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The Effect Of Angiotensin 2 Receptor Type 1 Gene Polymorphisms On The Development Of Hepatorenal Syndrome

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Abstract

Background: Hepatorenal syndrome (HRS) is a kidney function defect that happens in severe chronic liver disorder, particularly in cases of liver cirrhosis. Angiotensin II type I receptor (AT1R) has been associated with liver steatosis and fibrosis. This study intended to investigate a distribution of AT1R gene polymorphism in patients with HRS and the association between its genotypes and the prognosis of HRS. Moreover, this study assesses the polymorphism of AT1R gene as a risk factor and a predictor of HRS. Patients and methods: This study was carried out on 50 HRS patients with cirrhosis of the liver beside 50 healthy subjects acted as controls to evaluate AT1R (A1166C) gene polymorphism using Real-Time PCR. Results: AT1R genotypes distributions showed significant differences between HRS patients and controls as the mutant genotype CC (6%) and hetero genotype AC (24%) were more significant in HRS patients than controls (0% and 12%; respectively) with P value <0.01, hence there was a relationship between the HRS progression and AT1R genotypes. On the other hand, there were no statistically significance differences between alleles frequencies in patients and controls (P>0.05) as their frequencies were 96% for allele A and 4% for allele C in patients compared to 90% allele A and 10% allele C in controls. Furthermore, there was a relation between the genotypes of AT1R gene and creatinine clearance and the mean arterial pressure (MAP) in HRS patients. Conclusion: There was a link between AT1R gene polymorphism and the risk of developing HRS. In addition, the relationship between AT1R genotypes and creatinine clearance could be also used as a predictor of HRS progression.

KEYWORDS: Hepatorenal syndrome (HRS), Angiotensin II type I receptor (AT1R) gene, Liver cirrhosis, Mean arterial pressure (MAP).

1. Introduction

Hepatorenal syndrome (HRS), which is more common in cirrhotic individuals with portal hypertension and ascites, is the term used to describe the onset of renal failure in patients with severe chronic liver disease [1]. The pathological features of chronic liver diseases include enhanced fibrosis, oxidative stress and inflammatory markers. Portal hypertension is the end result of these processes, which are linked to sinusoidal capillarization and increased hepatic vascular resistance. In order to restore liver function, compensatory processes might lead to edoema, ascites, hyperdynamic circulation, and hepatorenal syndrome [2]. Around 40% of patients with cirrhosis and ascites will eventually develop HRS [1]. In Hepatorenal syndrome, the kidney histology is normal, and after a liver transplant, the kidneys work normally [3].

Renin-angiotensin system (RAS) is an enzymatic pathway involved in the control of blood pressure, the cardiovascular system, and electrolyte balance. Angiotensinogen, which rennin converted into angiotensin I, is mostly produced in the liver. Angiotensin converting enzyme then converts angiotensin I into angiotensin II [4]. The peptide hormone angiotensin, which is a part of the RAS and a primary target for blood pressure-lowering drugs, constricts blood vessels and raises blood pressure. Angiotensin also promotes the production of aldosterone. [5]. Angiotensin receptors are a type of protein-coupled receptor that binds to angiotensin II [6]. In the renin-angiotensin system, these receptors are in charge of signalling the vasoconstricting stimulus of the hormone angiotensin II [7]. The gene for angiotensin II type I receptor (AT1R) is located on chromosome 3q21-25 and is 55kb long [8]. AT1R is found on smooth muscle cells in the vascular

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system, the heart, the adrenal glands, and the kidneys [6].

The AT1R gene's rs5186 single nucleotide polymorphism (SNP) is also known as the A1166C variant. Despite the fact that this SNP does not occur in a coding or splicing region, it has the potential to affect mRNA stability and transcription [9]. The AT1R gene has been linked to a number of polymorphisms (32), the most thoroughly investigated of which is the A1166C gene polymorphism. A1166C gene polymorphism has been linked to disease processes such as left ventricular hypertrophy, coronary heart disease, nephropathy, and liver cirrhosis [10].

Despite extensive research into the A1166C gene polymorphism and HRS susceptibility, no consensus has been reached [11]. As a result, the purpose of this study was to look into the relationship between AT1R (A1166C) polymorphism and hepatorenal syndrome. This study was also carried out to correlate genotypes of AT1R gene with various parameters in HRS patients.

2. PATIENT AND METHODS

2.1. Patients

2.1.1. Patient's design

Fifty patients with HRS who were attending the inpatient clinic of the department of tropical medicine and gastroenterology at the hospital of South Valley University were recruited as patients in our study, while 50 healthy individuals provided as controls.

2.1.2. Patient's criteria

- *Inclusion criteria*

Patients with liver cirrhosis who meet HRS criteria, have a low glomerular filtration rate (eGFR, calculated by serum creatinine greater than 1.5 mg/dl or 24-hour creatinine clearance), (Ccr) ≤ 40ml/minute were included in the study.

$$eGFR = 186 \times (Creatinine/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black}).$$

$$Ccr = ((140-age) \times weight) / (72\ Scr) \times 0.85 \text{ if female}$$

- *Exclusion criteria*

Patients who have a renal impairment caused by conditions other than liver cirrhosis, patients with bacterial infections, and patients taking nephrotoxic drugs were all excluded from our study.

2.2 Methods

2.2.1. Laboratory finding and investigation

Complete clinical history taking to determine the demographic data, liver function test (serum bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), prothrombine time, prothrombine concentration, INR), kidney function test (urea, creatinine (Scr), creatinine clearance (Ccr), estimated glomerular filtration rate (eGFR), mean arterial pressure (MAP) and abdominal ultrasound to measure (liver size, spleen size, portal vein size, ascites degree moderate, mild, tense).

MAP "mean arterial pressure = 1/3 (SBP-DBP) + DBP
SBP: systolic blood pressure, **DBP**: diastolic blood pressure.
Normal value =" 65-110" mm/Hg [12].

2.2.2. Genetic investigation

Patients and controls were given venous blood samples, which were collected in EDTA vacutainer tubes. The samples were kept frozen at (- 80° C) until the assay. A DNA extraction kit was used to extract genomic DNA. Real-Time PCR was used to genotype and analyse the rs5186 variant of the AT1R gene for single nucleotide polymorphisms (SNPs).

DNA extraction was performed by using Qiagen protocol and concentration purity of the end product was measured by the nanodrop instrument. Analysis and genotyping of rs5186 variant for AT1R gene was performed by using real-time PCR (step1 classic real-time instrument), TaqMan Universal Master Mix II Kit. AT1R gene (A1166C) (rs5186) have two probes, one of these probes dyed by FAM dye and the other probe dyed by VIC dye, each of these probes have a different wavelength. FAM dye for C allele, VIC dye for A allele. These probes yield homozygous AA or homozygous CC and heterozygous AC genotypes according to the wavelength. If the result gives: 2 FAM curves indicate mutant homozygous CC; 2 VIC curves for wild homozygous AA; 1 VIC curve and 1 FAM curve for heterozygous AC. These are all possibilities we are looking for in the results on which our study is based.

STATISTICAL ANALYSIS

SPSS version 24 was used for data entry and analysis (Statistical Package for Social Science). The data was presented in the following formats: number, percentage, mean, and standard deviation. To compare qualitative variables, the Chi-square and Fisher Exact tests were used. To compare quantitative variables between groups, the independent sample t-test was used. When $P<0.05$, the P-value is considered statistically significant.

RESULTS

4.1. Demographic data for studied groups

The mean of age in patients were (60.32±9.16) years vs. (60.38±9.03) years in controls, we noted that, there is no statistical difference between patients and controls ($P>0.05$). As regard to

gender, 36 (72%) were males and 14 (28%) were females in patients vs. 39 (78%) were males and 11 (22%) were females in controls, no statistically significance difference between patient and control groups (P>0.05). The mean weight in patients was (77.70±10.43) kg vs. (77.86±9.76) kg in controls, no statistically significance difference between both groups (P>0.05) **(Table 1)**.

4.2. Liver function for studied groups

There were statistically significant higher values in ALT, AST, Bilirubin (mg/dl), prothrombin Time (sec) and INR (PR) in patients than the controls (P<0.000) and there were statistically significant lower values in albumin (mg/dl) and prothrombin concentration (%) between patients and controls (P<0.000) **(Table 2)**.

4.3. Kidney functions for studied groups

There were statistically significant higher values in creatinine (mg/dl) and urea (mg/dl) in patients than controls (P<0.000) and there were statistically significant lower value at creatinine clearance (ml/min) between both groups (p<0.000) **(Table2)**.

4.4. Mean arterial pressure (MAP) for studied groups (mmHg)

We noted that, there were statistically significant lower at MAP value between both patients and controls (p<0.000) **(Table 2)**.

4.5. Genotypes of AT1R (A1166C) for studied groups

- *Homozygous AA (Wild):* There were 35 (70%) homozygous AA in patients vs. 44 (88%) in controls and there were statistically significance lower value in patients compared to controls (P<0.01) **(Table3)**.
- *Heterozygous AC (Hetero):* There were 12 (24%) heterozygous AC in patients vs. 6 (12%) in controls and there were statistically significance higher value in patients in comparison to controls (P<0.01) **(Table 3)**.
- *Homozygous CC (Mutant):* There were 3 (6%) homozygous CC in patients group vs. no cases between controls and there were statistically significance higher value in patients when compared with controls (P<0.01) **(Table 3)**.

4.6. Allele frequency in studied groups

- *Allele A & Allele C:* There were 48 (96%) Allele A and 2 (4%) Allele C in patients vs. 45 (90%) Allele A and 5 (10%) Allele C in the controls, there were no statistically significance difference between Allele frequency in the patients and the controls (P>0.05) **(Table 4)**.

4.7. Predictors of HRS

The predictors of HRS were identified using regression analysis. The significant predictors were that genotypes of AT1R (AA, AC, CC) is the most predictor factors and creatinine clearance (p<0.001), creatinine, weight and MAP (p<0.05) most parameters were affected on HRS patients **(Table 5 & 6) and** (**Figure 1)**.

Table (1): Demographic data in patients & controls

	Patients	Controls	*p-value*
Age (yrs)	60.32±9.16	60.38±9.03	0.974$^{n.s}$
Sex			
• Male	36(72.0%)	39(78.0%)	0.372$^{n.s}$
• Female	14(28.0%)	11(22.0%)	
Weight (kg)	77.70±10.43	77.86±9.76	0.937$^{n.s}$

Data expressed as number and percentage or as mean±SD
Using Chi-Square test in categorical data or Using T-test in numeric data for comparison between patients & controls.
$^{n.s}$ p-value: non-significant

Table (2): Liver function and kidney function in patients & controls

Parameters	Patients	Controls	*p*-value
Liver function:			
ALT "UL/ml"	35.78±11.86	26.96±4.02	**<0.000*****
AST "UL/ml"	48.24±13.22	27.48±3.07	**<0.000*****
Bilirubin "mg/dl"	3.74±1.32	0.83±0.12	**<0.000*****
Albumin "mg/dl"	2.09±0.43	4.08±0.47	**<0.000*****
Prothrombin concentration"%"	66.08±16.76	93.51±6.53	**<0.000*****
Prothrombin Time "sec"	14.67±1.92	12.41±0.59	**<0.000*****
INR"PR"	1.33±0.19	1.06±0.65	**<0.000*****
Kidney function:			
Urea "mg/dl"	96.32±48.11	23.68±4.57	**<0.000*****
Creatinine "mg/dl"	2.90±0.96	0.97±0.11	**<0.000*****
Creatinine clearance "ml/min"	30.98±9.49	87.62±7.81	**<0.000*****
MAP "mmHg"	71.78±10.90	85.64±5.26	**<0.000*****

Data expressed as mean±SD
T-test for comparison between patients & controls *** *p-value highly significant*

Table (3): Genotypes distributions of AT1R (A1166C) gene in patients & controls

Genotypes	Patients	Controls	*p*-value
Homozygous AA (wild)	35(70.0%)	44(88.0%)	
Heterozygous AC (hetero)	12(24.0%)	6(12.0%)	**<0.01***
Homozygous CC (mutant)	3(6.0%)	0 (0%)	

Data expressed as number and percentage
Chi-Square test used to compare patients with controls * *p-value significant*

Table (4): Distribution of allele frequency in patients & controls

Item	Patients	Controls	*p*-value
Allele A	48 (96%)	45 (90%)	
Allele C	2 (4%)	5 (10%)	0.372$^{n.s}$

Data expressed as number (percentage)
Chi-Square test for comparison between patients & controls $^{n.s}$*p-value non-significant*

Table (5): Regression analysis for development of (HRS)

Item	OR	95%CI	*p*-value
AT1R			
AA	1	References	1
AC	27.72	7.8-15.02	**<0.001****
CC	5.18	1.04-21.33	**<0.02***
MAP	8.79	1.49-4.26	**<0.02***
Weight	7.05	1.27-1.95	**<0.03***
Creatinine Clearance	29.46	8.65-17.64	**<0.001****
Creatinine	7.88	1.33-1.76	**<0.03***
Urea	2.63	0.57-0.98	0.385$^{n.s}$

**p-value significant, **p-value moderate significant, ***p-value highly significant,* $^{n.s}$ *p-value non-significant*

Table (6): Area under the curve (AUC), cutoff, sensitivity and specificity for urea, creatinine and MAP

Parameters	AUC	Cutoff	Sensitivity	Specificity
Urea	0.636	16	100%	100%
Creatinine	0.857	0.75	100%	98.5%
MAP	0.385	42.0	100%	100%

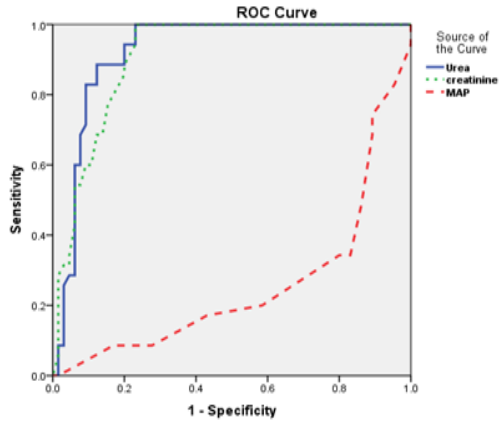

Figure 1: ROC curve for Urea, Creatinine and MAP for predictor HRS.

5. DISCUSSION

Hepatorenal syndrome (HRS) is defined by a significant impairment in kidney function that occurs in severe chronic liver disease, specifically liver cirrhosis [13]. HRS pathogenesis has been linked to numerous molecular and biochemical pathways. The renin-angiotensin system (RAS) is regarded as a critical pathway among these. RAS is made up of various subsystems that all contribute to the development of renal disease. RAS is made up of Renin, AGT, ACE, ACE2, AT1R, and AT2R [9, 11, 14, 15]. SNPs in HRS-related genes were discovered to have a significant impact on disease outcome, but no gene has been identified as conclusively indicating the presence of HRS.

In the current study, we looked at genotype distributions for the Polymorphism in the angiotensin II type 1 receptor (AT1R) gene. When the AA, AC, and CC genotypes in HRS patients and controls were compared, significant differences were found. Studies on the relationship between this polymorphism and hepatorenal syndrome in various ethnic patients produced contradictory results, with some studies failing to find an association [11, 16, 17].Our results were compatible with El-Shamaa et al. who reported that, the distributions of AC and CC genotypes were more pronounced in chronic kidney disease patients than in the control group. The C allele is regarded as a risk allele for patient group [16, 18]. Our findings, on the other hand, contradict those of Yukcu et al., who concluded that nephropathy patients did not differ from healthy controls in AT1R A1166C gene polymorphisms [10].

The fact that RAS control blood pressure by preserving vascular tone and sodium and water balance may explain the link between AT1R gene polymorphism and HRS [14]. AT1R is involved in the RAS activation/effector cascade. Angiotensin II acts as a powerful vasoconstrictor via the AT1R [14]. The activation of the AT1R is one of the primary causes of renal vasoconstriction in HRS. Since portal hypertension in cirrhosis results in splanchnic arterial

vasodilation, this lowers systemic vascular resistance and effectively increases the circulating blood volume. Renin-angiotensin-aldosterone system compensates by constriction of the renal arteries, which lowers renal blood flow and glomerular filtration rate (GFR) [17].

In the present study, there were statistically significance higher between (MAP) and genotypes of AT1R. These outcomes were in agreement with other studies in Budapest, Hungary, French, Serbia, Japanese, Chinese, Tunisian and Indonesian populations which suggested that AT1R (A1166C) gene polymorphism was linked to the risk of essential hypertension, but at this time, this gene cannot be recommended as a specific marker or early screening for hypertensive patients [19]. Furthermore, Fabris et al. reported that hypertension patients with the AT1R (A1166C) gene polymorphism had a higher rate of renal disease progression [20]. As a result, we presented that A1166C genetic variants could be identified in hypertensive individuals. As a result, the majority of hemodialysis individuals, to control their hypertension, they are given a combination of antihypertensive medications [21]. In contrast, another study found no link between the A1166C polymorphism and hypertension [22]. In addition, there wasn't a statistically significant difference between AT1R genotypes and hemodialysis patients with hypertension [23].

Multiple regression analysis in this study suggested that AT1R genotypes, creatinine clearance, weight, and creatinine were significant predictors of HRS. In the case of urea, Moreover, no statistically significant difference was found. This is consistent with El-banawy et al. [23], who discovered that AT1R, creatinine clearance, creatinine, and weight were the most important parameters influencing HRS progression, but urea could not predict the development of HRS [24]. This could be explained by the association between AT1R gene polymorphism and a more rapid decline in renal function [25], as well as dialysis-dependent end-stage renal disease [8]. Furthermore, a link between AT1R gene polymorphism AC/CC genotypes and renal damage was discovered [26]. The C-allele of the AT1R A1166C gene would increase renal and systemic Ang II activity [27], but the AA genotype was associated with earlier progression of renal damage in China and Spain [28]. According to the findings, genotype may be a potential genetic predictor for HRS in patients with uncompensated liver cirrhosis [29, 30].

6. CONCLUSION

HRS is a serious complication attendant with a poor diagnosis in patients with liver cirrhosis. There is still hope for lowering its prevalence and improving patient outcomes despite its high mortality rate if not recognized and treated promptly. As a result, the current study discovered a link between the progression of hepatorenal syndrome (HRS) and the AT1R (A1166C) gene polymorphism. The aforementioned gene, creatinine clearance, and MAP are also linked. As a result, AT1R genotypes, creatinine clearance, and MAP levels may be predictive of HRS. However, the findings of future studies on gene-gene and gene-environment interactions should be considered.

7. RECOMMENDATION

1. Patients with HRS who have the gene polymorphism AGTR1 (A1166C) should be prepared for liver transplantation as soon as possible.
2. In order to avoid the development of liver cirrhosis, these patients should be referred for treatment of potential causes of liver cirrhosis, such as Hepatitis B, C, and autoimmune liver disease, as soon as possible.
3. More research is being conducted to determine the link between the AGTR1 (A1166C) genotype polymorphism and other RAS-related diseases.

COMPETING INTERESTS

No conflict of interest.

COMPETING INTERESTS

No fund.

AUTHOR CONTRIBUTIONS

The authors all contributed equally to the work and read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data supporting the study's findings are publicly available.

ETHICAL CONSIDERATIONS

Before beginning data collection, the proposal was reviewed by the ethical review committee of the Faculty of Medicine at the University of Beni-Suef. The privacy and confidentiality of all data were guaranteed, and the purpose of the study was explained to each participant prior to filling out the questionnaire. Those who agreed to participate in our study provided informed written consent. FWA: 0 0015574.8.

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