International Journal of Research
Available at https://pen2print.org/index.php/ijr/
e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 21
October 2018

Analysis of role of Renin-Angiotensin-Aldosterone System in chronic kidney diseases in local population of Pakistan

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Abstract

Introduction: Chronic kidney disease (CKD) is a major public health problem, and preventing CKD and/or delaying progression of CKD patients to end-stage renal disease (ESRD) is a major task for the nephrology community. **Aim and objectives:** The basic aim of the study is to analyze the role of Renin-Angiotensin-Aldosterone System in the management of chronic kidney diseases. **Methodology of the study:** This study was conducted during March 2018 in the hospital----------. This study was basically conducted for the analysis of role of RAAS in the management of CKD. For this purpose we make a thorough analysis and study of RAAS. **Results:** The RAAS is directly involved in the regulation of CKD, 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 AII, which is generated both in the circulation and in the tissue. **Conclusion:** It is concluded that RAAS plays very important role in the management of CKD in local population of Pakistan.

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 21
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However there are some evidence that in patients with diabetic nephropathy that the antiproteinuric effect of mineralocorticoid receptor blockade (MRB) is at least in part mediated by a direct effect on the glomerular basement membrane and is not dependent solely on reduction in systemic BP, glomerular filtration or dietary factors.

Introduction

Chronic kidney disease (CKD) is a major public health problem, and preventing CKD and/or delaying progression of CKD patients to end-stage renal disease (ESRD) is a major task for the nephrology community[1]. This looks like an achievable target, in particular because of the availability of reno-protective drugs that may interfere with disease progression such as the inhibitors of the renin-angiotensin-aldosterone system (RAAS). After the first inhibitor of angiotensin II (AII) system, the angiotensin-converting enzyme (ACE) inhibitor captopril, became available for clinical use in the early 1980s[2], other drugs have become progressively available that interfere with RAAS activity, such as AII-type 1 receptor blockers (ARBs) and the aldosterone(Aldos) antagonists that inhibit AII and Aldos activity by competitively antagonizing their binding to specific receptors[3]. In a short future, novel agents that interfere with renin activity (such as aliskiren) will also become available for clinical use[4], which will further increase the armamentarium of drugs that may interfere with the sequence of events, eventually resulting in AII and Aldos production at different levels and that, used in combination, may achieve an almost complete inhibition of the RAAS. In addition, to identify the optimal regimens to

e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 05 Issue 21
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maximize reno-protection, major efforts should be made in identifying and treating all patients at risk, with the final aim to delay or even prevent the onset and progression of chronic renal disease and related complications[5].

The renin-angiotensin aldosterone system (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. Angiotensin II (AII) is the main effector of the RAAS and exerts its vasoconstrictor effect predominantly on the postglomerular arterioles, thereby increasing the glomerular hydraulic pressure and the ultrafiltration of plasma proteins, effects that may contribute to the onset and progression of chronic renal damage[6]. AII may also directly contribute to accelerate renal damage by sustaining cell growth, inflammation, and fibrosis. Interventions that inhibit the activity of the RAAS are renoprotective and may slow or even halt the progression of chronic nephropathies. ACE inhibitors and angiotensin II receptor antagonists can be used in combination to maximize RAAS inhibition and more effectively reduce proteinuria and GFR decline in diabetic and nondiabetic renal disease[7]. Recent evidence suggests that add-on therapy with an aldosterone antagonist may further increase renoprotection, but may also enhance the risk hyperkalemia. Maximized RAAS inhibition, combined with intensified blood pressure control (and metabolic control in diabetics) and amelioration of dyslipidemia in a multimodal approach including lifestyle modifications (Remission Clinic), may achieve remission of proteinuria and renal function stabilization in a substantial proportion of patients with proteinuric renal disease[8].

The RAAS is the best known regulator of blood pressure (BP) and determinant of target-organ damage from hypertension. It also controls fluid and electrolyte balance through coordinated effects on the heart, blood vessels, and kidneys. AII is the main effector of the RAAS. In the classic pathway of the RAAS, renin is secreted from the juxtaglomerular apparatus of the kidney and acts on the circulating precursor angiotensinogen to generate angiotensin I. Angiotensin I has little effect on BP and is converted in the lungs by ACE to AII. AII acts on the heart and the kidneys by binding to the G protein–coupled receptors type 1 (AT1) and type 2 (AT2)[9].

Aim and objectives

The basic aim of the study is to analyze the role of Renin-Angiotensin-Aldosterone System in the management of chronic kidney diseases in local population of Pakistan.

Methodology of the study

This study was conducted during March 2018 in the hospital ----------.
This study was basically conducted for the analysis of role of RAAS in the management of CKD. For this purpose we make a thorough analysis and study of RAAS. The purpose of the present review is to present a general view of the multiple actions of RAAS and their more relevant components in the development and progression of CVD and CKD, together with an analysis of present treatments based on RAAS blockade including new drugs and their combinations as a fundamental strategies for reducing their impact on mortality and morbidity cause by these entities.

Data collection

For this study the data was collected from 50 patients who was suffering from kidney disease. For this purpose we make two groups of study. One group was control group and the other group was suffering from kidney problems. Then we collect the socio economic status and therapy status of both groups. Then we analyze the data and find that either statin therapy is helpful for patients or not.

Analysis

Student's t-test was performed to evaluate the differences in roughness between groups. Two-way ANOVA was performed to study the contributions. A chi-square test was used to examine the difference in the distribution of the fracture modes (SPSS 19.0 for Windows, SPSS Inc., USA).

Results

The RAAS is directly involved in the regulation of CKD, 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 AII, which is generated both in the circulation and in the tissue[10].

In the classic pathway of the RAAS, renin is secreted from the juxtaglomerular apparatus of the kidney and acts on the circulating precursor angiotensinogen to generate AI. Renin hydrolyzes the

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Leu10-Val11 bond of angiotensinogen, to generate the decapeptide AI (1-10). Angiotensin converting enzyme (ACE) present in the endothelium and tissues convert AI to the octapeptide AII. In the heart, kidneys, and brain, AII is also produced by non-ACE pathways involving chymases, cathepsin G, kallikrein-like enzymes and endopeptidases and seems to exert effects on target tissues that are even greater than the effects of centrally generated AII. AII acts on the heart and the kidneys by binding to the G protein coupled receptors type 1 (ATR1) and type 2 (ATR2). The ATR1 receptor mediates the more deleterious effects of AII - that is, vasoconstriction and cardiac and vessel hypertrophy. The ATR2 receptor regulates opposing effects. In addition to the conversion of AI to AII, ACE inactivates two vasodilator peptides, bradykinin and kallidin.

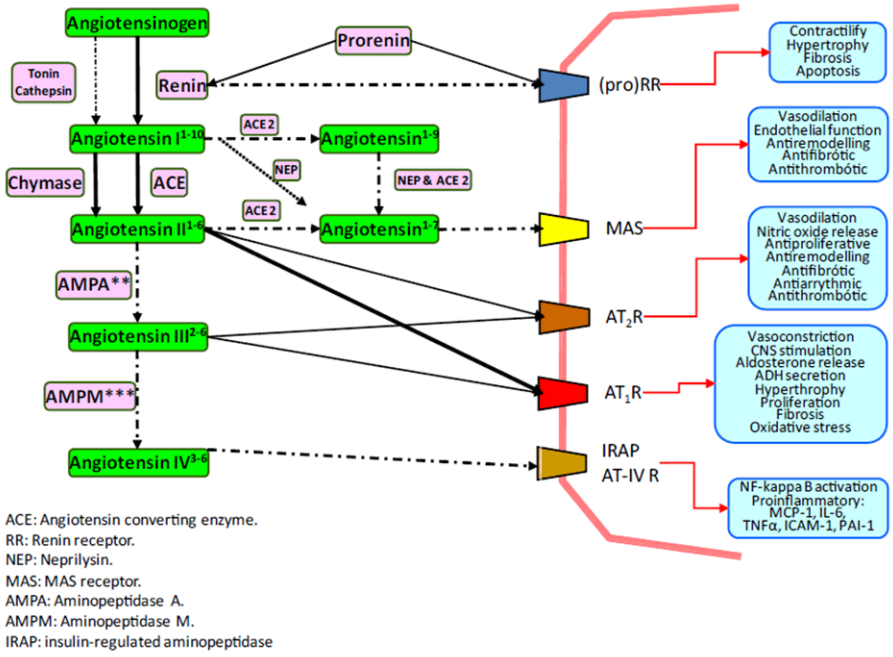

Figure 01: RAAS overview

Table 01 of the data shows the basic values of control group and patients. It shows the BMI, age, Total cholesterol level and other basic values. We can find that cholesterol level is high in patients as compared to normal values. We also shows the comparison of statin group and normal group.

Table 01: General values of Control group and diseased group

Variable	Diseases Group	Control Group	t Value	*p* Value
Age（Year）	56.56±8.46	53.64±8.36	1.716	0.081
BMI（kg/m2）	24.31±2.26	23.37±2.09	2.195	0.031
SBP（mmHg）	140.36±15.70	116.53±13.46	8.248	0.000
DBP（mmHg）	87.94±10.69	75.81±9.94	5.967	0.000
PP（mmHg）	52.42±12.87	40.72±8.74	5.426	0.000
FBG（mmol/）	5.12±0.65	5.06±0.49	1.764	0.081
TG（mmol/L）	1.74±0.75	1.69±0.86	1.838	0.071
TC（mmol/L）	4.95±0.76	4.88±0.82	1.712	0.090
HDL-	1.30±0.43	1.31±0.56	1.717	0.089
LDL-C	3.46±0.58	3.38±0.66	1.139	0.266

Tale 02 shows the values of analysis of statin therapy in patients. It shows the comparison between two groups on the basis of functional values.

Table 02: Comparison between two groups in structural and functional parameters

Group	IMT (μm)	CC (mm^2/KPa)	α	β
CKD Group	694.88±77.63	0.89±0.13	5.68±1.23	11.25±1.01
Control Group	586.87±62.12	0.96±0.08	4.77±0.62	9.24±1.24
T value	7.818	-3.115	4.712	9.004
P value	0.000	0.002	0.000	0.000

Discussion

The renin-angiotensin-aldosterone system regulates renal vasomotor activity, maintains optimal salt and water homeostasis, and controls tissue growth in the kidney. However, pathologic consequences can result from overactivity of this cascade, involving it in the pathophysiology of kidney disease[10]. An activated renin-angiotensin-aldosterone system promotes both systemic and glomerular capillary hypertension, which can induce hemodynamic injury to the vascular endothelium and glomerulus. In addition, direct profibrotic and proinflammatory actions of angiotensin II and aldosterone may also promote kidney damage. The majority of the untoward effects associated with angiotensin II appear to be mediated through its binding to the angiotensin II type 1 receptor. Aldosterone can also induce renal injury by binding to its receptor in the kidney[11]. An understanding of this system is important to appreciate that inhibitors of this cascade can reduce the progression of chronic kidney disease in proteinuric disease states. Pharmacologic agents that can interfere with this cascade include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone receptor antagonists[12].

Aldo plays a pathological role in CVD and kidney disease in part due to its mitogenic effects on a number of cell types in the systemic vasculature, heart and kidney. Other mechanism involve in Aldo CV injury include inflammation, oxidative stress, activation and enhancement of AII and accelerated fibrosis[13]. After binding to the MCR, Aldo is translocated into the nucleus, in which the complex dissociates and binds to regulatory regions of multiple genes that stimulate production of proteins involved in both sodium and potassium transport as well as inflammation and oxidative stress[14].

There are several pathogenetic factors in which Aldo, via the nongenomic pathway, may contribute to CKD. Experimental models of CKD have demonstrated a key role for Aldo-mediated glomerular and tubular injury and inflammation. This injury is mediated in part by activation of oxidative stress molecules, up-regulated in part by NADPH oxidase, including proinflammatory cytokines such as IL-6, MCP-1, ICAM-1, osteopontin and TGF-beta[14]. Both tubulointerstitial damage and glomerular injury, particularly of the podocytes, occurs secondary to this nongenomic effect of Aldo. Blockade of the MCR using drugs like spironolactone and eplerenone attenuate or abrogate all these effects[15]. An interesting finding is that some of the beneficial effects of Aldo blockade are believed to be, in part, by improvement in endothelial dysfunction[16].

Conclusion

It is concluded that RAAS plays very important role in the management of CKD in local population of Pakistan. However there are some evidence that in patients with diabetic nephropathy that the antiproteinuric effect of mineralocorticoid receptor blockade (MRB) is at least in part mediated by a direct effect on the glomerular basement membrane and is not dependent solely on reduction in systemic BP, glomerular filtration or dietary factors.

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