

## PLASMA ANGIOTENSIN II LEVELS IN WOMEN WITH TYPE 2 DIABETES WITH OR WITHOUT HYPERTENSION

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### ABSTRACT

**Background.** Hypertension is a major risk for the development and progressivity complication of macro and microvascular of diabetes mellitus. Renin-angiotensin-aldosterone system (RAAS), insulin resistance, endothelial dysfunction and autonomic nervous dysfunction play an important part in the pathogenesis of hypertension and type 2 diabetes mellitus. In RAAS, increased angiotensin II constricts arterioles, raises total peripheral resistance and blood volume. The rise in intravascular volume increases risk of hypertension. Glucotoxicity or hyperglycemia in type 2 diabetes mellitus can increase angiotensin II levels.

**Aim.** To evaluate plasma angiotensin II levels in type 2 diabetes mellitus women with or without hypertension.

**Methods.** Cross sectional design was conducted on subjects from outpatients' women with type 2 diabetes mellitus at endocrinology clinic, Dr. Sardjito General Hospital, Yogyakarta. Hypertension was assessed using criteria from Seventh Joint National Committee (2003). ELISA sandwich method was used to measure plasma angiotensin II levels from blood vein. Differences between groups were compared by student's unpaired t-test and Mann-Whitney test.

**Results.** Among 60 subjects, there are 30 with hypertension (50%) and 30 without hypertension (50%). Mean age were  $54.11 \pm 3.36$  years old. Plasma angiotensin II levels was higher in women with type 2 diabetes mellitus with hypertension than without hypertension although significance was not reached ( $0.30 \pm 0.15$  ng/mL vs.  $0.28 \pm 0.18$  ng/mL,  $p=0.93$ ).

**Conclusion.** The plasma angiotensin II levels are not significantly different between type 2 diabetes mellitus women with or without hypertension.

**Key words:** hypertension, plasma angiotensin II, type 2 diabetes mellitus, women

### INTRODUCTION

High prevalence of diabetes was a serious problem in the world since twenty years ago. Type 2 diabetes or non-insulin dependent of diabetes mellitus (NIDDM) is the most common type of diabetes (85-90%). In 2003, the world health organization (WHO) predicted that in Indonesia there were 5.1% or equals to 194 million people of 20-79 years old suffering from diabetes and this tends to increase in the year 2025 (almost 333 million people). Diabetes mellitus and hypertension were risk factors for morbidity and mortality from complication of cardiovascular disease, cerebrovascular disease and chronic kidney disease. Increasing normal systolic blood pressure of about 20 mmHg or diastolic pressure of about 10 mmHg in 12 years had correlation with high risk mortality due to coronary heart disease and stroke<sup>3</sup>. Many factors may influence blood pressure. Renin-angiotensin-aldosterone system (RAAS) is one of the factors that have an important role in controlling blood pressure and sodium homeostasis<sup>4</sup>.

Prevalence of hypertension in population with diabetes is greater than without diabetes. Hypertension is the most important factor in progressivity of chronic complications of diabetes, either macrovascular or microvascular complications<sup>4</sup>. The prevalence of diabetes mellitus increases in women because high prevalence of obesity in women, polycystic ovarii syndrome, gestational diabetes or premenopausal (due to the effect of low estrogen)<sup>5</sup>.

The decreasing of estrogen in women influence high activity RAAS and then increasing angiotensin II constricts arterioles, raises total peripheral resistance and blood volume. The rise in intravascular volume increases risk of hypertension.

Glucotoxicity or hyperglycemia in NIDDM can increase angiotensin II levels<sup>5</sup>.

The aim of the study was to evaluate plasma angiotensin II levels in type 2 diabetes mellitus women with or without hypertension.

#### RESEARCH METHODS

The study was performed as a cross-sectional study. The sample was selected consecutively from outpatients' women with the age 22-60 years in endocrinology clinic at DR Sardjito General Hospital – Yogyakarta using the ADA 2010 criteria of diabetes mellitus and JNC-7 2003 criteria of hypertension. The data was obtained from June to December 2010 after subjects sign the informed consent.

The protocol of the study had been approved by the human research ethics committee of the Faculty of Medicine Gadjah Mada University – Dr. Sardjito General Hospital. Excluded from the study were women who had congestive heart failure, chronic kidney disease, malignancy, liver cirrhosis,

sepsis, taking hormone drugs or contraceptions, pregnancy and lactating women.

#### STATISTICAL ANALYSIS

The mean difference of plasma angiotensin II levels between type 2 diabetes mellitus women with hypertension and without hypertension were analyzed by independent t-test on data with normal distribution or by Mann-Whitney U test on data with abnormal distribution. Kolmogorov Smirnov's test was performed to assess data distribution. All statistical analyses were performed with SPSS 13.0 for Windows (SPSS, Chicago, IL) and P values of <0.05 were considered significant<sup>6</sup>.

#### RESULTS

A total of 60 individuals with mean age of  $54.11 \pm 3.36$  years were studied; from among them 30 (50%) were type 2 diabetes mellitus women with hypertension. The characteristic of the study subjects can be seen in the **Table 1**.

**Table 1. Characteristic of Study Subjects**

Variables	Mean $\pm$ SD Median (min-max)	Frequency n (%)
Status of Hypertension		
With hypertension		30 (50)
Without hypertension		30 (50)
Status of type 2 diabetes:		
<5 years		26 (43)
$\geq$ 5 years		34 (57)
With oral antidiabetic (OAD) drugs		18 (30)
With insulin		20 (34)
With OAD + insulin		22 (36)
Age (years)	$54.11 \pm 3.36$	
Height (cm)	155 (144-167)	
Weight (kg)	57 (40-83)	
BMI (kg/m <sup>2</sup> )	$24.25 \pm 3.05$	
Systolic Blood Pressure (mmHg)	$133.24 \pm 11.36$	
Diastolic Blood Pressure (mmHg)	$79.19 \pm 8.07$	
Fasting Blood Sugar (mg/dL)	108.00 (78.00-292.00)	
2 Hour Post Prandial Blood Sugar (mg/dL)	140.50 (69.00-362.00)	
Plasma Angiotensin II (ng/mL)	$0.30 \pm 0.19$	
Total Cholesterol (mg/dL)	$182.14 \pm 36.28$	
LDL Cholesterol (mg/dL)	$118.09 \pm 19.24$	
HDL Cholesterol (mg/dL)	$60.08 \pm 26.09$	
Triglycerida (mg/dL)	139.00 (75-267)	

SD= standard deviation, BMI= body mass index, LDL= low density lipoprotein, HDL= highDensity Lipoprotein.

**Table 2. Data of Study Subjects with Type 2 Diabetes Mellitus with or without Hypertension**

Variables	Type 2 diabetes mellitus with hypertension (n=30)	Type 2 diabetes mellitus without hypertension (n=30)	P	CI 95%
Age (years)	$53.45 \pm 3.17$	$54.88 \pm 3.45$	0.067 **	-1.43 sd 0.11
Height (cm)	$155.97 \pm 5.05$	$155.97 \pm 5.05$	0.289*	
Weight (kg)	$61.41 \pm 8.99$	$41.41 \pm 8.99$	0.017 *	
BMI (kg/m <sup>2</sup> )	$25.14 \pm 2.76$	$18.04 \pm 2.76$	0.019 **	-3.03 sd -0.28
Systolic BP (mmHg)	$144.25 \pm 5.49$	$113.82 \pm 6.04$	0.00 **	-22.2 sd -16.9
Diastolic BP (mmHg)	$93.25 \pm 4.74$	$76.18 \pm 4.93$	0.00 **	-15.1 sd -10.6
Fasting BS (mg/dL)	$157.88 \pm 49.34$	$101.88 \pm 27.43$	0.00 *	
2HPP BS (mg/dL)	$235.92 \pm 83.97$	$124.81 \pm 51.43$	0.00 *	
Angiotensin II (ng/mL)	$0.30 \pm 0.15$	$0.28 \pm 0.18$	0.93 **	-0.94 sd 0.08
Total Cholesterol (mg/dL)	$183.32 \pm 33.81$	$180.74 \pm 39.45$	0.765 **	-14.6 sd 19.8
LDL Cholesterol(mg/dL)	$115.88 \pm 18.24$	$120.71 \pm 20.32$	0.285 **	-13.7 sd 4.11
HDL Cholesterol(mg/dL)	$67.62 \pm 26.79$	$51.20 \pm 22.51$	0.006 **	4.83 sd 28.01
Triglycerida(mg/dL)	$128.08 \pm 35.35$	$115.88 \pm 18.24$	0.007 *	

BMI= body mass index, BP= blood pressure, BS= blood sugar, 2HPP= 2 hour post prandial, LDL= low density lipoprotein, HDL= high density lipoprotein, \*= Mann-Whitney U test, \*\*= Independent t-test, CI= confidence interval

**Table 2** showed that plasma angiotensin II levels were higher in type 2 diabetes mellitus women with hypertension than without hypertension although without significance ( $0.30 \pm 0.15$  ng/mL vs.  $0.28 \pm 0.18$  ng/mL.  $p=0.93$ ).

#### DISCUSSION

Pre-menopausal women with low estrogen can increase activity of RAAS. That condition causes the losing a cardio-protective effect, endothel function, and a low response of coronary vasodilation<sup>5</sup>. Pathophysiology of hypertension from RAAS activity is one of the factors that have important role in insulin resistance or metabolic syndrome as a part form type 2 diabetes mellitus. Glucotoxicity or hyperglycemia in type 2 diabetes mellitus can increase RAAS activity and plasma angiotensin II<sup>7</sup>.

The prevalence rate of plasma angiotensin II levels was higher in type 2 diabetes mellitus with hypertension ( $0.30 \pm 0.15$  ng/mL) than without

hypertension ( $0.28 \pm 0.18$  ng/mL) although it did not show no significant statistically ( $p=0.93$ ). These prevalence rates were similar to the ones observed by Blucher *et al*<sup>8</sup> ( $0.32 \pm 0.21$  ng/mL vs.  $0.31 \pm 0.14$  ng/mL.  $p>0.05$ ).

The cross-sectional nature of the present study has precluded the causal inferences regarding the determination of the prevalence rate of high plasma angiotensin II in type 2 diabetes mellitus with hypertension in a group of individuals' representativeness of the national population. Participant selection, on the other hand, has reduced the generalizability of the findings. Large prospective studies in various districts are needed to better evaluate the prevalence increasing plasma angiotensin II in type 2 diabetes mellitus with hypertension. The second limitation of this study is the potential bias due to missing values in some variables. The large number of participants, however, may have compensated for these potential biases to some extent.

## CONCLUSION

There was no significant differences of plasma angiotensin II levels in women with type 2 diabetes mellitus women who also have hypertension when compared to the ones without hypertension. However the findings of the present study provide alarming evidences for health professionals and policy makers about the high prevalence of high plasma angiotensin II in type 2 diabetes mellitus in our population. Preventive and treatment strategies, notably in women, are urgently needed to prevent and promote healthy lifestyle habits.

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