ORIGINAL ARTICLE

CONTENTS

Association between plasma angiotensinogen level and response to valsartan among sample of Iraqi hypertensive patients

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ABSTRACT

Aim: The main aim of the present paper is to investigate allele frequencies of rs1799983 polymorphism eNOS genes and to determine association between rs1799983 polymorphism of eNOS gene and essential hypertension in Iraqi hypertensive patients.

Materials and Methods: Data obtained at the Al-Diwaniyah teaching hospital in Iraq by researchers from the Department of Pharmacology and Therapeutics in the College of Medicine at University of Al-Qadisiyah from July 2022 to July 2023. All participants (aged 20 to 70) had been taking valsartan 160 mg once day for essential hypertension for at least two weeks before to the study. There were a total of 90 participants, 37 males and 53 women. Initial investigations of hypertension have indicated that the angiotensinogen gene has a substantial impact in susceptibility to essential hypertension through observational cross sectional descriptive single center study.

Results: Indicate, in patients with essential hypertension, that the "AGT gene A>G (rs699) and C>T(rs5051)" have high angiotensinogen level, and there is no significant association between these two (rs699, rs5051) and responsiveness to valsartan (P >0.05).

Conclusions: Result showed the most common allele for rs699 was G allele (67%) while the most frequent genotype was AG (49%) and regarding rs5051 the most frequent allele was C (54%) while the most frequent genotype was CT (46%). In this study we demonstrate the lack of significant association between two these polymorphisms and clinical response to valsartan (P >0.05).

KEY WORDS: AGT Gen, polymorphism, essential hypertension, valsartan, Iraq

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INTRODUCTION

Essential hypertension is a complex illness influenced by both genetics and the environment. It has been postulated that the renin-angiotensin system (RAS) controls blood pressure. Through its interaction with renin, the protein angiotensinogen (AGT) generates angiotensin I, the prohormone of angiotensin II, which is then used to form angiotensin II, the primary effector molecule of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II (Ang II)'s inactive precursor is called angiotensinogen (AGT). Valsartan is typically used as a first-line treatment in patients with hypertension, despite the fact that therapeutic efficacy demonstrates inter individual variation in this patient population. High blood pressure, often known as hypertension, occurs when arterial blood pressure is consistently elevated to 140/90 mm Hg or greater. It's common, but if left untreated, it can be quite dangerous. Hypertension affects almost two-thirds of the world's 1.28 billion adults 30-79, all of whom live in low- and middle-income countries. Roughly 50% of people with hypertension are unaware that they have the condition. Less than half of adults 42% have been diagnosed with hypertension. Twenty percent or so of those who suffer from hypertension manage to keep it under control. Hypertension is a prominent cause of death among individuals around the world. One of the global targets for non-communicable illnesses is a 33 percent decrease in hypertension prevalence between 2010 and 2030. There may be no outward signs of hypertension in some patients [1].

Risk factors for hypertension include age, family history, body mass index (BMI), inactivity, food heavy in salt, and alcohol consumption. Changes in nutrition, smoking cessation, and increased physical activity have all been linked to reduced blood pressure. Some individuals might still benefit from taking medication. Blood pressure is measured using two numbers. Systolic pressure, or the pressure in the arteries during a complete cardiac contraction, is represented by the first value. The arterial pressure measured while

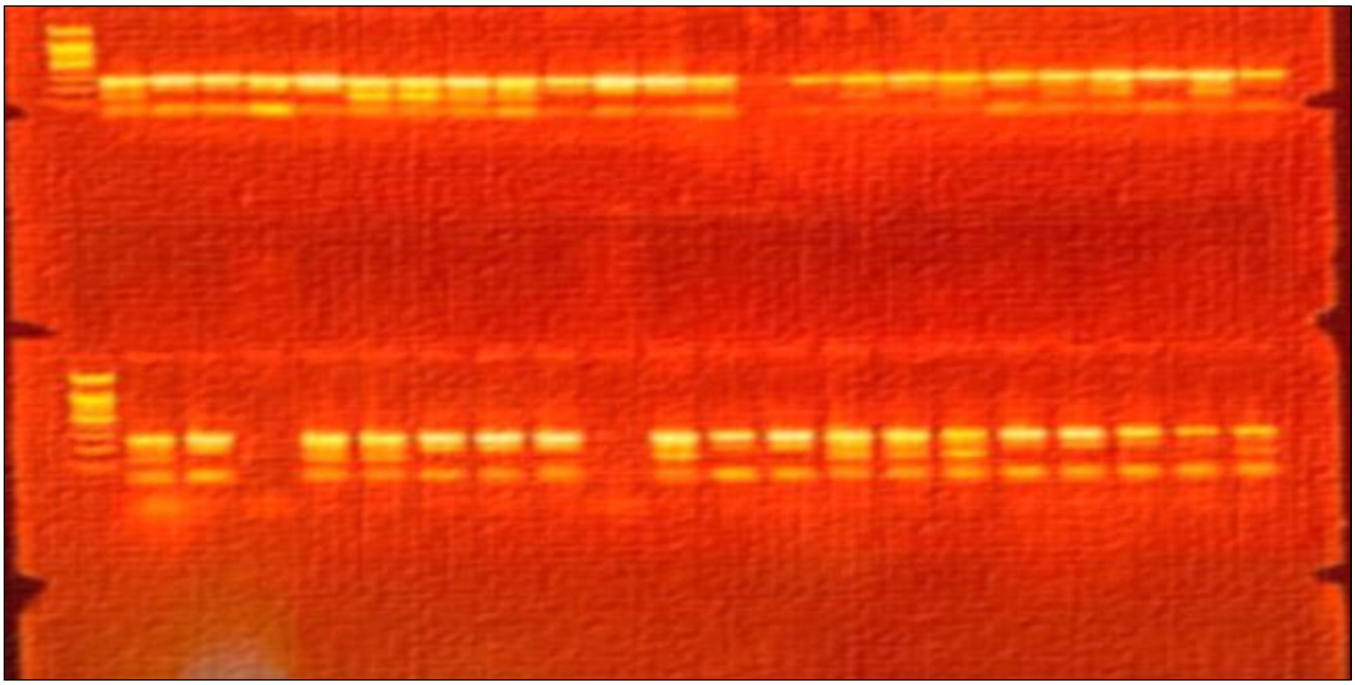

Fig. 1. The PCR product analysis of the AGT (rs5051) gene in a patient's blood, visualized on an agarose gel electrophoresis.

the heart is at rest (during diastole) is called diastolic blood pressure. Two separate measurements of blood pressure that show a systolic pressure of more than or equal to 140 mm Hg and/or a diastolic pressure of more than or equal to 90 mm Hg indicate the presence of hypertension (HTN), a condition that raises the risk of cardiovascular disease, kidney disease, neurological disease, and death. Early detection and intervention may mitigate the severity of this health issue.

According to the World Health Organization, hypertension affects up to 40 percent of Iraqis less than 25 years old, with a higher prevalence among females [2]. Prevalence estimates for HTN among patients aged 60 and over vary widely across Iraq, from 88.8% in Erbil (2019) [3] to 77.8% in Nasiriya (2014) [4] to 63.5% in Bagdad (2019) [4]. Over the past decade, Iraq was one of the Eastern Mediterranean countries caught up in a whirlwind of unrest, war, and other armed conflicts that has had a significant negative influence on the country's mental and physical health. Destruction of the health care system, absence of medical care, and health services contributed to and exacerbated many social and health problems during and after the conflicts and unstable situations. These variables may be contributing to the rising rate of hypertension in Iraq. There is evidence to suggest that being overweight is one of the leading causes of high blood pressure. It's possible that HTN and obesity are connected in Iraq because of the country's eating habits [5]. Since AGT was initially linked to the condition, it is possible that it is still "the most scrutinized" gene in this connection. Liver, adipose tissue, heart, vessel wall, brain, and kidney are only some of the tissues that express it, and their expression varies from cell to cell. AGT is expressed by astrocytes and certain neurons in the brain, hepatocytes in the liver, adipocytes in the adipose tissue, and epithelial cells in the proximal tubule of the kidney. The human AGT gene is a small 12 kb in size (starting at nucleotide 22715602) and is situated on chromosome 1 (1q42-q43) [6]. Drugs like valsartan, telmisartan, candesartan, losartan, olmesartan, and irbesartan all fall under the category of angiotensin II receptor blockers (ARBs). Hypertensive effects, including as vasoconstriction, promotion of aldosterone and ADH synthesis, cardiac stimulation, and renal reabsorption of sodium, are blocked by ARBs via binding preferentially to angiotensin receptor 1 (AT1). Reduced blood pressure, decreased aldosterone levels, decreased cardiac activity, and enhanced sodium excretion are all results of valsartan's physiologic effects [7].

AIM

The aim of this research is to ascertain if AGT polymorphism [rs699 (T235M), rs5051 (A-6G)] affects the success of valsartan treatment for essential hypertension in Iraqi patients.

MATERIALS AND METHODS

STUDY DESIGN, PATIENTS' RECRUITMENT, SETTING AND TIMING

Patients with hypertension diagnosed in accordance with ESH 2023 are the focus of this observational cross-sectional

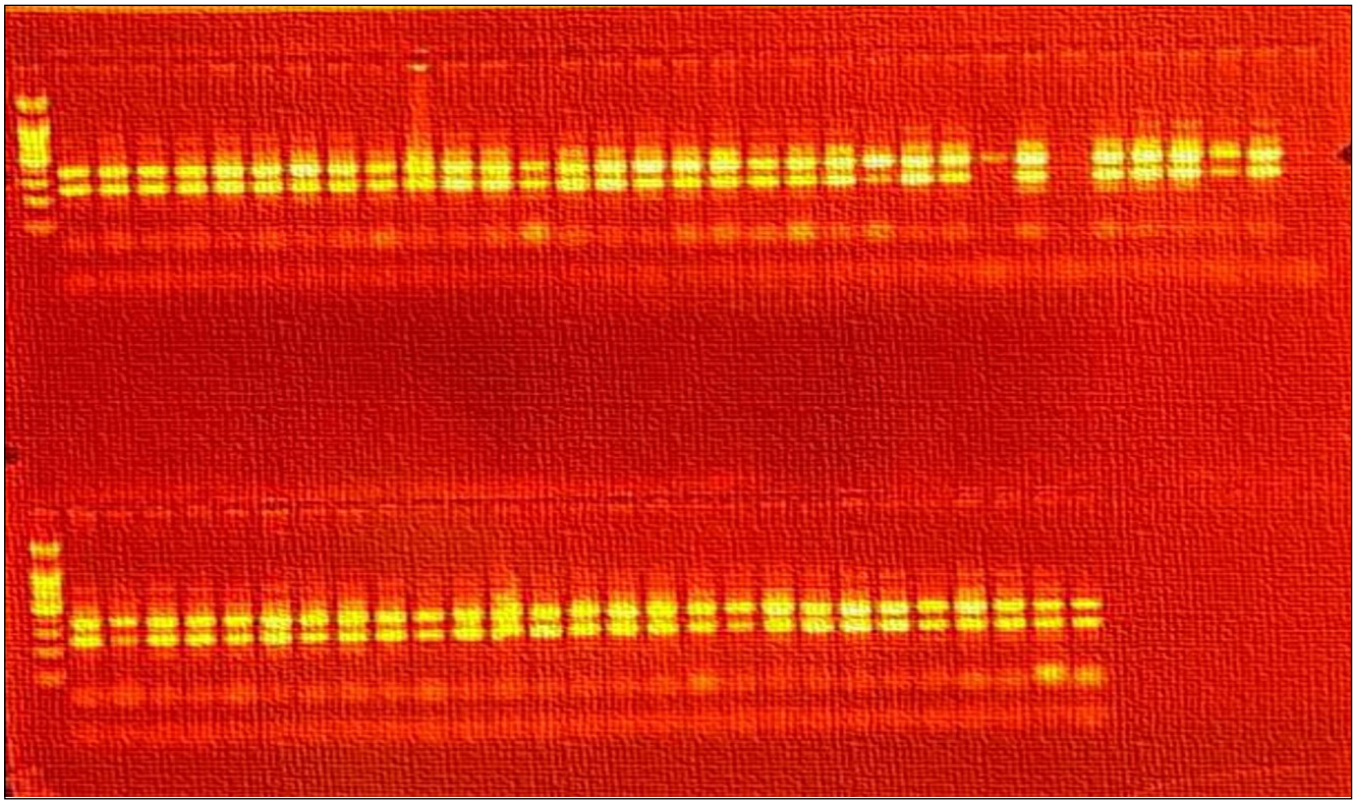

Fig. 2. The PCR product analysis of the AGT (rs699) gene in a patient's blood, visualized on an agarose gel electrophoresis.

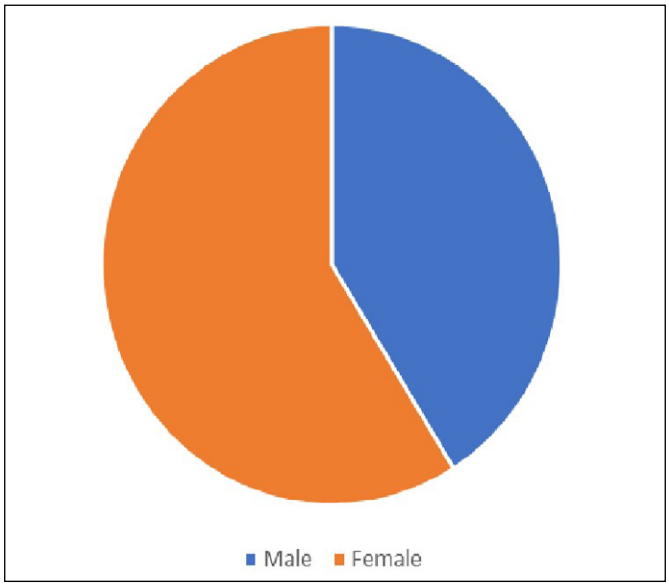

Fig. 3. Gender distribution of hypertensive patients participating in the study (n=90).

descriptive single-center study. All eligible patients were identified and recruited by a cardiologist or other cardiology professional. The study was conducted at the University of Al-Qadisiyah's College of Medicine and the Al-Diwaniyah Teaching Hospital in Iraq between July 2022 and July 2023. The experiments were carried out in the Department of Pharmacology and Therapeutics in the College of Medicine at Al-Qadisiyah University in Diwaniyah province. After receiving thorough and accurate information about the research design and purpose, all participants will be asked for their written informed consent prior to registration. Participants ranged in age from 20 to 70, with all having been diagnosed with essential hypertension. There were 90 participants in total.

QUESTIONNAIRE FORMULA

Information was taken from the patients: name, age, sex, race, weight, length, BMI, SBP, DBP, comorbidities (smoker, DM, IHD). and biochemical parameters were being measured for all patients with valsartan which were: urea, creatinine, uric acid, glucose serumlipid (LDL, HDL, total cholesterol, triglyceride, atherogenic index), aldosterone level, renin level, aldosterone/renin ratio and angiotensinogen level.

ETHICAL CONSIDERATIONS

The trial was approved by the Ethics Committee of the College of Medicine at Al-Qadisiyah University, and prior to patient enrolment, all methods were explained in detail, and informed permission was obtained.

PRIMERS USED IN THE CURRENT STUDY

Polymerase chain reaction (PCR) primers for *AGT (rs699)* and *AGT (rs5051)* gene were built using the Integrated

Table 1. The PCR primers with their sequence, amplicon size and annealing temp

Primer	Sequence	Amplicon	Annealing
AGT Rs5051 x	Inner forward CAGAACAACGGCAGCTTCTTCCACC	C-allele 173 bp.	66 °C
	Inner reverse TAAATAGGGCATCGTGACCCGGACA	T-allele 253 bp.	
	Outer forward TCCTCCTGTAAGACCCCAGGTGGG	Two outer primers 376 bp.	
	Outer reverse CGTGAGTGTCGCTTCTGGCATCTGT		
AGT Rs699	Inner forward GCTGTCCACACTGGCTCACG	G- allele 169 bp.	63 °C
	Inner reverse ATGGAAGACTGGCTGCTCCCTTAT	A-allele 122 bp.	
	Outer forward GATACTAAGTCCTAGGGCCAGAGCCA	Two outer primers 247 bp.	
	Outer reverse CTGAAGCAGCCGTTTGTGCA		

Table 2. Chemicals, manufacturers, and countries of origin used in this investigation

No.	Chemical materials	Company and Origin
1	TBE buffer	Intron (Korea)
2	Agarose	MarLiJu (Korea)
3	Ethidium bromide	BioBasic (Canada)
4	Ladder	Bioneer (Korea)
5	Primers	Macrogen (Korea)

DNA Technologies (IDT) website and National Center for Biotechnology Information data (NCBI). The primers were designed especially for this study using information for SNP sequence available online SNP data and online tool for tetra arms primer design and for sequence SNP primer design. In addition, the BLAST gene bank tool was utilized to check that the provided primers were complementary to the target gene and not the non-targeted gene. The lyophilized primers were dissolved in deionized distilled water (DDH2O) in the master tube to achieve 100 pmol/µl, and then 10 pmol/l was created as a working solution by transferring 10 l from the master tube to another tube and completing the volume to 100 l by adding DDH2O. Table 1 displays the primers provided by Bioneer Company, Korea.

CHEMICALS USED IN THE CURRENT STUDY

The chemical materials that were used in this study have been demonstrated with the corresponding country of origin and manufacturing company (Table 2).

BLOOD SAMPLING

Four milliliters of blood were taken from the patient's antecubital veins; one milliliter was placed in a tube containing EDTA for DNA extraction; and the tube was kept at -20 degrees Celsius until the time of DNA extraction. The serum was separated from the remaining 3 ml of blood by centrifuging it at 5,000 RPM for 5 minutes. This was done so that it could be used in biochemical tests.

BLOOD PRESSURE MEASUREMENT

A mercury sphygmomanometer was used to assess the subjects' blood pressure (BP). The respondent was asked to sit quietly for 5 minutes with his legs crossed and his right arm exposed to allow accurate measurements to be taken. Then the right hand was placed on the table with the palm facing up. The right size cuff was chosen. While readings were taken, the cuff was maintained at the same height as the patient's heart. The ESH classification is used to categorize patients (Table 3).

Score for BP control or response [8]

- Good Responders: were defined as patients that achieved a target BP in which (SBP < 140 mm Hg or DBP < 90 mm Hg).
- Moderate responders: were defined as patient that BP 150/100 mm Hg.
- Poor responders: were defined as patients that BP > 150/100 mm Hg.

GENOTYPING

Genomic DNA was extracted using gene aid DNA extraction kit (USA).

PCR – TETRA ARM TECHNIQUE

The PCR-TETRA ARM technique was performed for genotyping and detecting AGT (rs699) and AGT (rs5051)

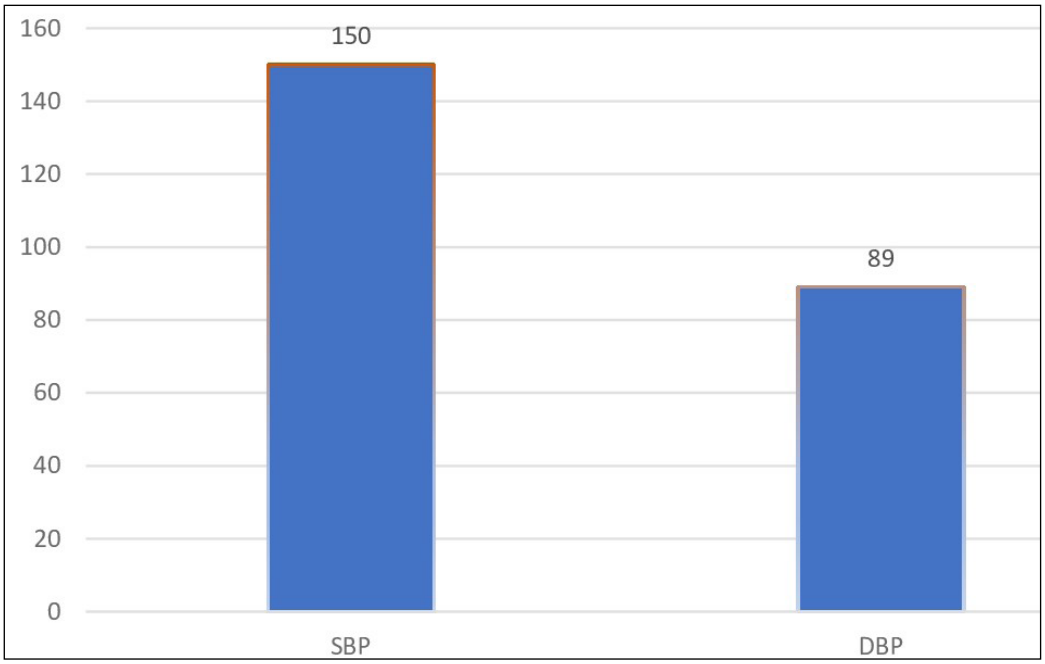

Fig. 4. Mean systolic and diastolic blood pressure of recruited hypertensive patients (n=90) who were took valsartan 160 mg/day. SBP – systolic blood pressure, DBP – diastolic blood pressure.

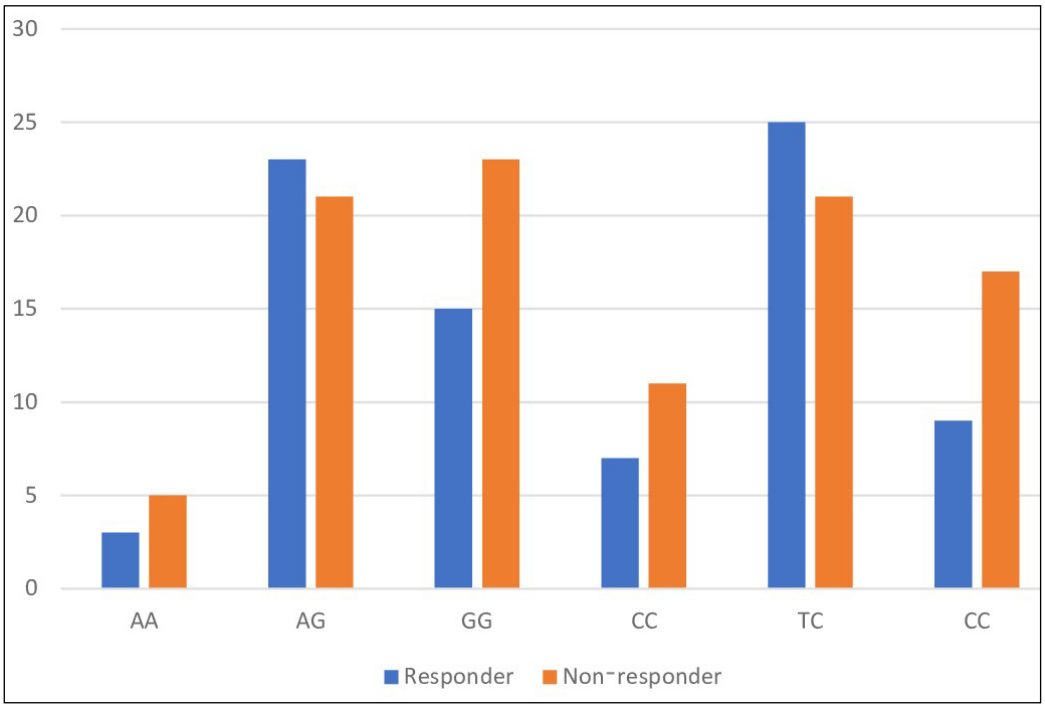

Fig. 5. Shows responder (< 140/90 mmHg) and non-responder (>140/90 mmHg) of Iraqi hypertensive patients with AGT rs699 (T235M) and rs45051 (A-6G) polymorphisms taken valsartan 160 mg/day.

gene polymorphism in blood samples of human. PCR reactions were performed by using Accupower kit (Bioneer, Korea) (Fig. 1, 2).

GENOTYPE

Table 4 show characteristics and consequences of the AGT SNPs in pathway of Angiotensin synthesis and their drug response data from pharm GKB.

STATISTICAL ANALYSIS

A mean and standard deviation (SD) were used to represent the data. Statistical analysis was performed using SPSS version 26. Analysis of variances (one-way ANOVA) was used to compare more than two means. The Fissure exact test and the Chi-square were used to see if there was a significant difference in demographic data between the two sets of categorical data. The allele frequencies of hypertensive patients and An-

Table 3. 2023 ESH classification of hypertension

Blood Pressure Category	Systolic Blood Pressure(mmHg)	Diastolic Blood Pressure(mmHg)
Optimal	<120	and <80
Normal	120-129	and 80-84
High normal	130-139	and /or 85-89
Stage 1 hypertension	140 – 159	and /or 90-99
Stage 2 hypertension	160-179	and /or 100-109
Stage 3 hypertension	≥180	and /or ≥110
Isolated systolic hypertension	≥140	and<90
Isolated diastolic hypertension	<140	and ≥90

Table 4. Characteristics and consequences of the AGT SNPs in pathway of angiotensin synthesis

Gene	Genomic position	Variation type	SNP ID	alleles	Effect	Pathway
AGT	Chrom 1 (intron)	SNP	Rs5051	C>T	T was associated with elevated plasma angiotensinogen levels and increased risk of elevated blood pressure	enzyme
		SNP	Rs699	A>G	G was associated with elevated plasma angiotensinogen levels and increased risk of elevated blood pressure	

Table 5. Illustrating values of blood urea, serum creatinine and metabolic profiles characteristics of recruited hypertensive patients (n = 90) taken valsartan 160 mg/day

	Minimum	Maximum	Mean	Standard Deviation
Blood urea	16.8	60	36.9	9.3
Creatinine	0.45	1.4	0.9	0.2
Cholesterol	105.0	357.0	195.9	44.8
Triglyceride	91.0	722.0	223.7	105.7
Atherogenic Index	0.3	2.7	0.7	0.3
Uric acid	2.9	12.5	5.2	1.5

Table 6. Effect of AGT rs699 (T235M) polymorphism on systolic and diastolic blood pressure in Iraqi hypertensive patients taken valsartan 160 mg/day

Genotype rs699	Systolic BP (mm/Hg)		P value	Diastolic BP (mm/Hg)		P value
	mean	SE		mean	SE	
AA	154	3.4		90	1.4	
AG	148	2,2	0.7^{NS}	88	1.05	0.08^{NS}
GG	151	2.9		89	1.4	

^{NS} – non significant

Table 7. Effect of AGT rs5051 (A-6G) polymorphism on systolic and diastolic blood pressure in Iraqi hypertensive patients taken valsartan 160 mg/day

Genotype rs5051	Systolic BP (mm/Hg)		P value	Diastolic BP (mm/Hg)		P value
	mean	SE		mean	SE	
CC	144	4.7	0.3^{NS}	88	1.4	0.6^{NS}
CT	152	1.9		89	0.9	
TT	149	2.8		90	1.2	

^{NS} – non significant

giotensinogen level were compared using odds ratios (ORs) and 95% confidence intervals (CIs). There was a statistically significant probability value (P value) in all statistical analyzes in this study at the p≤0.05 level. A Hardy – Weinberg law this law state that the allele and genotype frequencies in a population will remain constant from generation to generation in the absence of evolutionary influences.

Table 8. Association between AGT rs699 (T235M) and rs5051 (A-6G) polymorphism with responsiveness to valsartan 160 mg/day in Iraqi hypertensive patients [responder (<140 mmHg), non-responder (≥ 140 mmHg)

	Rs699			P value	Rs5051			P value
	AA	AG	GG		CC	CT	TT	
Responder	23	23	15	0.4^{NS}	9	25	7	0.2^{NS}
Nonresponder	5	21	23		17	21	17	

^{NS} – non significant

RESULT

DEMOGRAPHIC DATA

This study included 90 Iraqi hypertensive patients, 58.9% (n=53) females and 41.1% (n=37) males, with a mean ± SD of age (years) 53.2 ± 13.8 years old, and mean ± SD of BMI 29 ± 5.32 kg/m^2 (Fig.3).

METABOLIC PROFILE

Among study patients, the mean ± SD of total serum cholesterol, triglyceride, atherogenic index and uric acid was 195.8 ± 44.8 mg/dL, 223.7 ± 105.7 mg/dL, 0.7 ± 0.3, 5.2 ± 1.5 mg/dL respectively (Table 5).

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) (Fig.4).

EFFECT OF AGT POLYMORPHISM RS699 (T235M) ON BLOOD PRESSURE

Table 6 displays that there was no significant difference between the systolic blood pressures of patients who were homozygous for allele A (AA), heterozygous for allele G (AG), or homozygous for allele G (GG), with a P value of 0.7. However, the average diastolic BP of AA homozygotes, AG heterozygotes, and GG homozygotes was 90±1.4/88±1.05/89±1.4 mm/Hg, with a P-value of 0.08. AGT rs699 did not influence blood pressure on either the systolic or diastolic side.

EFFECT OF AGT POLYMORPHISM RS5051 (A-6G) ON BLOOD PRESSURE

Table 7 displays the mean±SE of systolic blood pressure of patients who were carriers of the CC allele, the CT allele, and the TT allele. The significance level was 0.3. However, the average diastolic BP of CC homozygotes, CT heterozygotes, and TT homozygotes was 88±1.4/89±0.9/90±1.2 mm/Hg (P=0.6) respectively. Systolic and diastolic blood pressure was not affected by AGT rs5051 in a statistically meaningful way.

EFFECT OF AGT POLYMORPHISM RS699 (T235M) AND RS 5051 (A-6G) ON VALSARTAN RESPONSIVENESS

The allelic and genotypic frequency of AGT polymorphism rs699 and rs5051 doesn't showed significant association between polymorphism and responsiveness to valsartan (Table 8, Fig.5).

DISCUSSION

GENOTYPE/PHENOTYPE RELATIONSHIP AND IMPACT OF AGT GENE RS699 AND RS5051 ON VALSARTAN EFFECT

Angiotensinogen concentration was shown to be significantly (P=0.001) related to rs699 genotype frequency. The AA genotype was found to have angiotensinogen levels that were lower than the GG genotype 2.9 ng/dl. There is no correlation between the rs699 AGT polymorphism and valsartan sensitivity, as measured by allelic and genotypic frequency. There was no significant difference between the GG genotype (15 responses, 23 non-responses) and the AA genotype (23 responses, 5 non-responses), P=0.4. There is no correlation between the rs5051 AGT polymorphism and valsartan sensitivity, as measured by allelic and genotypic frequency. We obtained a P value of 0.2 between the CC genotype (9 responses, 11 non-responses) and the TT genotype (7 responses, 17 non-responses. In this study, we discovered that polymorphism (rs5051 C>T and rs699 A>G) was significantly associated with angiotensinogen level in Iraqi patients with essential hypertension, but snps (rs5051 C>T and rs699 A>G) were not. There is not enough information to say whether or not the AGT gene (-20 A/C, -6 A/G) affects the effectiveness of antihypertensive drug treatment at this time. Here, we analyzed

the relationship between telmisartan's antihypertensive efficacy and the -6 A/G and -20 A/C polymorphisms in the AGT gene promoter region in Han patients with mild and severe hypertension for eight weeks [9, 10]. No association between telmisartan's antihypertensive impact and the AGT-6 A/G or -20 A/C genotypes was found. The available evidence does not support the AGT (M235T) variant's association with ARBs' blood pressure-lowering effects. Another study of the same AGT variant in Swedish patients with hypertension found that homozygous carriers of the AA alleles responded best to treatment with atenolol (17 mmHg compared to 3 mmHg for homozygous carriers of the GG variant), while there was no difference in response by genotype after treatment with the ARB irbesartan 80 mg [11, 12]. In addition to rs698, which results in the replacement of Thr235 for Met in AGT, rs699 has been widely researched in relation to therapy response in hypertension. We found no indication of a substantial difference in BP responses to multiple antihypertensive medications based on the AGT Met235Thr polymorphism genotype, which is consistent with the majority of previous studies [13]. Increased responsiveness to angiotensin II has been seen in individuals with the C allele of the AGTR1 polymorphism, which has also been linked to hypertension [14]. African-American women with the A/A genotype of AGTR1 have been demonstrated to have better blood pressure responses to HCT, however for losartan, it has been hypothesized that the C allele supports higher BP response. The study's limited sample size calls for additional prospective research to confirm the findings [15].

GENOTYPE/PHENOTYPE RELATIONSHIP AND IMPACT OF AGT GENE RS699 AND RS5051 ON BLOOD PRESSURE

Systolic blood pressure in this study was found to be similar across persons who were homozygous for allele A (AA), heterozygous for allele G (AG), and homozygous for allele G (GG), with a matching P value of 0.7. The average diastolic blood pressure of AA homozygotes, AG heterozygotes, and GG homozygotes was 90±1.4, 88±1.05, 89±1.4 mmHg, respectively (P=0.08). AGT rs699 did not influence blood pressure on either the systolic or diastolic side. Patients who were either homozygous for the CC allele or heterozygous for the CT allele had systolic blood pressure readings of 144±4.7 mmHg, 152±1.9 mmHg, and 149±2.9 mmHg, respectively (P=0.3), however, the average diastolic BP of CC homozygotes, TT heterozygotes, and TT homozygotes was 88±1.4/90±1.2 mmHg. The probability coefficient was 0.60. AGT rs5051 did not have a detectable impact. In this study of Iraqi patients with essential hypertension, we found no evidence of a link between polymorphism (rs5051 C>T and rs699 A>G) and systolic or diastolic blood pressure. Importantly, recent research has found that systolic blood pressure is significantly associated with rs5051 C>T and/or rs699 A>G in Black people in the UK Biobank, with a 4-fold bigger impact size than that identified in White participants [16,17]. Notably, rs699 A>G and rs5051 C>T allele frequencies are around twice as common in people of African ancestry as they are in people of European heritage. Minor allele frequencies aren't the only thing that vary between Whites and Blacks; it's also been established that the linkage disequilibrium blocks of AGT are different [18]. It is possible that rs5051 C>T or rs699 A>G mediate blood pressure changes more significantly in Black patients due to variations in AGT expression or abundance, given that salt-sensitive hypertensive phenotypes are more common in people of African ancestry [19]. Patients of African descent respond better to calcium channel blockers and diuretics than beta-blockers or RAS acting antihypertensive [20, 21] because of their reduced plasma renin activity and retained aldosterone levels. In line with this idea, the Eighth Joint National Committee (JNC 8) recommends distinct courses of first antihypertensive treatment for Caucasian and Black patients. The JNC only recommends angiotensin converting enzyme inhibitors as first-line therapy in Caucasian patients with normal kidney function [22]. Here, we present evidence that the genetic variants rs5051 C>T and rs699 A>G may be linked in the recognized discrepancies in antihypertensive medication efficacy between people of European and African ancestry. Despite this, there is substantial mixing among populations. This type of research will allow doctors to stop using racial identity as a stand-in for genotype [23] once whole genome sequencing becomes more widely available in clinical care. The AGTR1 1166 A/C and ACE I/D polymorphisms were not associated with BP responses. Studies on the AGT Met235Thr polymorphisms have shown that patients with the AGT 235Thr allele have a better response to beta-blockers and angiotensin-converting enzyme (ACE) inhibitors [24, 25], while other studies have found no gene-drug interaction between AGT Met235Thr genotypes and BP response to beta-blockers, ACE inhibitors, calcium channel antagonists, or angiotensin receptor blockers. We found no statistically significant association between the AGT Met235Thr genotype and blood pressure (BP) response to multiple antihypertensive medicines, which is in line with previous studies [26].

CONCLUSIONS

Our result showed the most common allele for rs699 was G allele (67%) while the most frequent genotype

was AG (49%), frequency of another genotype GG and AA were 38% and 8% respectively. Regarding rs5051 the most frequent allele was C (54%) while the most frequent genotype was CT (46%), frequency of other genotypes TT and CC were 2% and 29% respectively. In this study we demonstrate the lack of significant association between two these polymorphisms and clinical response to valsartan.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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