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ASSOCIATION OF END STAGE RENAL DISEASE WITH ANGIOTENSIN CONVERTING ENZYME INSERTION/DELETION POLYMORPHISM.

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ABSTRACT One of the major challenges is the increasing number of patients with end stage renal disease (ESRD). Therefore, a better understanding of the pathophysiology of chronic kidney disease (CKD) is mandatory to develop strategies to prevent the progression of renal disease. The renin-angiotensin-aldosterone system (RAAS) plays a pivotal role in many of the pathophysiologic changes that lead to progression of renal disease. RAAS is a well known regulator of blood pressure (BP) and determinant of target-organ damage. It controls fluid and electrolyte balance through coordinated effects on the heart, blood vessels, and Kidneys. Among the RAAS genes, angiotensin-converting enzyme (ACE) is said to be a major component and it has been extensively studied as a candidate gene for various disorders.ACE polymorphisms appear to have significant impact on the progression of ESRD. The focus of this paper is to review the RAAS component and their genetic characteristics and also the association between ESRD and ACE Insertion/ deletion (I/D) gene polymorphism.

KEYWORDS : Chronic kidney disease, End stage renal disease, Renin-angiotensin-aldosterone system and Angiotensin-converting enzyme.

INTRODUCTION

End Stage Renal Disease (ESRD) is a multifactorial disease and an advanced form of chronic renal failure. ESRD is a complex phenotypic structure of renal diseases affected by different etiologies.(1)Although ethnic, social and environmental factors play a part in development of the disease, to a large extent the cause of the disease is determined by genetic factors.(2)Working definition of ESRD: It is defined as i) an irreversible loss of endogenous renal function & ii) persons with an estimated glomerular filtration rate (eGFR) less than 15 ml per minute per 1.73 m^2 body surface area, or iii) those requiring dialysis irrespective of glomerular filtration rate.[1]

It is emerging to be an important chronic disease globally.[3] CKD is the 12th cause of death and the 17th cause of disability, respectively. CKD globally resulted in 753,000 deaths in 2010 up from 400,000 deaths in 1990.[4] Over 1 million people worldwide are alive on dialysis.[5] One reason is the rapidly increasing worldwide incidence of diabetes [6] and hypertension.[7,8]The prevalence of ESRD in the United States in 2007 was 527,283(1698 cases per million populations). In 2007, Japan also observed a relatively high incidence (285 per million populations) and prevalence (2060 cases per million populations) of ESRD, which included only persons receiving maintenance dialysis.[9]

In India, given its population >1 billion, the rising incidence of chronic kidney disease (CKD) is likely to pose major problems for both healthcare and the economy in future years. Indeed, it has been recently estimated that the age-adjusted incidence rate of ESRD in India to be 229 per million population (pmp) [10], and >100,000 new patients enter renal replacement programs annually in India.[11] On the other hand, because of scarce resources, only 10% of the Indian ESRD patients receive any renal replacement therapy (RRT).[12,13] The lack of community-based screening programs has led to patients being detected with CKD at an advanced stage.

Traditional risk factors for CKD progression include persistent proteinuria, dyslipidaemia, hypertension and smoking.[14,15] However, it has been postulated that non-traditional risk factors, such as oxidative stress, inflammation and immune processes, may also be important contributors to the pathogenesis of cardiovascular disease (CVD) as well as progression to ESRD.[16]

Pathophysiology of End Stage Renal Disease

The pathophysiology of CKD involves two broad sets of mechanisms of damage:- (1) initiating mechanisms specific to the underlying etiology (e.g. genetically determined abnormalities in kidney development or integrity, immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium) and (2) a set of progressive mechanisms, involving hyperfiltration and hypertrophy of the remaining viable nephrons, that are a common consequence following long term reduction of renal mass, irrespective of underlying etiology. The responses to reduction in nephron number are mediated by vasoactive hormones, cytokines, and growth factors. Eventually, these short term adaptations of hypertrophy and hyperfiltration become maladaptive as the increased pressure and flow predisposes to distortion of glomerular architecture, associated with sclerosis and dropout of the remaining nephrons. [17]

Genetics of End Stage Renal Disease

The susceptibility to develop ESRD has a significant genetic component. Genetic approaches have been used to identify genes that contribute to genetic susceptibility. Many studies have now been carried out assessing the contribution of specific "candidate genes", which correlate with different functions that are involved in the renal pathogenesis.[18] The genetic factors, such as DNA single nucleotide polymorphisms, may significantly influence the immune response, the levels of inflammatory markers, as well as the prevalence of atherosclerosis in ESRD patients.[19]Several studies have shown that renin-angiotensin-aldosterone system (RAAS) gene polymorphisms are highly associated with renal complications.

RAAS components and their genetic characteristics

The RAAS is directly involved in the regulation of blood pressure, fluid volume, and vascular response to injury and inflammation. The inappropriate activation of this system causes hypertension, fluid retention, and inflammatory, thrombotic, and atherogenic effects that may contribute to end-organ damage in the long term. Although aldosterone (Aldo), renin, and several breakdown products of angiotensin I (AI) are also involved, most of the effects of the RAAS on target tissues are mediated by angiotensin II (AII), which is generated both in the circulation and in the tissue. [20]

Renin

Renin, a protease mainly produced by the juxtaglomerular cells of the kidney, is encoded by the *REN* gene located on chromosome 1q32. Renin occurs in organs other than the kidney, e.g., in the brain, where it is implicated in the regulation of numerous activities. The enzyme which catalyzes the first step in the activation pathway of angiotensinogen to angiotensin I and its gene mutation have been associated with hyperproreninemia, hyperuricemic nephropathy, and renal tubular dysgenesis.

Angiotensinogen, angiotensin I, and angiotensin II

Angiotensinogen, a precursor of angiotensin and encoded by the *AGT* gene located on chromosome 1q42 – q43, is mainly produced by the liver and found in the α2-globulin fraction of plasma. In the RAAS, angiotensinogen is cleaved by renin and *AGT* mutations were related to renal tubular dysgenesis, susceptibility to essential hypertension, and preeclampsia.

Aldosterone synthase

Aldosterone synthase, encoded by the *CYP11B2* gene, located on

chromosome 8q21 – q22, is a steroid 11/18-β-hydroxylase that functions in mitochondria in the zona glomerulosa of the adrenal cortex to synthesize the mineralocorticoid aldosterone. Some studies described the importance of common polymorphisms in adrenal synthetic genes in altering corticosteroid biosynthesis. *CYP11B2* variants were associated with corticosterone methyloxidase types I and II deficiency (congenital hypoaldosteronism) and increased the aldosterone to renin ratio.

Angiotensin receptors 1 and 2

Two pharmacologically distinct subtypes of cell surface receptors, angiotensin receptors types 1 and 2 (AT1 and At2), interact with angiotensin II. *AGTR1* and *AGTR2* genes are located on chromosomes 3q21 – q25 and Xq21 – 23, respectively. AT1 seems to mediate the major cardiovascular effects of angiotensin II, leading to effects such as vasoconstriction, increased arterial blood pressure, increased myocardial contractility, and sodium and water retention. Some *AGTR1* variants were associated with susceptibility to essential hypertension and renal tubular dysgenesis.

Angiotensin converting enzyme (ACE)

ACE or kininase II is a dipeptidylcarboxypeptidaseencoded by the *ACE* gene, located on chromosome 17q23.3, whereas the *ACE2* gene is located on chromosome Xp22 and it may counteract some of the effects of ACE. ACE is mainly produced by the lungs and plays a pivotal role in the RAS by hydrolyzing angiotensin I into angiotensin II. This product is a potent vasopressor and it acts on the adrenal cortex causing the release of aldosterone. In addition, ACE is also able to inactivate bradykinin—a potent vasodilator. *ACE* genetic variants have been associated with renal tubular dysgenesis, microvascular complications of diabetes, progression of a severe acute respiratory syndrome, and the susceptibility to myocardial infarction and Alzheimer's disease. [21]

ACE I/D polymorphism & ESRD

Among the RAAS genes, angiotensin-converting enzyme (ACE) is said to be a major component and it has been extensively studied as a candidate gene for various disorders.ACE polymorphisms appear to have significant impact on the progression of ESRD. The ACE gene spans 21 kilo bases is located on the 17thchromosome q23 and consists of 26 exons and 25 introns. The I/D polymorphism exists in intron 16. The genotype is classified into three types: - deletion homozygotes, DD; insertion homozygote's II and heterozygote's, ID.A 287-bp Alu insertion/ deletion (I/D) polymorphism at intron 16 of ACE was found to be susceptible to essential hypertension, type 2diabetes mellitus, diabetic complications and ESRD in various populations.[22]

Several studies have reported that the DD homozygote of I/D polymorphism of the ACE gene is associated with an increased risk of developing ESRD.A review published in 1999, showed that the DD genotype is associated with increased progression of renal failure towards end-stage renal disease (ESRD).[23-25]

A positive association of the DD genotype with left ventricular hypertrophy[26],fatal and nonfatal CVD[27], and cerebrovascular disease[28] has been reported in ESRD patients. Furthermore, the 2 follow-up studies reporting a positive association between DD genotype and mortality were performed in diabetic dialysis patients [29] or in hemodialysis (HD) patients only. [30]

The renal ACE gene expression is associated with the ACE I/D genotype in healthy Japanese subjects. [31] The study [32] concluded that DD genotype identifies dialysis patients at an increased risk for mortality. One of the study support the idea that D allele or DD genotype was associated with increased risk of ESRD susceptibility in the overall populations, and DD genotype was associated with ESRD susceptibility in Caucasians.[33] The study [34] indicate that D allele or DD homozygous is associated with the ESRD susceptibility in DN patients. In contrast with other studies, Zohreh Rahimi et al study did not detect an association between the ACE I/D polymorphism and the risk of ESRD. [35]

SUMMARY AND CONCLUSION

Activation of the RAAS in the presence of elevated arterial pressure leads to renal injury and plays a pivotal role in the pathogenesis of ESRD. Angiotensin converting enzyme (ACE) is a key component of the RAAS. It is responsible for the conversion of Angiotensin I to Angiotensin II. Angiotensin II is a potent vasoconstrictor, and a stimulator of aldosterone synthesis which causes increased blood pressure.

In conclusion, there is an association between ESRD and ACE I/D polymorphism and also we can say that ACE-DD genotype may be a risk factor and it is also associated with an increased mortality risk in ESRD patients.

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