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Mini Review Article

Renin-Angiotensin System Polymorphism in Chronic Kidney Disease and Diabetic Nephropathy

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Abstract
The renin-angiotensin system (RAS) is a vital hormonal pathway that regulates blood pressure, fluid balance and vascular tone but its dysregulation has been linked to several renal ailments including chronic kidney disease (CKD) and diabetic nephropathy (DN). Angiotensin II, the key effector molecule of RAS, acts through receptors AGTR1 and AGTR2 thus influencing cell proliferation, inflammation, and angiogenesis. Current review summarizes the key RAS gene variations associated with CKDs. Genetic polymorphisms in RAS components particularly *ACE* (I/D), *AGTR1* (*A1166C*), and *AGT* (*M235T*) have been associated with increased susceptibility and progression of renal diseases. In CKDs, *ACE* DD and *AGTR1* CC genotypes correlate with higher ACE activity, hypertension, and faster disease progression highlighting their diagnostic and therapeutic significance. Hyperglycemia induced RAS activation has been associated with DN through elevation of Ang II levels. The elevated Ang II leads towards oxidative stress and vascular injury. Overall, RAS genetic polymorphism plays a central role in renal disease pathogenesis, hence offering valuable insight for personalized medicine and targeted therapy.
Key Words: Renin-angiotensin system, Polymorphism, Chronic kidney disease, Diabetic nephropathy

INTRODUCTION

Renin angiotensin system (RAS) is a central hormonal cascade traditionally recognized for its essential role in regulating blood pressure, electrolyte balance, and vascular homeostasis. Emerging evidence suggests RAS involvement in diverse pathological processes including chronic kidney disease (CKD), diabetes-associated complications such as diabetic nephropathy (DN), cancer progression and cardiovascular diseases [1]. Angiotensin II (Ang II) is the principal effector peptide of RAS. It is produced when renin cleaves angiotensinogen to form Ang I which is further converted into Ang II by angiotensin converting enzyme (ACE) [2]. Ang II exerts its biological actions mainly through two receptors AGTR1 (AT1R) and AGTR2 (AT2R). The AGTR1 expressed abundantly in adrenal gland, heart, kidney and adipose tissues in adult, in comparison the AGTR2 is highly expressed in fetal tissue. However, their occurrence in adults restricted to adrenal gland, uterine myometrium, kidney and brain, decreases in normal condition [1].

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AT1R mediates vasoconstriction, inflammation, fibrosis, and proliferative signaling. AT2R generally acts in opposition to the AT1R mediating vasodilation, anti-inflammatory and anti-proliferative effects [3].
Genetic variations of RAS have been linked to multiple renal diseases like CKD and DN. Hence, representing RAS not only as a regulator of cardiovascular physiology but also as a crucial molecular network involved in renal pathology. ACE or Peptidyl-Dipeptidase A is a zinc-dependent dipeptidyl carboxypeptidase which splits a dipeptide from the carboxyl terminal of Ang I to convert Ang II [4]. Angiotensin II, is a peptide hormone, is a large vasoconstrictor which performs its function through the AGTR1 [3].
Chronic RAS overactivity drives hypertension and progressive kidney injury. Inhibition of ACE or AT1R (ARBs) reduces intraglomerular pressure and proteinuria, slowing CKD/DN progression [5]. Thus, genetic variation in RAS genes (ACE, AGT, AGTR1) can modulate Ang II levels or receptor signaling and alter susceptibility to CKD and DN.

Methodology of Literature Review

Databases Searched	PubMed, Scopus, Web of Science, Google Scholar
Study Period Covered	2006–2025
Study Types Included	Case–control studies (Human subjects), cohort studies, systematic reviews, meta-analyses
Key Search Terms	Renin–Angiotensin System, ACE I/D polymorphism, AGT M235T, AGTR1 A1166C, AGTR2 polymorphism, Chronic Kidney Disease, Diabetic Nephropathy, ESRD
Inclusion Criteria	Renin–Angiotensin System, ACE I/D polymorphism, AGT M235T, AGTR1 A1166C, AGTR2 polymorphism, Chronic Kidney Disease, Diabetic Nephropathy, ESRD
Data Extraction Focus	Gene variants studied, population ethnicity, disease type, clinical outcomes, odds ratios or risk estimates

RAS Polymorphism and Chronic Kidney Diseases

The RAS regulates sodium balance, amount of extracellular fluid (ECF), renal and systemic vascular resistance. RAS acts as most active regulator of blood pressure [6]. The RAS is a central regulator of both blood pressure and renal function and plays an important part in their interactions. Both RAS blockers, angiotensin receptor blocker and ACE inhibitors minimize or avoid kidney damage and also lower blood pressure. Genetic diversity in the genes of various RAS components is appropriate to lead to a heterogeneous relationship in patients with renal disease. ACE-1 is an essential element of RAS, and its suppression delays the rate of development in most chronic nephropathies [7].

ACE gene coding is susceptible to I /D (insertion / deletion) polymorphism which is a significant determinant of tissue level and ACE plasma level [7]. The three genotypes (DD, DI, and II) are created because of insertion / deletion of ACE gene polymorphism at chromosome 17, intron 16 [8]. DD homozygotes with circulating tissue ACE are four times higher than DI heterozygotes or II homozygotes were recorded. The D allele could pose a risk factor for kidney parenchyma damage [8]. ACE genes have a regular I / D (insertion-deletion) polymorphism and are distinguished by the repeated sequence of Alu 278bp in intron 16 [8]. This polymorphism correlates with the degree of circulating ACE [9, 10].

Polymorphisms of *AGT M235T* and *AGTR2 C3123A* were closely related to higher risk of chronic renal disease in general population [8]. Methionine combined with threonin (*M235T* Polymorphism) has been studied extensively in kidney and cardiovascular diseases [9, 10]. The *M235T* T allele is linked to higher circulating AGT levels and increased Ang II generation. While *AGT* variants are well established as genetic risk factors for hypertension, their independent association with non-diabetic CKD progression has been inconsistent. Most recent studies suggest that AGT polymorphisms do not strongly predict CKD susceptibility or progression when diabetes is excluded, indicating that their pathogenic relevance may be context dependent.

AGTR1 polymorphism A1166C is caused by the replacement of cytosine with adenine in non-translated region of position 1166 at 30 [9]. Meta-analysis was conducted to explore the relationship between *AGTR1 A1166C* and *AGTR2 A1332G* polymorphisms with kidney diseases such as CKD, end-stage renal disease (ESRD), IgA nephropathy, and vesicoureteral reflux but found no significant associations suggesting these variants are not reliable predictors of renal disorders [6]. *ACE* polymorphisms showed no significant link to ESRD, the *AGT* T allele and *AGTR1* C allele (*A1166C*) were associated with faster progression to ESRD, independent of hypertension, indicating these genotypes (CC/AC) could serve as early markers for renal failure risk [9]. Similarly, in pediatric CKD patients, those with *ACE* DD and *AGTR1* CC genotypes had higher ACE activity, left ventricular mass, and a greater prevalence of hypertension especially in patients on hemodialysis highlighting the role of these polymorphisms in disease severity and potential value in guiding personalized treatment for kidney disease [7].

RAS Polymorphism in Diabetes and Diabetic Nephropathy

A significant genetic cause for diabetic problems is the RAS [11]. RAS plays an important part in sodium metabolism, regulating blood pressure or renal hemodynamic, mainly through angiotensin II [12]. Hyperglycemia activates the RAS which plays a crucial part in the regulation of blood pressure, sodium metabolism, renal hemodynamic, vascular tone and vascular modeling. In diabetic patients, hyperglycemia raises Ang II in tissue, which causes oxidative stress,

inflammation, glomerular hyperfiltration, thrombosis, vascular remodeling, and endothelial injury [13]. The most probable candidate genes for diabetic nephropathy have been confirmed by genes that encode certain RAS elements like *ACE* [angiotensin-converting enzyme (*MIM 106180*)], *AGT* [angiotensinogen (*MIM 106150*)] and *AGTR1* [angiotensin II type 1 receptor (*MIM 106165*)] [14]. Due to central role of ACE in RAS, research has analyzed the role of insertion / deletion (I/D) polymorphism in vascular diseases, particularly in diabetes [15]. I/D (Insertion / deletion) polymorphism at 16th intron of the *ACE* gene has been identified consistently to plasma levels of angiotensin converting enzyme and blood pressure [14].

The involvement of *AGTR1 A1166C* polymorphism in diabetes mellitus (DM) and diabetic nephropathy (DN) susceptibility has been analyzed in some studies, but with contrasting results [13]. *AGTR1 A1166C* polymorphism can cause DN, especially in the patients of type 2 diabetes mellitus (*T2DM*). AGTR1 expression is significantly linked to the presence of C allele at the position of 1166 and has a higher affinity to Ang II. Increased Ang II activity has led to increased sensitivity of the kidney and in turn, hyperglycemia due to systemic or renal hemodynamic deficiencies or to a decrease in the activity of the kidney cells. Ang II is a powerful vasoconstrictor that induces salt and water holding capacity contributing to severe hypertension, and to a significant risk factor for diabetes nephropathy (DN) [16] (Eroglu et al, 2008).

M235T polymorphism of the *AGT* gene was initially stated to be related to hypertension, and *M235T* polymorphism of TT genotype was also found to increase the risk of developing diabetic nephropathy [14]. A meta-review reports a modest but significant association between the *M235T* variant and DN risk (pooled OR ≈ 1.21). However, results across studies are heterogeneous, with some analyses showing no overall association. Notably, gender-specific effects have been reported, with stronger associations observed in male patients. Evidence for the *T174M* variant remains inconsistent, and most large meta-analyses do not support a significant role for this polymorphism in DN [5]. Data on *AGTR2* polymorphisms in DN are limited but intriguing. A small study identified an association between the -1332G>A variant and DN in women, suggesting possible sex-dependent genetic effects. However, these findings require replication in larger, multiethnic cohorts [17].

Pharmacogenomic Implications

Given that RAS blockers are cornerstone therapies in CKD/DN, RAS genotypes might modulate drug response. *ACE I/D* clearly affects circulating *ACE: DD* carriers have higher ACE levels than II [18]. Some pharmacogenomic studies suggest that *ACE DD* patients may achieve less relative reduction in proteinuria under ACE inhibitors (since their baseline ACE is higher) although results are mixed. More compelling data come from AGTR1 a prospective trial of candesartan in heart failure found that 1166C carriers exhibited a greater compensatory rise in renin activity and blunted aldosterone suppression during long-term ARB therapy [19]. This implies that C carriers maintain higher RAS drive despite AGTR1 blockade which could affect antihypertensive efficacy. Diabetic patients with the 1166C allele might respond differently to ARBs though this has not been directly tested in DN trials [20]. Overall, these findings highlight that RAS gene variants can influence pharmacodynamics of ACE inhibitors/ARBs, but larger clinical studies are needed to link genotypes to outcomes such as BP control, albuminuria reduction or CKD progression.

CONCLUSION

This study examined the association of RAS gene polymorphisms with chronic kidney disease and diabetic nephropathy. The *ACE I/D* variant and *AGTR1 A1166C* polymorphism are the strongest genetic contributors to DN risk while *AGT M235T* may exert modest effects. In CKD RAS variants show weaker and more population-specific associations. These findings support the concept that genetic modulation of RAS activity contributes to diabetes specifically renal injury and may influence disease progression as well as therapeutic response to RAS blockade.

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