderate correlations, restricts the statistical power and generalizability of the findings.

There was a potential for selection bias due to the uneven distribution of confounding factors between case and control groups, such as genetic variations, lifestyle, physical activity, psychological stress, and family history of other diseases. Further research in a cohort design can be conducted using a larger sample size to assess a more accurate correlation between the variables studied and the occurrence of hypertension and CVDs.

CONCLUSION

These findings signify differences in Ang II in normotensive young adults with offspring of essential hypertension and without offspring hypertension. There was a significant correlation between Ang II and HOMA-IR in normotensive young adults, who are the offspring of essential hypertension.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest in this study.

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