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Angiotensin II Type 1 Receptor Gene Polymorphism in Egyptian Patients with Chronic Renal Failure

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Abstract: Background: The rate of progression of renal damage varies significantly, however individual genetic variations contribute to the variability in rates of progression. Polymorphisms of the angiotensin II type 1 receptor (AT1R) gene have been associated with a variety of cardiovascular and renal effects. The aim of this study was to evaluate the association of AT1R gene A1166C polymorphism as one of the renin angiotensin system (RAS) gene family, with chronic renal failure (CRF) in Egyptian patients on hemodialysis. Methods: Genotyping for AT1R gene A1166C polymorphism was performed in 35 patients undergoing hemodialysis and 20 healthy volunteers acting as control using polymerase chain reaction restriction fragment length polymorphism (PCR-RELP) method. Results: AC genotype frequency of AT1R gene A1166C was higher in CRF patients group than the control group 18/35 (51.4%) versus 5/20 (25%) while control group had higher AA genotype frequency versus CRF group 15/20 (75%) versus 17/35 (48%) .Yet this difference did not reach a statistical significance (P = 0.056).AC genotype was significantly higher in hypertensive than normotensive (73.91%) versus (26.1%) while AA was significantly higher in normotensive than hypertensive (75%) versus (25%) (p =0.00). Conclusion: Our finding, enlightens the significant association of AT1R A1166C polymorphism and hypertensive group of CRF .This can shed Light on the pathophysiology by which RAS has dual mechanism on kidney affection in case of hypertension leading to ESRD.

Key words: ATIR, A1166C gene, chronic renal failure, hypertension.

INTRODUCTION

Chronic renal failure (CRF) is defined as an irreversible reduction in the glomerular filtration rate (GFR) (Yaqoob, 2005).The rate of progression varies significantly, however individual genetic variations contribute to the variability in rates of progression. Genetic susceptibility may play an important role in rate of renal function decline. Clustering of renal disease occurs within families, with up to 30% of patients with end stage renal disease (ESRD) having an affected sibling. Like many complex disorders, it is unlikely that a single genetic polymorphism will explain all susceptibility to accelerated renal function decline. However, certain genetic alteration that affect the expression or function of a key protein product, so called functional polymorphism may influence pathological processes which are either promoted or prevented by that key protein(Lin *et al*.,2009).

Possible mechanisms of progressive renal damage include hemodynamic factors, hypertension, proteinuria, angiotensin II, and other chemical mediators such as cytokines and growth factors. The renin-angiotensin system (RAS) has been strongly implicated in the pathogenesis of essential hypertension, cardiovascular disease and progressive renal disease. Angiotensin II, as RAS activity, is both a powerful vasoconstrictor and a potent mediator of cellular proliferation and extracellular matrix protein synthesis and accumulation. These effects contribute to progressive fibrotic disease in various organ systems. Association studies between disease states and the various components of the RAS, including renin, angiotensinogen, angiotensinII and angiotensin-converting enzyme (ACE) have yielded variable results. Most of the physiological effects of the RAS are mediated by the angiotensin II receptor. Polymorphisms of the angiotensin II type 1 receptor (AT1R) gene have been associated with a variety of cardiovascular and renal effects (Kirn *et al*., 2000).

The renin-angiotensin system (RAS) regulates renal vasomotor activity, maintains optimal salt and homeostasis, and controls tissue growth in the kidney. However pathologic consequences can result from over activity of this cascade, involving it in the pathophysiology of kidney disease. An activated renin-angiotensin system promotes both systemic and glomerular capillary hypertension which can induce hemodynamic injury to the vascular endothelium and glomerulus. In addition, direct pro fibrotic and pro inflammatory actions of Angiotensin II may also promote kidney damage (Schweda *et al*., 2012). Classically, the angiotensin II receptor includes two subtypes: type 1 (AT1R) receptor and type 2 receptor. The AT1R receptor, which is the primary pathogenic effector for angiotensin II, is a member of the G-protein-coupled receptor superfamily expressed in most tissues, where receptor activation leads to vasoconstriction, water retention and vascular smooth muscle

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cell proliferation and hypertrophy (Wu *et al*., 2009). The AT1R receptor gene, composed of five exons and four introns, is located on the long arm of chromosome 3 (3q21- 25). Several polymorphisms of the AT1R receptor have been identified, but the most studied Al166C variant is located in the 3' untranslated region, in which there is either an adenine (A) or a cytosine (C) base (A/C transversion) A1166 polymorphism (Kikuya *et al*., 2003).

The aim of this study was to evaluate the association of AT1R gene Al166C polymorphism as one of the RAS gene family, with chronic renal failure (CRF) in Egyptian patients on hemodialysis.

MATERIAL AND METHODS

The present study included 55 subjects; the subjects were divided into 2 groups: group (1) including patients with chronic renal failure (CRF) undergoing hemodialysis. They were selected from those attending Nephrology Outpatients Clinic and hemodialysis unit in Kasr El Aini hospital, Cairo University, and group (2) including twenty healthy volunteers who are age and sex matched with the patients group. They had no evidence of chronic kidney disease as shown by normal kidney functions absence of proteinuria or active urinary sediment, as well as normal kidney size and shape on abdominal ultrasound scans. They had a blood pressure ≤130/80. The study was conducted between january2010 until January 2011. All participants gave an informed consent and approval by local ethics committee was obtained. Both groups were subjected to: Full History taking and thorough clinical examination and laboratory investigation.

Sampling:

Blood samples were collected after a 12-14 h fast from all subjects. Serum and EDTA samples were stored at -20 until assay time.

Assay of renal functions (urea, creatinine and uric acid), lipid profile (cholesterol and triglycerides), fasting blood glucose, calcium and phosphorus were performed on automated analyzer Hitachi 917 Germany using commercial kits supplied by Roche diagnostics (Mannheim Germany). Electrolytes (Na and K) were assayed on Dimension using commercial kits supplied by Dade Behring (Siemens Health Care Diagnostic, Deerfield USA) automated electrolyte analyzer AVL 9180.

Molecular Analysis Of The A1166C Polymorphism Of The ATI R Gene:

Genomic DNA was extracted from whole blood samples collected with EDTA using salting out technique (Sambrook *et al*., 1989).Genotype analysis was performed using the polymerase chain reaction-restriction fragment length polymorphisrn(PCR-RFLP) method (Lapierre*et al*., 2006) using the followingprimers: 5'AATGCTTGTAGCCAAAGTCACCT and 5' GGCTTTGCTTTGTCTTGTTG. PCR amplification was performed in 30 µl reaction containing, 1.0 µg genomic DNA, 1.66 mM MgCl2, 200 µM deoxynucleotide triphosphates, 1µM primers and 1.5 U of Taq DNA polymerase, the primers and master mixture were supplied by The Midland Certified Reagent Company Inc.(Midland .Texas) lot number (260109-97F). Amplification was performed by PCR using Hybaid thermal cycler supplied by Promega Co. (Promega Corporation 2800 Woods Hollow Road Madision, W 153711-5399, USA).The conditions for PCR amplification consisted of two minutes denaturation at 94°C, followed by 40 cycles of one minute at 94°C, one minute annealing at 60°C, extension for two minutes at 72°C, and final extension for 10 minutes at 72°C, PCR products of the expected size (850bp) were analyzed on 0.8% agarose gels. To characterize the polymorphism, PCR products were digested overnight with the restriction endonuclease Dde I (BioLabsInc, England) at 37°C which cuts the product into two pieces, 600bp and 250bp long . An additional Dde I recognition site is created in the C- type variant at nucleotide 1166, which is located within the 250bp fragment. Thus, the homozygote AA produces two bands (600 and 250bp long), and the heterozygote AC produces all four bands (600,250, 140 and 110bp long). Digestion products were detected on 3% agarose gel stained with ethidium bromide staining using gel electrophoresis apparatus supplied by Promega Co.(USA) and ultraviolet transillumination.

Statistical Methods:

The SPSS 10.0 for windows was used for data management and the Microsoft power point for charts. Parametric quantitative data were presented as mean ± SD. For comparison of the two group means, The Student's t-test was used. Non parametric quantitative data were expressed as median (percentiles), and Mann-Whitney test was used for comparison of medians. Quantitative data were expressed as frequency and percentage. Association between qualitative data was done using Chi-square test. Spearman correlation coefficient was used to correlate between quantitative variables. Risk estimate was done by odds ratio. P value was considered as significant at 0.05.

Results:

This study was conducted on fifty five individuals (32 males and 23 females) with an age range from 17-63 years. It included 2 study groups:

Group (1) this group included thirty five patients with chronic renal failure undergoing hemodialysis. They were 20 males (57.1%) and 15 females (42,9%) and their age ranged from 17 - 63 years with mean (34.34±14.23) ,their time on dialysis ranged from l-48 months with mean (15.8±12.7).

Group (2): This group included twenty healthy volunteers as a control group, 12 males (60%) and 8 females (40%) with age range from 26 - 49 years (mean 35.7 ± 7.23).The clinical and laboratory data is shown in table (1).

Table 1: Clinical and laboratory data of the studied groups.

Variable	CRF group n = 35	Control group n=20	P Value
Sex M/F	20/10	12/8	
Duration of dialysis(months)	15.8±12.7	-	
Hypertension (n)	25	o	
Age(years)	25(22-36)	35 (29-42)	0.135
BMI (kg/m2)	22.12 ± 1.23	21.34±1.87	0.651
urea (mg/dl)	144(91-160)	26.5 (22.2-28.7)	0.001 *
creatinine (mg/dl)	7.8 ± 2.49	0.92±0.19	0.001 *
Na (mmol/L)	137.02 ±3. 18	138.75 ±2.14	0.036 *
K (mmol/L)	5.16±1.13	3.83 ±0.36	0.001 *
Ca (mg/dl)	8.3 (7.7 -8.7)	8.7(8.9-9.2)	0.019
Phosphorus (mg/dl)	4.14 ±0.59	4.02 ± 0.24	0.403
Uric acid (mg/dl)	6.2 (5.7 -6.9)	5.6(5.4-6.4)	0.033
Fasting blood glucose (mg/dl)	98 (90-109)	97.5 (88.2 -100)	0.072
Cholestrol (mg/dl)	157.74 ± 42.68	145.65 ±37.6	0.322
TG (mg/dl)	152 (119-175)	125 (112-149)	0.053

Values are mean ±SD or median (quartile range).

*P < 0.05 (significant) from the control group.

CRF group showed significantly higher concentration than control group as regard urea 144mg/dl (91 -160) versus 26.5mg/dl (22.2-28.7), creatinine mg/dl (7.8±2.49) versus (0.92 ± 0.19), k (5.16 ± 1.13) versus (3.83 ± 0.36), uric acid 6.2 mg/dl (5.7-6.9) versus 5.6 (5.4-6.4) (p=0.00, 0.00, 0.00, 0.03 respectively).

CRF group showed significantly lower concentration than control group as regard Ca 8.3mg/dl (7.7 -8.7) versus 8.7 (8.4-9.2), Na (137.02 ± 3.18) versus (138.75 ± 2.14) (p = 0.019, 0.036 respectively).

There was no significant difference between two groups as regard age, phosphorus, blood glucose, cholesterol, and triglycerides (p =0.135, 0.403, 0.072, 0.322, 0053respectively).

Comparison between hypertensives and nonhypertensives is shown in table (2).There was no significant difference between hypertensives and normotensives CRF subjects as regard age, time on dialysis, urea, creatinine, Na, K, Ca, Phosphorus, uric acid, blood glucose, cholesterol and triglycerides (p =0.321, 0.113, 0.843, 0.103, 0.371, 0.661, 0.558, 0.635, 0.08, 0.062, 0.82, 0.183 respectively).

Table 2: Descriptive statistics of clinical and different studied laboratory parameters in comparison between hypertensive and normotensive CRF subjects.

Variable	Hypertensive n=25	Normotensive n=10	P. Value
Age (years)	26 (21 -43.5)	24 (21.5-26,25)	0.321
Time on dialysis (m)	18(6-24)	9 (2-15)	0.113
Systolic BP	148±18.285	114±6.179	0.001*
Diastolic BP	87.7±8.32	75±4.08	0.001*
BMI	22.04±1.42	21.96±1.32	0.651
Urea (mg/dl)	114(95.5-158)	111.5 (82-180.75)	0.843
Creatinine (mg/dl)	7.37 ±2.28	8. 89 ±2.78	0.103
Na (mmol/1)	136.72 ±3.42	137.8 ±2.44	0.371
K (mmol/1)	5.1(4.1 -5.9)	4.9 (4.4-6.1)	0.661
Ca (mg/dl)	8.2 (7.7 -8.7)	8.5 (7.3-9.2)	0.558
Pho sphorus (mg/dl)	4.11 ±0.673	4.22 ±0.35	0.635
Uric acid (mg/dl)	6.13 ±0.716	6.73 ± 1.24	0.08
Fasting blood glucose (mg/dl)	100 (94-114)	92 (82-100)	0.062
Cholestrol (mg/dl)	155.68 ±44.85	159.4 ±38.79	0.82
TG(mg/dl)	158.92 ±37.61	139.71 ±38.1	0.183

As regards AT1R A1166C in CRF patients and controls AC genotype frequency of AT1R A1166C was higher in CRF patients group than the control group 18/35 (51.4%) versus 5/20 (25%) while control group had higher AA genotype frequency versus CRF group 15/20 (75%) versus 17/35 (48%).Yet this difference did not reach a statistical significance (P = 0.056).

C allele frequency was higher in CRF patients group than the control group 18/70 (25.7%) versus 5/40 (12.5%), while A allele frequency was higher in control group than the control CFR group 35/40 (87.5%) versus 52/70 (74.3%). Yet this difference did not reach a statistical significance (P = 0.144). This is shown in table (3).

Table 3: Genotype and allele frequency of Angiogenesis II receptor gene.

Genotype	CRF group (n = 35)		Control group (n = 20)		P. value
	frequency	percentage %	frequency	percentage %	
AC	18/35	51.4%	5/20	25%	0.056
AA	17/35	48.6%	15/20	75%	
A Allele	52/70	74.3%	35/40	87.5%	0.144
C Allele	18/70	25.7%	5/40	12.5%	

AT1R A1166 C genotypes showed 3.2 times more risk for CRF than AA genotype and C allele showed 2.4 more risk for CRF than A allele. Yet AC genotype and C allele didn't reach statistical significance as risk factor for CRF. This is shown in table (4).

Table 4: Risk estimate of AT1R A1166C genotypes and alleles for developing CRF.

	CRF	Control	Odd ration	95% CI	P-value
AC	18/35(51.4%)	17/35(48.6%)	3.2	0.9-10.7	0.05
AA	5/20 (25%)	15/20 (75%)			
A	52/87 (59.8%)	35/87 (41 .2%)	2.4	0.8-7.1	0.07
C	18/23 (78.3%)	5/23 (21.7%)			

There was no significant association between different A1166C genotypes frequency and sex of CRF subjects and control group. The frequency of AC and AA genotype in male versus female were 12/23 (52.2 %) and 20/32 (62.5%) versus 11/23 (47.8%) and 12/32 (37.5%) respectively

AC genotype was significantly higher in hypertensives than normotensives (73.91%) versus (26.1%) while AA was significantly higher in normotensives than hypertensives (75%) versus (25%) (p =0.00) This is shown in (fig 1).

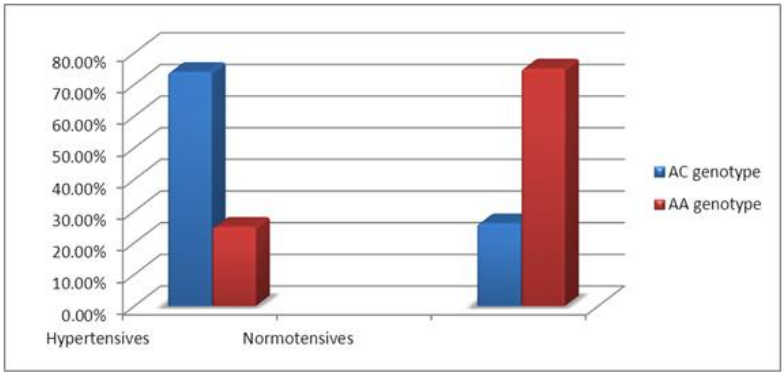

Fig. 1: Angiotensin II Receptor (A1166C) genotype frequency in hypertensive and normotensive subject.

AC genotype showed statistically significant higher concentration than AA genotype as regard serum triglycerides (159.39 ± 41.1.3) versus (136.97 ± 29.09) (p = 0.031).

AC genotype showed significantly lower serum Na concentration than A A genotype (136 .96± 3.44) versus (138.34±2.35) (p = 0.039).

There was no significant difference between AC genotypes and AA genotype as regard age, Urea, Creatinine, K, Ca, phosphorous, uric acid, Cholesterol, blood glucose. (p = 0.375, 0.086, 0.339, 0.905, 0.488, 0.260, 0.713, 0.249, 0.877 respectively).

On the other hand risk estimate for AT1R A1166 C genotype showed 8.5 times more risk for Hypertension than AA genotype (OR=8.5, 95%CI (2.4-29), P=0.00).AC genotype reached a highly statistical significance as risk factors for hypertension (p=0.00) this is shown in table (5).

Table 5: Risk estimate of AT1R A1166C genotypes in hypertensive and normotensive subjects.

	Hypertensive	Nomotensive	OR	95%	P-value
AC	17/23 (73.9%)	6/23(26.1%)			
AA	8/32 (25%)	24/32 (75%)	8.5	2.49-29	0.00

Discussion:

In our study AT1R 1166 AC genotype was significantly higher in hypertensives than normotensives, while AA was significantly higher in normotensive than hypertensives. Risk estimate for ATR1 A1166C AC genotype showed 8.5 times more risk for Hypertension than AA genotype.

The results of this study showed that AC genotype frequency of AT1R gene is higher in CRF patients group versus control group while control group had higher AA genotype frequency versus CRF group, yet this difference did not reach a statistical significance.

C allele frequency was higher in CRF patients group versus control group, while A allele frequency was higher in control group versus CRF group, yet this difference did not reach a statistical significance.

We found that the Risk estimate for ATR A1166C AC genotypes showed 3.2 times more risk for CRF than AA genotype. And C Allele is 2.4 times more risky for CRF than A allele. Yet AC genotype and C allele didn't reach statistical significance as risk factors for CRF.

Coll *et al* reported that AT1R 1166 C variant has been associated with renal disease (Coll *et al*., 2003). These result also coincide with Julie *et al*, who showed that the AGT1R 1166C allele was directly and significantly associated with renal dysfunction (Julie *et al*., 2009).

Lee *et al* confirmed these results and stated that the AT1R All66 C gene polymorphism is associated with the patient's susceptibility to CRF or ESRD (Lee *et al*., 2009).

In a study done in Egypt in pediatric age group with chronic renal failure and on maintenance hemodialysis, the association of the AT1R A1166C genotype with the development of renal disease and progression to end-stage renal failure was shown (Elshamaa *et al*., 2011). On the other hand Gumprecht *et al*. didn't find any association of RAS with impaired renal function(Gumprecht *et al*., 2000).

In our study AC genotype was significantly higher in hypertensives than normotensives, while AA was significantly higher in normotensives than hypertensives . Risk estimate for A1166 C genotype showed 8.5 times more risk for hypertension than AA genotype.

In agreement with our study Wu *et al* reported that AT1R gene have been identified as genetic factor involved in the pathogenesis of high blood pressure (Wu *et al*., 2009) . Zhu and Meng ascertained our results by reporting that AT1R (A1166C) polymorphism is associated with essential hypertension in the Chinese population(Zhu and Meng, 2006) (14). Niu W and QjY confirmed these findings and showed that the AT1R 1166 C allele conferred an increased risk of hypertension Niu and Qi, 2010).

A meta-analysis in a Chinese population suggests that the AT1R 1166 AC/CC genotype is associated with susceptibility to hypertension in the Chinese population (Wang *et al*., 2010).

In an effort to relate the AT1R gene polymorphism to hemodynamic function, Benetos *et al*. found increased sensitivity to ACE inhibition, as measured by aortic stiffness reduction, in hypertensive individuals with the A1166C polymorphism. This observation suggests that the C allele is associated with increased activity of the RAS (Benetos *et al*., 1995)

In hypertensive patients it is suggested that the combination of DD polymorphism type and AC/CC for AT1R gene, could contribute in a synergistic way to organ damage. The AT1R mediates the more deleterious effects of angiotensin II-that is, cardiac and vessel hypertrophy including extracellular matrix production (Nakayama *et al*., 2009). Studies on the general population and in selected families have shown that the AT1R gene polymorphism may increase the susceptibilities to essential hypertension. The ATIR A1166C polymorphism has been found to be associated with higher angiotensin II sensitivity in hypertensive patients on a high-salt diet (Bonnarddeaux *et al*.,1994).

Conclusion:

Our finding, enlightens the significant association of AT1R Al166C polymorphism and hypertensive group of CRF .This can shed light on the pathophysiology by which RAS has dual mechanism on kidney affection in case of hypertension leading to ESRD through vascular damage and extracellular matrix deposition through induction of tissue growth and fibrosis. Hypertensive patients with AC genotype can be enrolled in researches for early intervention and follow up aiming to minimize renal affection and control kidney damage.

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