Genetic polymorphism of angiotensin II type 1 receptors and their Effect on the clinical outcome of captopril treatment in Arab Iraqi patients with acute coronary syndrome (Mid Euphrates)

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Abstract

Genetic variation in the angiotensin II type 1 receptor (AT1R) has an important effect on the outcome of acute coronary syndrome (ACS) initiated treatment with captopril. This study aims to investigate the impact of genetic polymorphism of AT1R rs5186 and rs275651 on the ACS outcome in Iraqi patients treated with captopril. A total of 250 Iraqi individuals with ACS were included in this case - control study and they were divided into two study groups; Study group 1 included 125 participants who were prescribed captopril 25 mg twice daily and study group 2 included 125 participants who received no captopril as part of their ACS treatment (control study). The AT1R gene (rs5186) CC genotype was found to be associated with ST-elevation myocardial infarction (STEMI) (Odd's ratio (OR)= OR=1.2, P=0.7), while AC was associated with Non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) (OR=1.2, P=0.8). AC genotype is more prone to have Percutaneous coronary intervention (PCI) after ACS attack (OR=1.2, P=0.6). CC genotype had a risk to get less improvement (OR=1.6, P=0.5), so might require higher doses of captopril during acute coronary insult. The AT1R gene (rs275651) AA genotype was associated with UA (OR=1.3, P=0.9). AA and AT genotypes were more prone to have PCI after ACS attack (OR=3.9 P=0.2, OR=3.5 P=0.3 respectively) and thus requiring higher doses of captopril. We conclude that the AT1R rs5186, rs275651 genetic polymorphisms might partially affect the clinical outcome of ACS patients treated with captopril and might have captopril resistance which requires higher doses.

Keywords: AT1R; genetic polymorphism; captopril; acute coronary syndrome; renin-angiotensin-aldosterone system.

Introduction

Acute coronary syndrome (ACS) carries higher rates of morbidity and significant mortality despite of having recent advances in the diagnosis and management technology [1, 2].

Interaction between environmental and genetic factors is responsible for the development of ACS which is a multi-factorial disorder, thus it results from various combinations of gene-gene and gene-environment interactions [3, 4].

The most common method used to identify the genetic variables that are linked with the ACS is the single-nucleotide polymorphism (SNP). SNP present at a frequency of greater than 1% in the normal population are identified in the candidate gene and genotyped in a group of patients (cases) and in controls, then the genotypes and allele frequencies are analyzed, and an association between them and the disease is formed, if the presence is statistically significant between cases and control [5, 6].

The renin-angiotensin-aldosterone system (RAAS) is the most important system that controls the blood pressure, fluid volume, and sodium-potassium balance [7]. Angiotensin II is the most potent vasoconstrictive and inflammatory component of the RAAS. Most of its pressor, inflammatory, and proliferative actions are regulated by AT1R which is expressed in the myocardium [8].

AT1R A1166C gene polymorphism has been found to be associated with the myocardial infarction risk, there was a significant association between C allele and myocardial infarction susceptibility whereas AA genotype was protective [9]. In China, it has been stated that individuals carrying C allele and CC genotype had increased risk of coronary artery disease (CAD) compared to those with AA genotype [10]. A meta-analysis showed that the A1166C polymorphism has been related with a statistically increased hypertension risk in Asian and Caucasian populations but not in Africans [11]. AT1R A1166C polymorphism was markedly associated with left ventricle end diastole, end systole dimensions, and mean left ventricular ejection fraction, the study suggests that AT1 A1166C polymorphism may play an important role in conferring genetic susceptibility to left ventricular dysfunction, whereas another study found that AA genotype was significantly associated with hypertension in Turkish population [12, 13].

Despite the progressive advances in cardiovascular pharmacology still there is enough inter-individual variation in drug response regarding both efficacy and safety profiles. Drug-gene associations are

considered as significant factor determining a spectrum of response to therapy [14]. ACE activity is highly affected by the variations of genes at the ACE loci in hypertensive subjects, identification of genetic variations among individuals is an important Approach to differentiate between ACE-inhibitor responders from non-responders [15, 16].

According to our best knowledge, this is the first pharmaco-genomics study in Iraq, reporting the genotype and allele frequency of AT1R gene and their impact on captopril effectiveness on ACS outcome in Arab Iraqi population of Mid-Euphrates. This paper will also discuss the correlation between different types of ACS and their respective genetic polymorphism frequencies [17].

Materials and Methods

Study Population

This case control study was conducted from January 2016 to March 2018 with 250 patients (both males and females). The participants were Arabic Iraqis aged between 30-60 years diagnosed with ACS according to diagnostic algorithms for ACS [18]. All of them were included from the Coronary Care Unit (CCU) of AL-Sader Teaching Hospital in Najaf government, and Al-Diwanyah teaching hospital in Al-Diwanyah government, Iraq.

The cases group included 125 patients with 77 men and 48 women who were kept on captopril 25 mg twice daily upon CCU admission in addition to the traditional treatment of ACS. The traditional treatment of ACS includes patient's stabilization, control of the ischemic pain. Antithrombotic therapy is necessary to reduce further myocardial damage and prevent additional ischemia. Sedatives, oxygen supply, sublingual (or intravenous nitro-glycerin). A loading dose of soluble aspirin, and clopidogrel are given as initial treatment [19].

The control group had 125 patients with 76 men and 49 women, similar with cases in terms of age and gender diagnosed with ACS and was prescribed with traditional treatment of ACS except for captopril. Patients with diabetes mellitus, renal or hepatic impairment, pregnancy, heart failure, captopril contraindication (hypersensitivity to captopril, angioneurotic edema after other ACE inhibitors, bilateral renal artery stenosis) were excluded from the study. Patients already used captopril prior to CCU admission, and patients with mental disorders were not included for the study.

Informed consent

Informed consent was obtained from all individual participants included in the study.

All patients were diagnosed during their CCU stay nearly for 3-4 days for vital signs (pulse rate PR, blood pressure BP) on admission and discharge along with the assessment of clinical outcomes (improvement of symptoms, need for Percutaneous coronary intervention (PCI), development of arrhythmia, or development of heart failure HF).

Biochemistry

After 12 hour fasting, five milliliters of venous blood samples were withdrawn from all participants after 48 hours of captopril initial dose. Ethylenediaminetetraacetic acid (EDTA) tubes were used to store blood for the determination of different genotypes of AT1R gene by polymerase chain reaction (PCR).

DNA extraction and Genotyping

Genomic DNA from blood samples was extracted by using genomic DNA mini extraction kit (Frozen Blood) Geneaid, USA.

PCR-RFLP method was used for genotyping the SNPs. The PCR was performed by taking of 5µl of DNA template+1.5µl of forward primer+1.5µl of the reverse+12µl of PCR water kept in standard Accu Power PCR PreMix Kit which contains Taq DNA polymerase, dNTPs, Tris-HCl pH: 9.0, KCl, $MgCl_2$ and loading dye. After digestion, PCR products were separated on a 1% agarose gel to determine the genotypes.

Statistical analysis: Mean ± standard error (SE) were measured for quantitative variables. Chi-square test was used for the statistical representation of categorical variables (gender, types of ACS, and the clinical outcome). Student t-tests and one-way ANOVA tests were used to compared the study groups.

Results

Demographic and laboratory data of participants are presented in **Table 1.** No significant differences in demographic and clinical variables were noticed between cases and control groups, except the plasma angiotensin II level which is highly significant (P-Value=0.0001).

The genotype and allele frequencies of AT1R (rs5186 & rs275651) genes

The genotypes and allele frequencies of both genes were not significantly differed between cases and control groups and all were consistent with Hardy-Weinberg equilibrium. However, there were generally less AC and CC genotypes in the captopril treated group as compared to the normal control group, however, this was not statistically significant (P>0.05). Figure 1 A shows the Restriction Fragment Length Polymorphism (RFLP) for the AT1R (rs5186) using DdeI restriction, Figure 1 A.

There was more AA genotype in the captopril treated group as compared to the normal control group, however, this was not statistically significant (P>0.05). At genotype, from the other side, was less in the captopril treated group as compared to the control group (P>0.05). Figure 1 B shows the RFLP for the AT1R (rs2756515186) using AluI restriction, Figure 2.

Relation of different Genotypes of AT1R (rs5186 & rs275651) with the type of ACS

Table 2 compares the association of different rs5186 genotypes with the incidence of ACS. The CC genotype have 1.2 fold increment in STEMI risk as compared to the AA and AC genotypes, P=0.7. However, the AC genotype have 1.2-folds increased risk of developing NSTEMI when compared to both AA and CC genotypes, P=0.8. The unstable angina (UA) incidence appears to be much higher (1.2 folds) in the AC genotype but it was much less in the CC genotype (less than 50%) when compared to the AA genotype, P=0.8 (**Table 2**).

No risk detected among both AA, AT genotypes to have STEMI over the TT genotype carriers. As for NSTEMI, there was no significant difference in occurrence among different genotypes in cases and control groups. However, UA appears to be much higher (1.3 folds) among the AA carriers as compared to the TT genotype, P=0.9 (**Table 2**).

Relation of different Genotypes of AT1R gene (rs5186 & rs275651) with the clinical outcome

There was no significant variation in the number and percentage of patients improved in the captopril treated cases and the control groups (P-Value more than 0.05). However, the CC genotype less improved when compared to the AA, AC genotypes. There was also a borderline difference in number and percentage of patients underwent PCI for CC genotype between cases and control groups while AC genotype has 1.2 increased risks to undergo PCI post ACS attack, P=0.6. No significant difference in number and percent of patients getting Heart Failure or Arrhythmias in cases and control groups (**Table 3**).

There was no significant difference between the two study groups among the three different genotypes (AA, AT and TT), (P value > 0.05). However, the AA, AT genotypes have more risk to develop PCI (OR=3.9 fold P=0.2, OR=3.5 fold P=0.3 respectively) when compared with TT genotype, (**Table 3**).

Discussion

ACS is a global public health concern since it has high prevalence and poor prognosis with high rate of morbidity and significant mortality [20]. CHD deaths in Iraq reached 32,582 (18.50%) of total deaths according to the latest WHO data published in 2017 which will necessitate ongoing improvements in patient management and follow up to minimize the disease complications and improve the disease outcome [21].

Genetic factors have significant function in the etiology of complex and multifactorial diseases like the CAD. The most important genetic factors are the genetic polymorphism of the RAAS together with biochemical and environmental risk factors play an important role in the onset of CAD particularly AT1R genetic polymorphism. According to our knowledge, this is the first pharmaco-genomics study in Iraq and Arabic countries that demonstrate the association between AT1R genetic polymorphism and captopril treatment outcome in Arab Iraqi patients with ACS.

Various studies have suggested that the A/C1166 polymorphism of AT1R is a major risk factor for cardiovascular disorders. The AT1R mediate most harmful action of angiotensin II including the

process of vascular hypertrophy, sodium retention, cardiac remodeling, hypertension and fibrinogenesis [22]. Results of the studies reporting the role of AT1R gene A/C polymorphism as a risk factor for myocardial infarction are controversial. Some studies have reported a positive association, while other studies could not find this association [9, 10, 22, 23]. This controversy may be due to differences in study populations, genetic background, study design, reporting bias, and publishing bias.

In our study there was no significance in distribution of AA, AC and CC genotypes in cases and control groups (P-Value >0.05). However, there was no increment in risk among AC, CC genotypes (odd ratio<1) compared with AA genotype.

In addition, the CC genotype have 1.2-fold increment in STEMI risk while no risk detected among AC genotype. In a condition of NSEMI, AC genotype have 1.2-folds increased risk, while for UA no risk detected among CC carriers but among AC carriers the risk was increased also by 1.2- folds (Table 2). It has been shown that AT1R expression is markedly increased in the CC homozygotes in comparison to AA and AC genotype carriers [24]. The C allele and the AC/CC genotypes are associated with significantly increased risk of CHD [9, 10, 22]. CC genotype get a risk of 1.74-fold of essential hypertension in Indian population and it has found that the AT1R gene might serve as a predictive marker for the hypertension susceptibility and causes the risk of hypertension stratification [25]. No significant difference in number and percentage of patients improved in cases and control groups (P-Value more than 0.05). CC genotype has increased risk to get less improvement than AA, AC genotypes (Table 3).

The CC genotype of the A1166C polymorphism is associated with the increased ACE activity and cardiac troponin I levels with acute myocardial infarction, it affects serum ACE activity and causes the activation of cardiac sympathetic activity, leading to death of cardiac myocytes. The presence of the C allele of A1166C polymorphism will cause failure of down regulation of gene expression so there will be greater risk to develop hypertension, but when the major allele A1166 is present there will be down regulation of gene expression [26].

AT1R A1166C polymorphism has been associated with an increased response to angiotensin II in isolated human arteries. The A1166C mutation is in a non-translated region of the gene, and this A1166C polymorphism may be in linkage disequilibrium with a functional mutation that alters angiotensin II responsiveness [27].

CC genotype is more associated with STEMI, while AC is more associated with NSTEMI and UA, AC,CC genotypes are more prone to have PCI after ACS attack so in the same way may be in need for higher doses of captopril during acute coronary insult [28].

rs275651 is located in the 5′ region of the AT1R gene, it was not detected as a risk factor for hypertension, however in our study AA genotype is associated with UA of ACS, no other data about involvement of rs275651 in ACS available till now [28]. No risk detected among AA, AT to have STEMI or NSTEMI over TT genotype carriers, while for UA there is 1.3 folds increased risk among AA carriers. AA genotype is more prone to have UA.

Analysis of some selected genetic variants have been proposed for patients treated with ACEIs in order to assess the pharmaco-genetic risk stratification in order to tailor the treatment among those patients. rs275651 and rs5182 in the AT1 receptor gene are significant modifiers of the perindopril treatment effect [29]. AA, AT genotypes get more risk to have PCI (3.9, 3.5 folds respectively) as compared with TT genotype (OR>1).

Conclusions: The AT1R gene (rs 5186) CC genotype is more associated with STEMI while AC is more associated with NSTEMI and UA. In addition, the AC, CC genotypes are more prone to have PCI after ACS and may be in need for higher doses of captopril during acute coronary insult**.**

On the other hand, the AT1R (rs275651) AA genotype is more associated with UA. AA and AT genotypes are more prone to have PCI after ACS attack. Hence, we recommend the use of genetic analysis of the AT1R gene to be included as an additional step in the ACS management to adjust the appropriate therapeutic dose of captopril.

Declaration of interest

The authors have declared no conflicts of interest.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Faculty of Medicine, University of Kufa, reference number KUM456) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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TABLES

Table 1. Demographic and laboratory data (overall subjects).

Variable	Cases n=125	Control n=125	P-value
Age (years)	49.3 ± 0.7	49.5 ± 0.6	0.8
Gender			
Male (%)	85 (68%)	91 (72.8%)	0.9
Female (%)	40 (32%)	34 (27.2%)	
Mean pulse rate (beat/min) on admission	82.3 ± 0.7	80.8 ± 0.5	0.1
Mean pulse rate (beat/min) on discharge	71.1 ± 0.4	71.2 ± 0.4	0.9
Mean systolic blood pressure (mmHg) on admission	139.28 ± 1.1	140.9 ± 0.9	0.3
Mean systolic blood pressure (mmHg) on discharge	115.8 ± 1.1	115.9 ± 1.1	0.950
Mean diastolic blood pressure (mmHg) on admission	86.97 ± 1.1	87.5 ± 0.9	0.734
Mean diastolic blood pressure (mmHg) on discharge	67.2 ± 1.01	68.1 ± 0.9	0.5
Angiotensin II by ELISA (pg/ml)	0.9 ± 0.05	55.02 ± 1.5	0.0001

Table 2. Comparison of relation of different Genotypes of AT1R gene (rs5186 & rs275651) with the type of ACS.

TYPE	AA		AC		CC	
	Cases N (%)	**Controls N (%)**	**Cases N (%)**	**Controls N (%)**	**Cases N (%)**	**Controls N (%)**
			AT1R gene (rs5186)			
STEMI	58 (62.4%)	54 (58.1%)	26 (28%)	32(34.4%)	9 (9.7%)	7 (7.5%)
		1	OR=0.8 (0.4-1.4)		OR=1.2 (0.4-3.4)	
			P=0.4		P=0.7	
NSTEMI	10 (55.6%)	9 (50%)	8 (44.4%)	6 (33.3%)	0 (0%)	3 (16.7%)
		1	OR=1.2 (0.3- 4.8)		OR=---	
			P=0.8		P=0.2	
			AT1R gene (rs275651)			
TYPE	**AA**		**AT**		**TT**	
STEMI	63 (67.7%)	65 (69.9%)	25 (26.9%)	24 (25.8%)	5 (5.4%)	4 (4.3%)
		OR=0.8 (0.2-3.02)		OR=0.8 (0.2-3.5)		1
		P=0.7		P=0.8		
NSTEMI	13 (72.2%)	11 (61.1%)	5 (27.8%)	6 (33.3%)	0 (0%)	1 (5.6%)
		OR=--		OR=--		-
		P=0.4		P=0.6		
UA	9 (64.3%)	7 (50%)	4 (28.6%)	6 (42.9%)	1 (7.1%)	1 (7.1%)
		OR=1.3 (0.07-24.4)		OR=0.7 (0.03-14.3)		1
		P=0.9		P=0.8		

Table 3. Comparison of relation of different Genotypes of AT1R gene (rs5186 & rs275651) with the clinical outcome.

Outcome	AA		AC		CC	
	Case N (%)	Control N (%)	Case N (%)	Control N (%)	Case N (%)	Control N (%)
AT1R gene (rs5186)						
Improved	32 (61.5%)	19 (52.8%)	12 (23.1%)	14 (38.9%)	8 (15.4%)	3 (8.3%)
	1		OR=0.5 (0.2- 1.3) P=0.2		OR=1.6 (0.4- 6.7) P=0.5	
PCI	36 (59%)	38 (55.9%)	24 (39.3%)	21 (30.9%)	1 (1.6%)	9 (13.2%)
	1		OR=1.2 (1.6- 2.5) P=0.6		OR=0.1 (0.01-0.9) P=0.05	
HF	3 (50%)	6 (66.7%)	2 (33.3%)	3 (33.3%)	1 (16.7%)	0 (0%)
			OR=----- P=0.4		OR= --- P=0.3	
Arrhythmia	4 (66.7%)	7 (58.3%)	2 (33.3%)	5 (41.7%)	0	0
			OR=--- P=0.7		OR=--- P=0.8	
AT1R gene (rs275651)						
Outcome	**AA**		**AT**		**TT**	
Improved	37 (71.2%)	27 (75%)	11 (21.2%)	8 (22.2 %)	4 (7.7%)	1 (2.8%)
	OR=0.3 (0.04- 3.2) P=0.4		OR=0.3 (0.03-3.7) P=0.4		--	
PCI	41 (67.2%)	42 (61.8%)	19 (31.1%)	22 (32.4%)	1 (1.6%)	4 (5.9%)
	OR=3.9 (0.4-36.4) P=0.2		OR=3.5 (0.4-33.6) P=0.3		--	
HF	5 (83.3%)	6 (66.7%)	1 (16.7%)	2 (22.2%)	0 (0%)	1 (11.1%)
	OR=--- P=0.6		OR P=0.8			
Arrhythmia	2	8 (66.7%)	3 (50%)	4	1 (16.7%)	0 (0%)

	(33.3%)	(33.3%)
	OR=---	OR=----
	P=0.2	P=0.4