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REVIEW ARTICLE

Association between Aldosterone Renin ratio and Response to Valsartan in Iraqi Patients with Essential Hypertension

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Abstract:

background

Damage to the heart and blood vessels, as well as to other organs and premature death, have all been related to hypertension, a multifactorial, progressive cardiovascular disease. The aldosterone-renin ratio (ARR) is a useful screening measure for secondary hypertension, which can be caused by primary aldosteronism. Angiotensin II receptor blockers (ARBs) are the most often utilized medications that influence the renin-angiotensin system. These drugs prevent the physiological effects of angiotensin II by binding to angiotensin type 1 receptor AT1R. Blood pressure can be lowered by inhibiting AT1R, as this results in decreased production of vasopressin and aldosterone with subsequent relaxation of blood vessels.

Objective :To determine the association between aldosterone renin ratio and response to valsartan in iraqi patients with essential hypertension.

Method: This is an observational cross sectional descriptive single center study for 90 hypertensive patients of Iraqi nationality who taking valsartan tablet 160 mg/oraly once daily for at least two week.

Result:There is no significant relationship between aldosterone renin ratio and response to valsartan(p>0.05).

Conclusion: There is no association between aldosteron /renin ratio and response to valsartan .

Keywords: iraq, essential hypertension, aldosterone-renin ratio, valsartan, response.

Introduction

Systolic blood pressure (BP) of 140 or above requires long-term therapy (1) in the office or clinic. Individuals with hypertension may have a wide range of symptoms. Headache/severe feeling in the nape, (vertigo), heart palpitations, blurred vision, ringing in the ears (tinnitus), and nosebleeds are the most common symptoms of hypertension. In humans, blood pressure naturally rises and falls during the day, and maintaining a constant reading can be dangerous (2) Hormones like adrenaline and noradrenaline are released in the morning to help the body function. Because of the Circadian rhythm, which is a 24-hour cycle that affects our sleep/wake cycles, these hormones deliver bursts of energy but can also increase blood pressure and fall at night(3). About 95% of patients with hypertension have essential hypertension (primary), in which the underlying causes are unknown, and the remaining 5-7% have secondary hypertension. Hormonal issues, a narrowing of the big blood vessels, and a narrowing of the kidney vessels are just a few of the known reasons of hypertension, affecting only 5%- 10% of the population (4). In low and middle-income nations, One of the primary causes of death from cardiovascular disease is

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hypertension. However, only 54% of people with hypertension had their BP treated to a systolic/diastolic BP of 140/90 mmHg or below (5), despite the availability of safe, well-tolerated, and cost-effective antihypertensive treatment. Body mass index (BMI), insulin resistance, alcohol use, salt intake (in salt-sensitive patients), advancing age, lack of physical activity, stress, potassium shortage, and calcium deficiency are all factors that raise the likelihood of developing hypertension (6, 7). Essential hypertension has multiple causes, including shifts in cardiac output and peripheral resistance. The endocrine renin-angiotensin-aldosterone system (RAAS) is one example of such a mechanism. Renin is a protease that is secreted into the bloodstream and has effects on blood pressure and arterial stiffness. In order to produce angiotensin I, renin must first convert angiotensinogen. One of the products of the conversion of angiotensin I (Ang I) is angiotensin II (Ang II) (8). Angiotensin II is the strongest vasoconstrictor and has the most vasoactive potential. High blood pressure affects the peripheral resistance and the artery muscle. The result is an instant decrease in sodium retention. Angiotensin II produces a rise in blood volume and blood pressure by stimulating the adrenal glands to create aldosterone, which in turn stimulates the kidney epithelial cells to enhance their reabsorption of sodium and water. The hormone renin is typically seen in higher concentrations in patients with hypertension. Secondary hypertension typically results from one of the following: Adrenal cortical adenoma or bilateral hyperplasia are the most common causes of autonomous aldosterone hypersecretion., is the underlying cause of primary aldosteronism (PA). Aldosterone-producing adenomas were found in 4.8% of the population, and 6.4% of the population had idiopathic hyperaldosteronism (IHA). Increased aldosterone levels increase the risk of cardiovascular disease, renal disease, metabolic syndrome, and diabetes; therefore, early detection is crucial since PA may be a treatable cause of hypertension and its sequelae. As a result, numerous institutions now use PA screening procedures (9). As a result, numerous authorities have established PA screening requirements. The most widely used recommendation is from the Endocrine Society's 2016 guidelines, which say that plasma aldosterone-renin ratio (ARR) (10). The ratio of renin to angiotensin II to aldosterone is lowered by valsartan's effect on the renin-angiotensin-aldosterone axis (10). The prevalence of high ARR varies from study to study, population to population, degree of hypertension, prospective vs. retrospective data, and type of test utilised, with estimates ranging from 1% to 30%(11). Twelve percent of people in the Framingham offspring research had increased ARR (12) due to untreated hypertension.while up to 7% of hypertensive patients showed increased ARR in two German epidemiological investigations (13). Using both screening ARR and further confirmatory tests, researchers in Italy led by Torino showed that the frequency of PA varied from 3.9% in those with stage I hypertension to 11.8% in those with stage III hypertension (14).There is a lack of data on ARR in the Middle East; the highest rate we could find was 17.4%, from a random hypertensive cohort in Turkey-Trabzon(15). and 26% of Iraqi individuals with hypertension who meet screening criteria have an elevated ARR. Due to the study's limitations, this may not be indicative of the true frequency of a high ARR ratio (16).

Materials And Methods:

Study design: Hypertensive patients of Iraqi nationality, diagnosed in accordance with the 2020 ISHguideline(1), will be the focus of this observational cross-sectional descriptive single-center study. All eligible patients were identified and recruited by cardiologists who specialized in their care. The research took place between July 2022 and July 2023 and approved by the scientific and ethical committee (No.30/2707 in 18/7/2023). This experiment was conducted in the province of Al-Diwaniyah at Al-Qadisiyah University/ Department of Pharmacology and Therapeutics at the College of Medicine. Before enrolling in the study, all volunteers will be given a thorough explanation of the technique and the reason for conducting the research.

Patient's inclusion Criteria:

Male and female patients with hypertension who had been taken valsartan 160 mg for at least 2 weeks.

patient Exclusion criteria

Patient Exclusion criteria include patients with renal or hepatic impairment, Pregnancy, Heart failure. Valsartan contraindication (Hypersensitivity to valsartan, Obesity (BMI ≥ 30) and Psychiatric patient

Subjects

The study included 90 adults were enrolled in this study (36 male and 54 female) both males and females, aged 20-70 years diagnosed with essential hypertension, taking valsartan for at less two weeks.

Questionnaire formula

Name, age, gender, weight, height, body mass index, and comorbidities like smoking, diabetes, and ischemic heart disease were collected from patients.

Taking ethics into account:

All patients were given an explanation of the procedures and

gave their informed consent before the study was conducted, which was authorized by the Ethics Committee of the University of Al-Qadisiyah's collage of Medicine.

Clinical assessment of study patients

Measurement of blood pressure

Blood pressure (BP) measures were obtained using a mercury sphygmomanometer. Before taking measurements, the participant was advised to sit silently for five minutes with their legs uncrossed and their right arm uncovered. The right arm was positioned with the palm facing upwards on the table and measure three reading and take the average of last two reading (1) he correct cuff measurement was determined. During measurement, the cuff was maintained at the same level as the heart. Patients are classified according to the ISH 2020 (1) as shown in table (1):

Table 1 : 2020 ish classification of hypertensio

Classification	Systolic(mmHg)		Diastolic (mmHg)
Normal BP	<130	And	<85
High- normal BP	130 – 139	and/or	85-89
Grade1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	≥160	and/or	≥100

Patients divide into two groups (17):

- Good Responders: were defined as patients that reached a target blood pressure of SBP less than 140 mm Hg or DBP less than 90 mm Hg.
- non-responder (Bp ≥ 140/90 mmHg.

Collection and preparation of samples

Blood samples were collected from the non fasting patientsthat were aspirated from antecubital vein. 3 ml blood that was centrifuged to extract serum for measuring (lipid profile, blood urea, serum creatinine, uric acid, random blood sugar, serum renin level, serum aldosterone level).

Biochemical analysis

Renin ELISA was used to determine DRC (reference range: 7.54-42.3 ng/L). Aldosterone ELISA assessed plasma aldosterone concentration (PAC) (1.3-23.1 ng/dL reference range). The ARR formula is: ARR = PAC/DRC, with a normal ARR 5.7 (16).

Statistical analysis

Statistical analysis was performed using SPSS version 26.

Results

Demographic data:

This study included 90 Iraqi hypertensive patients, (58.9%) (n = 53) females and (41.1%) (n = 37) males, with a mean age of ± SD age (years) 53.2 ± 13.8 years old, and mean BMI of ± SD BMI 29 ± 5. 3.2 kg/m².

Blood pressure

All patients participated in this study were hypertensive on valsartan 160mg/day , so the mean ± SD of systolic blood pressure was 150±14.9 mmHg while the mean ± SD of diastolic blood pressure was 89.3± 6.9 mmHg. From these 90 hypertensive patients (45.6 %) (n = 41) meet the target level of blood pressure (responders<140/90 mmHg) while (54.4 %) (n = 49) remain doesn't meet the target of treatment (≥ 140 mmHg non-responders)

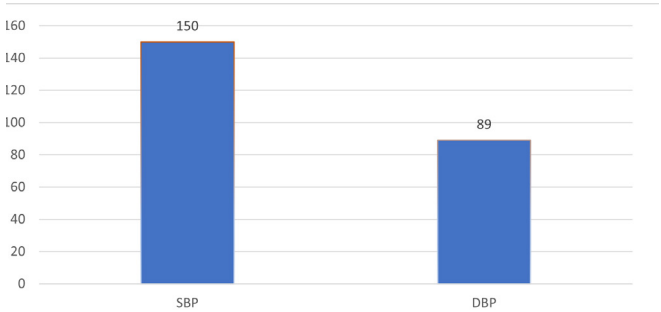
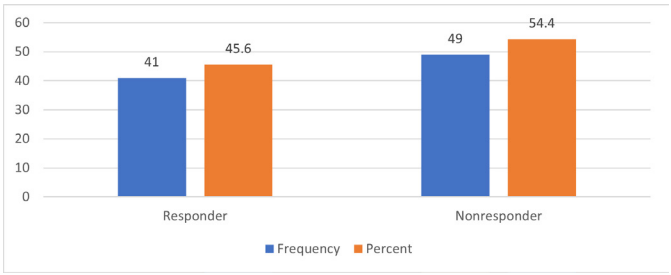


Figure (1)Shows the mean systolic and diastolic blood pressure of recruited hypertensive patients (n = 90) who were took valsartan 160 milligram per day.



Figure(2) Shows the number and the percent of responder (Bp less than 140/90 mmHg)and non-responder (Bp equal or more than 140/90 mmHg) to valsartan treatment of hypertensive patients.

As show in table (1), the mean of renin and aldosterone were 45 and 37.9 respectively and SE was 1.03 and 1.7 respectively.

Table (1): Shows the mean of serum renin and aldosterone of hypertensive patients (n = 90) that were took valsartan 160 mg/ day.

	Mean	SE
Aldosterone	37.9	1.7
Renin	45	1.03

The mean of ARR equal to 0.84 (normal is defined as an ARR less than 5.7).

Table (2): Shows the relationship between the mean of aldosteron/renin ratio and responsivness to valsartan 160 mg/ day in 90 hypertensive patients .

	Mean aldosteron/renin	P value
Responder	0.79	0.7(NS)
Non responder	0.85	

Discussion

In this study from these 90 hypertensive patients (45.6 %) (n = 41) meet the target level of blood pressure (responders<140/90 mmHg) while (54.4 %) (n = 49) remain doesn't meet the target of treatment (≥ 140 mmHg non-responders), and the mean of ARR equal to 0.84 (a cut-off of ARR < 5.7 considered normal). That mean all patients have false negative result of ARR may be related to the effect of valsartan that decrease aldosterone and increase renin level.

Certain parameters must be met to reduce the possibility of erroneous results from biochemical testing, both positive and negative. Blood samples for ARR should be taken first thing in the morning, after patients have been up for at least 2 hours and have been seated for at least 5 minutes (according to the guidelines). The patient should not restrict their salt consumption and should have adequate potassium levels before the test. Many medications, including valsartan, can affect the renin-angiotensin-aldosterone axis and should be discontinued in the weeks leading up to any necessary tests. Stage 1 hypertensive participants are safe candidates, but other patients may be at risk (18(.Several blood pressure medications affect aldosterone secretion and/or renin activity (or concentration), both of which in turn affect the ARR (10 .(Inhibitors of angiotensin-converting enzyme (ACEI) and angiotensin II receptor (ARBs) decrease the ARR by increasing renin and decreasing plasma aldosteron concentration (19).

The Endocrine Society guidelines from 2016 recommend beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and dihydropyridine calcium antagonists must be discontinued for at least 2 weeks before ARR testing. Patients with mild hypertension are a good candidate for this, but those with more severe cases may have trouble (10). Our study agree with study of Thomas D. Giles M that demonstrate increase in renin level and decrease aldosteron level and there is no decrease in systolic and diastolic blood pressure(20). also agree with study that demonstrate the, administration of valsartan monotherapy resulted in a dose-dependent increase in plasma renin activity(21).

Conclusion

there is no relationship between aldosteron /renin ratio and response to valsartan,Ideally, PA testing would be done without the use of medicines that affect the renin-angiotensin-aldosterone axis. However, evaluating patients with more severe/resistant hypertension, very high cardiovascular risk, or severe hypokalemia is challenging because of the risks related to suboptimal control of blood pressure and serum potassium level during the evaluation period. This can add weeks to the diagnostic process. However, interpreting renin and aldosterone values for the purpose of diagnosing PA becomes problematic when testing is performed while on interfering antihypertensive medicines.

Acknowledgments

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Limitations

Small sample size ,is the limitation of study due to a difficult obtaining hypertensive patients with monotherapy or have on other systemic disease.

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