Angiotensin II type 1 receptor gene polymorphism in chronic kidney disease

Thesis

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BY

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Abstract

Chronic renal failure is characterized by a persistently abnormal glomerular filtration rate. It represents a developing process that is initiated by various causes; Renin angiotensin system may affect chronic kidney disease (CKD) through induction of tissue growth and fibrosis.This study was to evaluate the association of AT1R gene (A1166C) polymorphism as one of the RAS gene family, with chronic renal failure (CRF). This association was evaluated to shed light on pathophysiology of CRF and identify risk assessment

AC genotype frequency of AT1R gene (A1166C) was higher in CRF patients group versus control group (p =0.056).

AC was significantly higher in hypertensive than normotensive (p =0.00).

Key words: Chronic kidney disease – Renin angiotensin system – Angiotensin II type1 receptor

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ACTH	Adrenocortico trophic Hormones
ADH	Antidiuretic Hormone
ARBS	AT1 receptor blockers
ANP	Atrial natriuretic peptide
ANG1	Angiotensin I
ANGII	Angiotensin II
ANGIII	Angiotensin III.
ANGIV	Angiotensin IV
ARF	Acute Renal Failure
ATN	Acute tubular necrosis
AT1R	Angiotensin II Type 1 Receptor
AT2R	Angiotensin II Type 2 Receptor
BP	Blood Pressure
CCPS	Catherin coated pits
CKD	Chronic Kidney Disease
CRF	Chronic Renal Failure
CRI	Chronic Renal Insufficiency
DM	Diabetes Mellitus
ESRD	End Stage Renal Disease
GFR	Glomerular Filtration Rate
GK	Glycerol Kinase
HIV	Human immunodeficiency virus
LPL	Lipo Protein Lipase
PAI1	Plasminogen Activator inhibitor 1
PAI2	Plasminogen Activator inhibitor 2
PCKD	Polycystic Kidney Disease

PCR- RFLP	Polymerase Chain Reaction-Restriction Fragment Length Polymorphism
RAS	Renin Angiotensin System
SFO	Sub fornical organ
SNP	Single nucleotide polymorphism
TGFB	Tissue Growth Factor B
UTR	UnTranslated Region

Introduction:

Chronic renal failure is characterized by a persistently abnormal glomerular filtration rate. It represents a developing process that is initiated by various causes, all with the common end result of persistent and usually progressive damage of varying severity to the kidneys. The rate of progression varies significantly, however individual genetic variations contribute to the variability in rates of progression. Possible mechanism of progressive renal damage includes hemodynamic factors, hypertension, proteinuria, angiotensin II, and other chemical mediators such as cytokines and growth factors **(Topaloglu, 2005).**

Renin angiotensin system (RAS) plays a central role in regulation of blood pressure, sodium metabolism and renal hemodynamic, with its actions mediated primarily by angiotensin II **(Buraczynska et al., 2006)**.

Renin angiotensin system may affect chronic kidney disease (CKD) through induction of tissue growth and fibrosis **(Hsu et al., 2006).**
Renin angiotensin system also plays a major role in determining the rate of chronic renal disease progression **(Freundich, et al., 2008)**.

Angiotensin II (Ang II) is one of the key factors in progressing to renal failure; renin splits the angiotensinogen into angiotensin I, which is converted to angiotensin II by Angiotensin converting enzyme (ACE).

Ang II binds to two types of receptors Angiotensin IItype1receptor(AT1R)& Angiotensin IItype2receptor(AT2R) and the resulting multiple effects are mediated by these receptors .Angiotensin II can be produced locally in the kidney, this plays a critical role in renal auto-regulation and physiologic developments **(Topaloglu, 2005).**

Angiotensin II type 1receptor is the predominant receptor for RAS, and the(A1166C) polymorphism may be more susceptible to vascular damage and extracellular matrix deposition in the context of hypertension exposure **(Hsu et al.,2006).**

Aim of the work:

The aim of this study was to evaluate the association of AT1R gene (A1166C) polymorphism as one of the RAS gene family, with chronic renal failure (CRF). (This association was evaluated to shed light on pathophysiology of CRF and identify risk assessment).

Review of Literature

Chapter 1

Chronic renal Failure

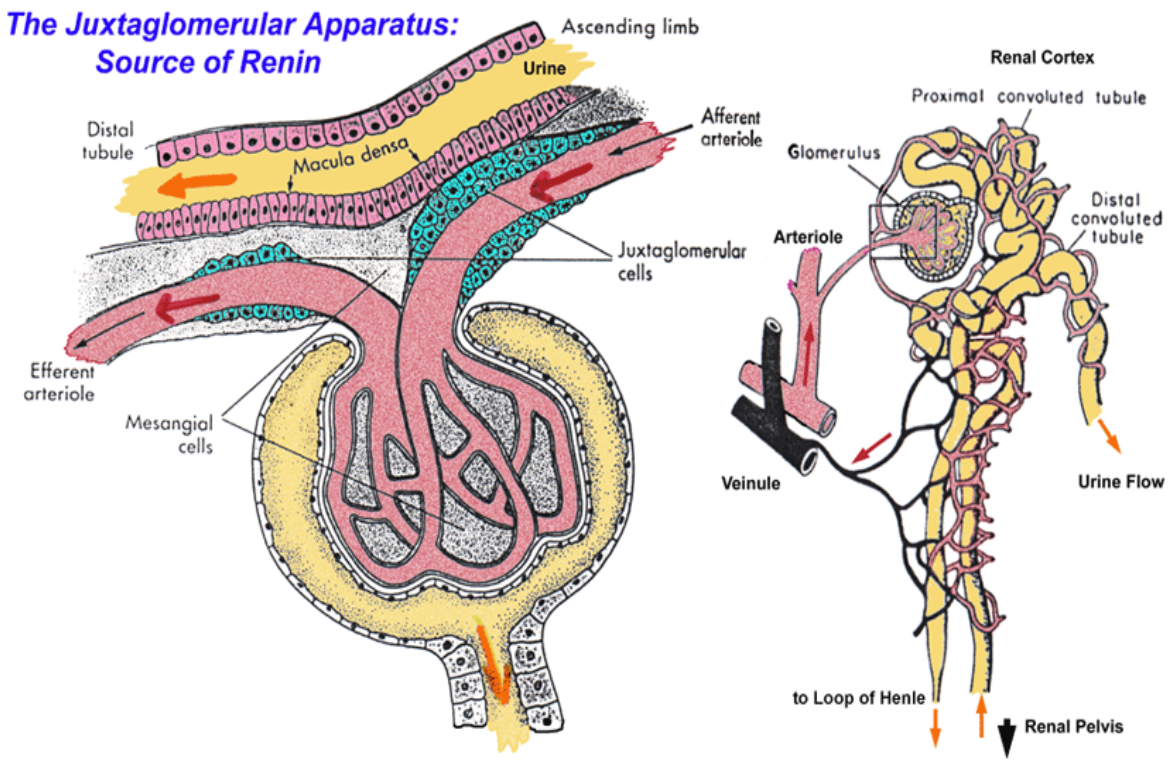
Anatomy of the kidney:

The kidneys are a paired organ system located in the lumbar region. They filter the blood, excrete the end-products of body metabolism in the form of urine, and regulate the concentrations of hydrogen, sodium, potassium, phosphate, and other ions in the extracellular fluid. In an adult, each kidney is about 12 cm long and weighs about 150 g in men and 135 g in women. The functional unit of the kidney is the nephron (Figure 1B). Each kidney may contain up to 1 million nephrons, the nephron consists of a glomerulus, proximal tubule, loop of Henle, distal tubule, and collecting duct **(Yaqoob, 2005).**

The glomerulus is a high-pressure filtration system, composed of a specialized capillary network. It generates an ultra-filtrate that is free of blood and significant amounts of blood proteins. Renal damage or alterations in glomerular function affect the kidneys' ability to remove metabolic substances from the blood into the urine. Bowman's capsule forms the beginning of the tightly coiled, proximal convoluted tubule. The proximal tubule is the most metabolically active Part of the nephron, facilitating the reabsorption of 60% to 80% of the glomerular filtrate volume **(Nankivell, 2001).**

Juxtaglomerular Apparatus:

Juxtaglomerular apparatus (JGA) is where the ascending Loop of Henle passes very close to the Bowman's capsule of its own nephron, the cells of the tubule and the afferent arteriole show regional specialization (**Figure 1A)**. The tubule forms the macula densa and the arteriolar cells are filled with granules (containing renin) and are innervated with sympathetic nerve fibers. The JGA plays an important part in maintaining systemic blood pressure through regulation of the circulating intravascular blood volume and sodium concentration **(Eknoyan et al., 2009).**



(A) **(B)**

Figure 1: Structure of the kidney.

(A) The Juxtaglomerular Apparatus **(Stanton and Koeppen, 2003).**

(B) The nephron **(Hadley and Levine, 2006).**

Kidney Function:

The main biological functions of the kidneys are excretion, homeostatic regulation, and endocrine. The kidneys integrate these functions to maintain homeostasis.

Excretion:

In normal adults, adequate homeostasis is maintained with a urine output of about 500 ml/day. Alterations in urinary output are described as anuria when urine volume is less than 100 ml for 24 hours; oliguria when the volume is less than 400 ml for 24 hours. Urine output above 3000 ml is designated polyuria **(Yaqoob, 2005).**

Regulatory Function:

The regulatory function of the kidneys has a major role in homeostasis. The mechanisms of differential reabsorption and secretion, located in the tubule of a nephron, are the effectors of regulation. The mechanisms operate under a complex control system in which both extra-renal and intra-renal humoral factors participate to maintain electrolyte and water homeostasis **(Delaney et al., 2008).**

Endocrine Function:

In the normal person, the kidneys metabolize 25-hydroxyvitamin D to active 1, 25 dihydroxy-vitamin D (calcitriol), which regulates absorption of calcium from foods and affects bone

formation. Kidneys are critical to erythropoietin formation, which stimulates red blood cell production. They also regulate renin, which regulates blood volume and blood pressure. The kidneys function as excretory, biosynthetic, and metabolic organs, vital for maintaining normal physiology. Although dialysis can replace some kidney functions, it cannot replicate the biosynthetic and metabolic activities of the normal kidney **(Peter, 2007).**

Chronic renal Failure

Definition

Renal failure is defined as the inability of the kidney to maintain homeostasis leading to the accumulation of nitrogenous wastes. It is distinguished from renal insufficiency where renal function is abnormal but capable of sustaining essential body functions. Renal failure is categorized as Anuria when urine volume is less than 100 ml. for 24 hours; Oliguria when the volume is less than 400ml for 24hours; and. Urine output above 3000 ml is designated Polyuria **(Bush et al., 2005).**

Chronic renal failure (CRF), also known as chronic kidney failure (CKF) or chronic kidney disease (CKD), or chronic renal insufficiency (CRI) is a slowly progressive loss of renal function over a period of months or years, and defined as an abnormally low glomerular filtration rate, which is usually determined indirectly by the creatinine level in blood serum ,CRF that leads to severe illness and