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Review Article

RENIN ANGIOTENSIN SYSTEM AND ITS THERAPEUTIC APPROACHES

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ABSTRACT
The renin–angiotensin system (RAS) has an important role in the control of blood pressure, hypertension, diabetes, and in the regulation of salt and volume homeostasis of organisms as well as in the heart failure, and other related renal dysfunctions. Renin is the main protease enzyme of the RAS. In kidney, Juxtaglomerular (JG) cells are most important site for renin production. Renin act on Angiotensinogen (AOG) and cleave Angiotensin I and form different Angiotensins-ANG II, ANG 1-7, ANG 1-9 using Angiotensin converting enzyme (ACE) and Angiotensin receptors (AT-R). RAS inhibition using β-Blockers, Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), Direct Renin Inhibitors are proven important for the study of prevention of several renal diseases and cardiovascular diseases. Additionally, several drugs such as vitamin D receptor activators, endothelin antagonists, Aldosterone antagonists, or monocyte chemotactic protein-1 antagonists are also used in controlling blood pressure, endothelial dysfunction and heart failure. Aliskiren, Enalapril and other inhibitors has proved a valuable therapeutic approach in different diseases.

Key Words: *Renin–Angiotensin System (RAS), Juxtaglomerular (JG) cells, Angiotensinogen(AOG), Renin inhibiton, Renin inhibitors, Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs).*

INTRODUCTION
Renin Angiotensin System
The renin–angiotensin system (RAS) has an important role in the control of blood pressure, hypertension and in the regulation of salt and volume homeostasis of organisms as well as in the cardiac hypertrophy, heart failure, advanced liver disease, atherosclerosis, and renal artery stenosis, is also known as the renin-angiotensin-aldosterone system (RAAS) which is take part in the both pathophysiological and physiological properties (Castrop *et al,* 2010; Balakumar *et al,* 2011).

Renin is a protease enzyme which belongs to the aspartic proteinase family and it includes cathepsin-D, pepsin, and chymosin (Bhandari *et al,* 2010). Renin is the main enzyme of the renin-angiotensin system (RAS) and it is act as a protease and also as a hormone. Therefore, renin is intracellularly processed and packed into vesicles like a typical lysosomal protein and also it is glycosylated like a typical secretory protein (Castrop *et al,* 2010). Properties of renin includes, the molecular weight of human renin is about 41,000, pH optimum is at about 5.5-6.0, and isoelectric point is about 5.2-5.8 (Skott *et al,* 1993), it works best at body temperature-37^{o}C, it can acting optimally on hemoglobin at pH 3-7, Crystalline renin has low solubility and more stability and it can be dried easily without decomposition (Berridge, 1945).

Enzymatically active renin is release from the kidney (Castrop *et al,* 2010). There are many renin producing cells present in the kidney but juxtaglomerular (JG) cells are mostly taking part in renin production, which are present at middle layer of the afferent artiole located to the vascular poles of the glomeruli (Kurtz *et al,* 1999). Pro-renin is contain 406 amino acids and it is stored in vesicles and convert into active renin which have about 339-341 amino acids, and then released as per requirement. Actions of (pro) renin are mediated by (pro) renin receptors, angiotensin II and angiotensin-(1–7) (Castrop *et al,* 2010; Balakumar *et al,* 2011). Angiotensin II is considered a most important effector of the RAS induced

physiological actions through its type 1 receptor (AT1) which exerts peripheral vasoconstriction, renal and sympathetic effects directed toward blood pressure increase and water and salt retention (Figure 1) (Perez-Rosas *et al,* 2011). While Ang II regulate (pro)renin synthesis on the individual cellular level in the part of the nephron, explosion of the intact CNT has larger scale effects on RAS activation by increasing the whole population of the (pro) renin-producing primary cells (Peti-peterdi *et al,* 2008). The cAMP (stimulatory) and Ca^{+2} (inhibitory) signaling pathways can control the release of renin (Castrop *et al,* 2010).

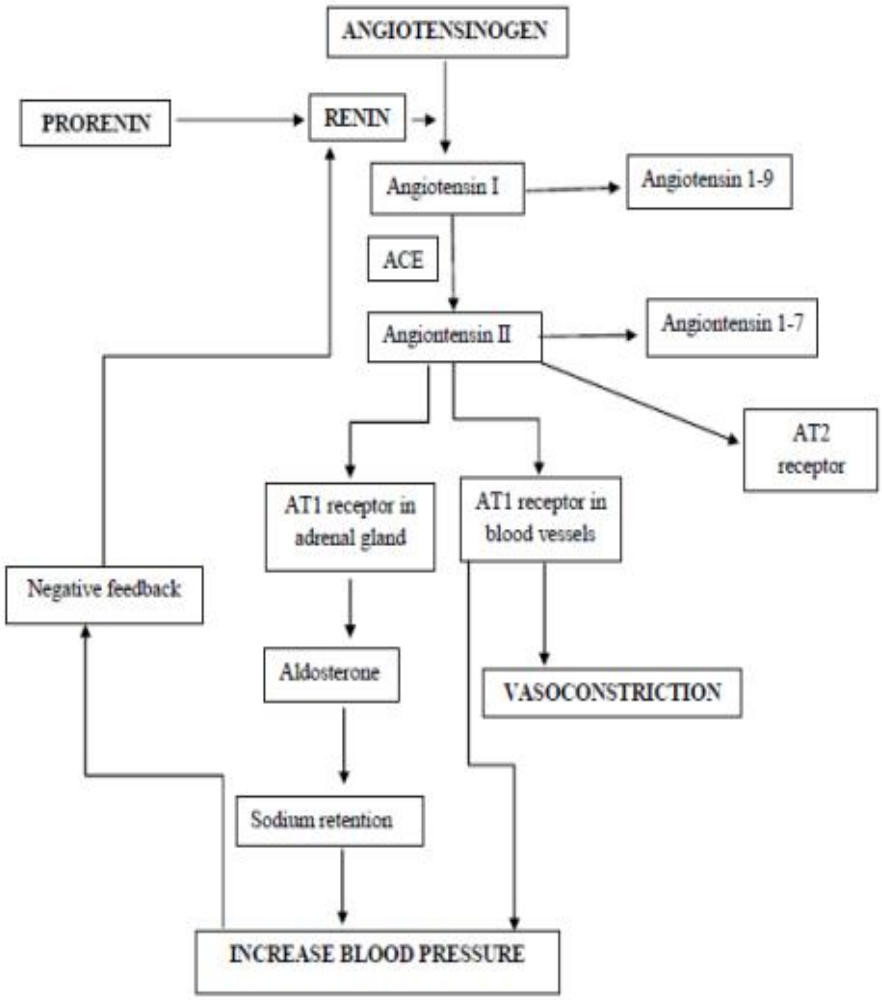

Figure 1: Renin Angiotensin System and Action of Renin (Based on Atlas, 2007).

Action of renin: Prorenin is convert into active renin which act upon the key substrate Angiotensinogen (AOG) which has high molecular weight and cleave decapeptide Angiotensin I (ANG I). From that, using Angiotensin converting enzyme (ACE) i.e. zinc dependent protease convert into octapeptide Angiotensin II (ANG II), ANG II is an active endocrine hormone which formed in the extracellular space by sequential proteolytic cleavage of its precursors (Balakumar *et al.,* 2011; Atlas, 2007). After that ANG II is bind with Angiotensin receptors (AT-R) and increase regulation process of Blood pressure, Inflammation, Hypertrophy, Sodium balance, Proliferation. On other hand ACE2 converts ANG I into

ANG 1-9 and ANG II into ANG 1-7. ANG 1-9 is also convert into ANG 1-7 which bind with the Mas receptor (Mas-R) and release aldosterone, increase sympathetic outflow, direct vasoconstriction that lead to regulation process of Blood pressure, Inflammation, Hypertrophy, Sodium balance, Proliferation, and renal abnormalities (Balakumar *et al,* 2011; Skott *et al,* 1993).

RAS - Its Inhibition and Pathophysiology

In the RAS, angiotensinogen which is a product of the α-globin gene, is expressed in the liver and unregulated during the acute phase of immune response (Daniels *et al,* 2007). The inhibition of renin-angiotensin system at different steps using Beta Blockers, Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), Direct Renin Inhibitors are proven important for the study of prevention of several renal diseases and cardiovascular diseases (Fisher *et al.,* 2005). In the presence of conditions predisposing to hyperplasia, hypertrophy, and tissue remodeling, such as hypertension, atherosclerosis, diabetes, and others, even a normal activity of the RAS may result in inadequately elevated and thus it cause a further progression of the disease (Volpe *et al.,* 2002). The inhibition of renin angiotensin system involves following steps: The initial step of formation of Ang-I from AOG can be blocked by using direct renin inhibitors. Formation of Ang-II from Ang-I can be inhibited by using ACE inhibitors. Then the actions on cardiovascularrenal system of Ang-II can be prevented by using AT1 receptor blockers and the release of renin is reduced by using β-Adrenergic blocking agents reduce renin release and in this way, by interfering with these inhibitors, increase renin levels for pathophysiological uses (Balakumar *et al.,* 2011; Fisher *et al.,* 2005).

RAS inhibitors

In the prevailing 50 years, ACE inhibition and angiotensin II receptor type 1 (AT 1) blockade have indeed become integral apparatus of cardiovascular pharmacotherapy (Bhandari *et al.,* 2010). The basic types of RAS inhibitors are:

1. β-Blockers

B-adrenergic receptor blockers are frequently disregarded as potent suppressors of renin secretion and most probably of angiotensin II formation. They have antihypertensive efficacy comparable to ACE inhibitors (Blumenfeld *et al.,* 1999). Beta-blocker therapy (propranolol) efficiently lowers plasma renin levels by blocking sympathetically (β1)-mediated renin release by the kidney (sealey *et al.,* 2007). It also showed that reduced aldosterone secretion and the reduction in plasma renin level (by about 75%) was closely correlated with reductions in blood pressure (Atlas, 2007). β-blocker therapy can also suppress production of Ang II and Plasma renin Activity (PRA) during in hypertensive subjects but at that time its catalytic activity is blocked (sealey *et al.*, 2007).

2. Angiotensin-Converting Enzyme Inhibitors (ACEIs)

ACEIs competitively block conversion of Ang I to Ang II by blocking the action of ACE and thus reduce the concentration of Ang II (Atlas, 2007). ACEIs also decrease aldosterone and vasopressin secretion and sympathetic nerve activity and can block the actions of the RAAS. Short-term ACEI therapy is linked with a decrease in Ang II and aldosterone and leads to an increase in renin release and Ang I and promote sodium and water excretion (Sood *et al,* 2012). It also found that the ACEIs also may prevent the progression of microalbuminuria to proteinuria, reduce proteinuria in patients with established glomerular disease, and prevent or delay the progression of renal disease (Atlas, 2007).

3. Angiotensin Receptor Blockers (ARBs)

AT1 receptor mediates the different actions of Ang II which contribute to hypertension and volume dysregulation (renal sodium reabsorption, aldosterone secretion and vascular smooth muscle contraction and dipsogenic responses) as well as to cardiovascular damage (prothrombotic and proinflammatory effects, cellular hypertrophy or proliferation, and superoxide formation). ARBs act by blocking Ang II action at the receptor level, rather than by inhibiting its synthesis hence they ought to antagonize AT1-mediated effects of Ang II no matter how it is synthesized (Atlas, 2007). As monotherapy, it is probably ACE inhibitors are more efficient than ARBs as an antihypertensive agent (Blumenfeld *et al.,* 1999).

4. Direct Renin Inhibitors

The most recent class of agents which block the RAS to be introduced as the direct renin inhibitors it blocks the synthesis of all angiotensin peptides and useful into the prevention of the compensatory increase in renin activity (Atlas, 2007). Direct Renin inhibitors such as aliskiren is a prototype; involve the fourth class of drugs to lower blood pressure by blocking the renin-angiotensin system was recently approved for treatment of hypertension (sealey *et al,* 2007).

RAS and Its Therapeutic Approaches

Blood Pressure There are various animal models used for the studies of blood pressure, which shown use of either equivalence of ACE and renin inhibition or a small advantage of one or the other for the regulation of blood pressure (Fisher *et al,* 2005). Several studies shows that a high sodium diet decease the antihypertensive-antialbuminuric response to RAAS inhibition and therefore using low sodium diet potentiates the blood pressure and antialbuminuric response to RAS inhibition (Hiddo *et al,* 2011).

β-blocker therapy useful for the suppression of Ang II production and Plasma Renin Activity (PRA) during in hypertensive subjects and beta blockade may also inhibit intrarenal conversion of prorenin to renin (Atlas, 2007). Before β-adrenergic blockade, the mean prorenin level was about 40% lower in hypertensive subjects, whereas mean PRA remain stable (Blumenfeld *et al,* 1999). ACEIs and ARBs do not produce complete renin–angiotensin system inhibition that is why the clinical trials testing for ancillary-blood-pressure have yielded mixed results so, direct renin inhibitors (DRIs) such as aliskiren may afford greater protection from hypertensive complications by achieving more complete renin–angiotensin system inhibition (Bonanni *et al,* 2012).

Aliskiren, the first rennin inhibitor caused significant falls in trough clinic Blood Pressures both systolic and diastolic by taking only the 300-mg dose of aliskiren (sealey *et al,* 2007). Additionaly, several drugs such as vitamin D receptor activators, endothelin antagonists, or monocyte chemotactic protein-1 antagonists are also used for lowering blood pressure (Hiddo *et al,* 2011). Min *et al.* showed that increased numbers of endothelial progenitor cells (EPCs) could be cultured from ramipril-treated patients with stable coronary artery disease and this type of ACE inhibition resulted in improvement of various functional properties such as adhesion, migration, proliferation, and *in vitro* vasculogenesis assay, independent of any impact on blood pressure (Imanishi *et al,* 2009). Angiotensin can stimulate proliferation of glomerular mesangial and endothelial cells present in cell cultures, these findings is used in the treatment with high-dose enalapril was associated with diminished mesangial cell proliferation and normalization of the number of endothelial cells. But it cannot be concluded if these effects can be directly attributed to angiotensin II inhibition or they are secondary responses to other components, such as decreased blood pressure or reduced glomerular scarring (Meer *et al,* 2010).

Hypertension

Hypertension is a very common disease, itself it is not a disease but it cause risk factor for cardiovascular morbidity and mortality (Sood *et al,* 2012). Hypercholesterolemia and an activated renin-angiotensin system are well-established risk factors for Hypertension. Various pharmacological treatments of both risk factors using 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase inhibitors (statins) and ARBs reduce endorgan damage and cardiovascular mortality and morbidity. Other than cholesterol and blood pressure lowering mechanisms such as NO availability, and reduced oxidative stress are additional mechanisms underlying these protective effects of both therapies (Imanishi *et al,* 2009). Antihypertensive drugs and medications which could alter blood pressure, the renin-angiotensin-aldosterone system, or the action of thiazide diuretics were withdrawn (Victor *et al,* 2001).

Various RAS inhibitors are used for the treatment of hypertension including Angiotensin receptor (AT1 receptor) blockers (Candesartan, Valsartan, Irbesartan, Telmisartan.), ACE inhibitors (Enalapril, Lisinopril, Captopril, Ramipril, etc.) (Sood *et al,* 2012). Renin inhibitor, aliskiren is use for the treatment of hypertension and other related disorders which can prevent formation of ANG-1 from AOG. Aliskiren is use alone or in the combination with the other antihypertensive agents such as, an ACE inhibitor,

valsartan, and AT1 receptor blocker or benazepril but the use in the combination with valsartan is more effective than use as alone as antihypertensive effects and easily tolerated (Balakumar *et al,* 2011) and the combination dose of valsartan and Aliskiren increase Plasma renin concentration (PRC) (sealey *et al,* 2007).

Angiotensin-Converting Enzyme Inhibitor (ACEIs) block the action of ACE completely and thus block the conversion of Ang I to Ang II and thus reducing local levels of Ang II and circulating (Sood *et al,* 2012). An increased ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA) is referred to as the aldosterone-renin ratio, has been reported to distinguish patients with primary aldosteronism from those with essential hypertension (Victor *et al,* 2001). Angiotensin Receptor Blockers (ARBs) can block Angiotensin II activity at the receptor level rather than inhibiting its synthesis ARBs including valsartan, irbesartan, candesartan, eprosartan, telmisartan, and olmesartan are used in the reduction of blood pressure by decreasing systemic vascular resistance; they do not affect heart rate and have minimal effect on cardiac output in the non failing heart (Sood *et al,* 2012). Aliskiren is also advantageous for the reduction of Urinary (but not plasma) aldosterone and Brain natriuretic peptide (BNP) (Bonanni *et al,* 2012).

Angiotensin-dependent mechanisms are also used in the maintainance of glomerular capillary hypertension via increased systemic BP and vasoconstriction of the efferent arterioles. After causing glomerular hypertension, angiotensin II has been suggested to promote progressive renal damage through a variety of mechanisms directly, including increased extracellular matrix (ECM) deposition, induction of growth factor release and immune activation and Direct effects of angiotensin II also leads to increased protein ultrafiltration in the urinary space and alters the size-selective properties of the glomerular capillary barrier, which further increases protein filtration into the urinary space (Meer *et al,* 2010). The additive antirenin system effects of losartan and ACE inhibitors contributed significantly to the enhanced antihypertensive effect (Blumenfeld *et al,* 1999).

Diabetes

Diabetes is defined as a metabolic disorder which is characterised by hypertension, chronic hyperglycaemia, microalbuminuria, dyslipidaemia and inflammation. Moreover, it is also associated with number of vascular complications such as retinopathy, neuropathy and nephropathy. Diabetic nephropathy is the major cause of end-stage renal disease in about 25-40% of patients with diabetes (Sourris *et al,* 2012).

In the patient with diabetes, the renin angiotensin system has been activated through the treatment with ACE inhibitors and use of the oral contraceptives. In the diabetes patient, the relation to prorenin to total renin is different. The concentration of prorenin in plasma is 10-fold higher than renin. This increasing is due to several factors such as, autonomic dysfunction and glycation of a responsible enzyme and it is associated with microalbuminuria and with the development of nephropathy (Fisher *et al,* 2005), (Bonanni *et al,* 2012).

Activation of the local renal RAS is independent of the systemic RAS activation. In diabetes patients, the local RAS has been appears to be up-regulated, while the systemic RAS found to be down-regulated within the kidney. The most effective treatments for diabetic nephropathy target the RAS (Sourris *et al,* 2012). Prorenin is bind with the renin receptor and convert into renin for active response and lead to intracellular signalling pathways without involvement of angiotensin generation which are processed by activation of mitogen-activated protein kinases, ERK-1 and ERK-2. If these processes cause pathophysiology then ACE inhibitor or ANG II antagonist use for the treatment of diabetes by blocking the renin activity (Fisher *et al,* 2005).

In diabetes mellitus type 1 (T1DM) and type 2 (T2DM) clearly show that the glomerular filtration rate (GFR) generally starts to decline only with the appearance of macroalbuminuria, i.e. when proteins larger than albumin appear in the urinary space (Meer *et al,* 2010). Long-term trials with ACEIs have been demonstrated effective particularly in patients with nondiabetic nephropathies or in patients with insulin-

dependent (type 1) diabetes (Sood *et al,* 2012). It is documented that angiotensin receptor antagonists increase the number of endothelial progenitor cells (EPCs) in patients with type II diabetes mellitus (Bahlmann *et al.*) (Imanishi *et al,* 2009). Investigators have shown that aliskiren was as effective as losartan in promoting left ventricular (LV) mass regression in the Aliskiren in Left Ventricular Hypertrophy (ALLAY) study (Bonanni *et al,* 2012).

Improvement of Renal Structure in Non-Diabetic Nepropathy

In patients with mild to proliferative glomerulonephritis and relatively mild proteinuria were treated with an ARB, showed a decrease in mesangial matrix expansion and interstitial fibrosis although the global glomerular sclerosis ratio was not significantly altered by treatment (Meer *et al,* 2010). If in certain pathological states such as diabetic nephropathy, ACE2 is reduced in the glomeruli, this would lead to impaired Ang II degradation with its consequent accumulation within the glomerulus (Batlle *et al.* 2008).

Improvement of renal structure in diabetic nepropathy

Diabetic nephropathy is defined as a progressive decline in glomerular filtration rate which is accompanied by proteinuria and other end-organ complications such as retinopathy and is characterized as the major cause of end-stage renal disease (Sourris *et al,* 2012). Several studies have attempt to investigate the effect of angiontensin II in the improvement of renal structure in diabetic nepropathy (Meer *et al,* 2010).

Heart Failure

The heart and kidney are closely interactive with each other and in patients with heart disease and often suffer with renal disease, and vice versa (Schroten *et al*, 2012). When the cardiac cell growth is stimulated then in the cardiac myocyte, a local (autocrine-paracrine) RAS is activated which results in the stimulation of cardiac cell growth through Protein Kinase C. In conditions of hypertension, endothelial damage, or atherosclerosis, the same system also can be activated in smooth muscle cells. Angiotensin II is the most important Gq stimulator of the heart compared to the α1 adrenoreceptors and endothelin-1 during hypertrophy (Sood *et al*, 2012). The RAS and Kallikrein-kinin system (KKS) are endocrine pathways that play a vital role in cariac function by acting in opponent to regulate vascular pressure (Daniels *et al*, 2007). In patients at various stages of heart and kidney disease, from early disease (hypertension and diabetes mellitus) to advanced severe end-organ cardiorenal failure (including nephropathy, heart failure, and combined cardiorenal failure), dysfunction or blockade of the RAAS with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists aldosterone antagonists (ARAs) has increasingly become an efficient treatment (Schroten *et al*, 2012). There are mainly two different agents such as Spironolactone and eplerenone use that act as aldosterone antagonists are available, both aldosterone antagonists seem to be closely associated with an increased risk for renal adverse effects (Turgut *et al,* 2010).

ARBs and ACE inhibitors are influential, but it has been a little difficult to conclusively show that these drugs suggest benefit further than what would be seen with BP reduction alone, except in the case of heart failure and renal disease (Moser *et al*, 2007). The effect of RAS dysfunction may be limited due to the loss of an inhibitory feedback of angiotensin II on renin production The subsequent increase in renin and pro-renin may activate several alternative pathways which include the (pro-) renin receptor, angiotensin II escape via cathepsin and chymase, and the formation of various angiotensin subforms such as angiotensin III, and angiotensin IV, angiotensin 1–7 (Schroten *et al,* 2012).

Aliskiren is also used in the management of cardiovascular risk and nephropathy, particularly in patients with diabetes and those with existing cardiovascular disease and renal dysfunction (Bhandari *et al,* 2010). Recent studies have provided additional evidence that cardiovascular risk prediction is carried out using plasma renin activity (PRA) (Imanishi *et al,* 2009). Recently, aliskiren has been proven in reducing plasma renin activity (PRA) effectively and found to provide additional (tissue) RAAS blockade as compare to angiotensin-converting enzyme and angiotensin receptor blockers. By increasing concentration of plasma renin (PRC) decreasing the plasma renin activity (PRA) and may exert direct

effects independent of PRA through the recently discovered (pro-) renin receptor. The other various studies are also shown that the blockadge in the RAAS is also carried out using vitamin D receptor activation, as well as the increased knowledge on alternative pathways, Renin and prorenin are pivotal since these are at the base of all of these pathways (Schroten *et al,* 2012). In the patients with heart failure, Aliskiren Observation of Heart Failure Treatment (ALOFT) is effective by treating with an ACEI (or ARB) and β-blockers were randomized to 3 months of treatment with aliskiren 150 mg/day (Bonanni L *et al,* 2012).

Enalapril, a long acting oral converting enzyme inhibitor for the renin-angiotensin system has proved a valuable therapeutic approach in patients with severe chronic congestive heart failure. Enalapril is orally active compound, is an ethyl ester converting enzyme inhibitor that undergoes de-esterification and convert to the physiologically active form (Cody *et al,* 1983). Only Captopril is the ACE inhibitor take part in the experimental Chagas heart disease and it can decrease fibrosis, necrosis and cardiac inflammation (Daniels *et al,* 2007).

Angiotensin II acts on the adrenal cortex and causing it to release aldosterone, a hormone which responsible for causes the kidneys to retain sodium and potassium loss. Higher the plasma angiotensin II levels, higher the aldosterone levels present during the luteal phase of the menstrual cycle (Sood *et al,* 2012). Although after initiation of ACE inhibition therapy, initially reduction is occur in plasma levels of both Ang II and aldosterone, during prolonged ACE inhibition aldosterone levels may increase the so it is called as aldosterone escape (Imanishi *et al,* 2009). Aldosterone antagonists are use for the treatment of patient with hypertension and heart failure by inhibiting the effects of Aldosterone (Balakumar *et al,* 2011).

Kidney Repair

Chronic kidney disease (CKD) is very common disease in worldwide and due to this disease approximately 8, 30,000 death causes per year the reason behind this is that the high cost for renal replacement therapies. That is why, alternative mechanisms are been developed for the decreasing of CKD and other related diseases including progressive renal function loss and fibrosis (Meer *et al,* 2010). In patients with CKD, the comparative effects of a low sodium diet or diuretic therapy to potentiate the response to ARB are also investigated (Hiddo *et al,* 2011). In patients with CKD, it has been shown that the addition of aldosterone blocker to other RAAS blockers further reduces proteinuria (Turgut *et al,* 2010).

RAS inhibition therapy is currently use for improving renal functions and preventing the structural and functional changes of kidney which also used in the advanced phases of renal failure (Meer *et al,* 2010). Other than angiotensin II inhibitiors, angiotensin-converting enzyme inhibitor (ACEI) also used because angiotensin-converting enzyme inhibitor (ACEI) therapy reduced the risk of serum creatinine doubling in non-diabetic patients with chronic proteinuric nephropathies as well as prevent the risk of end-stage renal failure (ESRF) (Meer *et al,* 2010). In patients with CKD, the diuretic therapy or a low sodium diet have been also shown comparative effective to potentiate the response to ARB (Hiddo *et al,* 2011).

Double RAS inhibition may also effective in the antiproteinuric therapy by using the addition of ARB to an ACE inhibitor increase the effects of angiotensin II while the addition of ACE inhibitors to an ARB can limits the production of angiotensin II. Report of studies on patients with primary glomerulonephritis and proteinuria showed that double RAS inhibition was and was more effective and safer than single inhibition treatment in treating proteinuria (Meer *et al,* 2010).

In patients with stable coronary artery disease, Ramipril is an angiotensin-converting enzyme (ACE) inhibitor which is used for the reduction of RAAS activation (Imanishi *et al,* 2009). It was indeed not anticipated that aliskiren would motivate kidney renin secretion more than the other anti-renin system drugs (sealey *et al,* 2007). The studies show that comparable BP control, treatment with the ACE inhibitor-ramipril reduced the glomerularfiltration rate (GFR) decline and progression to end-stage renal failure (ESRF) in patients with non-diabetic proteinuric nephropathies (Meer *et al,* 2010). It is

demonstrated that co-treatment with valsartan and fluvastatin significantly inhibits neointimal formation induced by cuff placement around the femoral artery (Horiuchi *et al.*) (Imanishi *et al,* 2009). Moreover, it was found that for the complete regression of proteinuria and prevention of renal failure, the combined treatment with ACE inhibitors, ARBs and statin is more effective than the use of combined treatment with ACE inhibitors, ARBs and led (Meer *et al,* 2010).

Aldosteronism

In patients with definite primary aldosteronism, mean PAC is significantly greater and mean PRA is significantly lower than in patients with essential hypertension hence the Aldosterone-Renin ratio is used for the screening of primary Aldosteronism (Victor *et al,* 2001). RAAS blockade either by ACEI or ARB therapy, aldosterone production is initially concealed but subsequently may return to pretreatment levels; this is known as the aldosterone escape process (Turgut *et al,* 2010). Aldosterone levels independently use for the prediction of cardiovascular risks (Imanishi *et al,* 2009). An alternative screen for primary aldosteronism may be to categorize individuals in whom PRA is low and PAC is elevated. This approach can be based on the observed frequency distribution of each trait in the target population and no statistical modeling or no assumption regarding the relationship between PAC and PRA is required (Victor *et al,* 2001). Aldosterone induction is inhibited by Mineralocorticoid receptors and reduced NADPH oxidase-mediated increase in O2 generation and increases eNOS phosphorylation at Ser1177, an effect which may be mediated *via* inhibition of protein phosphatase 2A activation (Imanishi *et al,* 2009).

Endothelial Dysfunction

The endothelium is a dynamic organ which can regulates Nitric oxide (NO) production as well as mitogenic, anti-inflammatory, and contractile activities of the vessel wall and also the haemostatic process within the vessel lumen and the endothelium is the site for the synthesis of Ang II and NO both (Imanishi *et al,* 2009). Ang II may contribute to synthesis both vascular and tissue dysfunction, leading respectively to endothelial dysfunction, remodeling and hypertrophy of tissue, fibrosis and atherosclerosis, and loss of cells fibrosis remodeling in ischemia (Volpe *et al,* 2002) and it also diminished insulin-encouraged phosphorylation of NOS and nitric oxide production, and these effects were upturned by ACE2 gene transfer in endothelial cells (Batlle D *et al.* 2008). The expression of endothelium Nitric oxide (eNOS) and NO production is regulate by Ang II, whereas the AT1-receptor is down-regulates by NO (Imanishi *et al,* 2009). From human subjects, in kidney biopsies, ACE2 is expressed in tubular and glomerular epithelium, as well as in vascular smooth muscle cells and the endothelium of interlobular arteries (Batlle *et al.* 2008).

Nitric Oxide is involved in the vasoprotective effects which maintain important physiological functions such as antioxidative capacity, anticoagulation, vasodilatation, and inhibition of leukocyte adhesion and smooth muscle proliferation. On the other hand, Ang II involved in inflammatory, vasoconstrictor, thrombotic, and fibrotic effects such as it increases inflammation, oxidative stress, and alters endothelial function (Imanishi *et al,* 2009). Captivatingly, neoexpression of ACE2 was established in glomerular and peritubular capillary endothelium (Batlle *et al.* 2008).

Mechanism explaining the beneficial effects of renin-angiotensin-aldosterone system inhibition in Ang II-induced endothelial dysfunction is described as follow: Formation of Ang II can stimulate the formation of superoxide from the vascular NADPH oxidase *via* AT1 receptor and carry out the oxidation of the eNOS cofactor tetrahydrobiopterin (BH4), both peroxynitrite (ONOO-) and O2 take part into BH4 oxidation. An eNOS with oxidized forms of BH4 or Cofactor-deficient eNOS produces large amounts of O2 using stimulation of the enzyme. Both ACE inhibitors and ARBs contributed in the reduction of Ang II and results in stimulation of NADPH oxidase activation and increased generation of O2 by the AT1 receptor. ACE inhibitors also effecient in the increasing in eNOS expression that may be mediated *via* a bradykinin-mediated mechanism (Imanishi *et al,* 2009). Production of Endothelial NO and prostaglandin also causes vasodilatation of the afferent arteriole directly, which may be significant in the development of glomerular hyperfiltration (Peti-peterdi *et al,* 2008).

Novel strategies to improve endothelial function may become useful for the potential to improve prognosis in vascular disease. Although ACE inhibitors and ARBs have provided an excellent starting point for therapies targeting the RAS, other clinical therapies such as use of the catheter-type NO sensor is a potentially important for investigating the relationship between increased NO bioavailability and reduced atherosclerosis which can reduced endothelium-derived NO bioavailability in patients with cardiovascular diseases. It also impotrant to found out whether combined treatment (e.g. ARBs and renin inhibitors) could improve NO bioavailability (tested with the NO sensor) and induce plaque regression and/or stabilization (tested using intravascular ultrasound (IVUS) and optical coherence tomography (OCT)) more effectively than monotherapy (Imanishi *et al,* 2009).

Albuminuria

In patients with renal insufficiency, achieving optimal blood pressure and albuminuria/proteinuria control is a major therapeutic treatment. Angiotensin converting enzyme-inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the important component of therapy because they are proven efficient into lowering blood pressure and albuminuria which both are important risk markers for renal and cardiovascular disease progression (Hiddo *et al,* 2011). In illumination of available substantiation the use of ACEIs or ARBs either to control BP or to slow down the progression of CKD in elderly patients, especially in patients with proteinuria, but with measures to minimize risks which are associated with their intake as already mentioned (Turgut *et al,* 2010).

The reduction in blood pressure is results into the reduction in albuminuria which achieved with ACEIs or ARBs may be the critical step in achieving renal (and cardiovascular) protection (Hiddo *et al,* 2011). Clinical studies have focused on the renoprotective effects of angiotensin II inhibition because of the important role of angiotensin II in inducing and sustaining glomerular hypertension and proteinuria and its deleterious consequences (Meer *et al,* 2010). During renin angiotensin- aldosterone-system inhibition, the initial reduction in albuminuria is associated with long-term renoprotection and it shown that the larger the reduction in albuminuria, the larger the long-term renal risk reduction and by further lowering the albuminuria it act as antihypertensive dose, aldosterone antagonist and reduction of diatary sodium intake (Hiddo *et al,* 2011). Recent analysis shows that the use of anti aldosterone therapy reduces proteinuria in patients already on ACE inhibitor or ARB therapy, but this approach carries a high risk of hyperkalemia, especially in patients with advanced renal failure, especially in patients with nondiabetic nephropathies (Meer *et al,* 2010). The combination therapy did not show clear benefit even though proteinuria was reduced. It must be pointed out that most of the patients in that study had normal renal function without proteinuria (Turgut *et al,* 2010).

Several studies have shown that a regimen treatment including mineralocorticoid receptor blocker (MRB) using either spironolactone or eplerenone, on top of ARB or ACEI markedly reduces albuminuria. The results demonstrate that a treatment regimen with combining an ACEI and an ARB conferred a lower reduction in proteinuria (15% reduction in proteinuria) than consisting of an ACEI and MRB alone (48%) (Hiddo *et al,* 2011).

Combination therapies using ACE inhibitor and an ARB used for the treatment of reducing proteinuria is more effective than therapies using alone (Fisher *et al,* 2005). It also found that by adminisration of high dose of ACE inhibitors in the patients with advanced non-diabetic proteinuric nephropathy it can reduce the volume of sclerosis in most glomeruli and increased the volume of normal capillary tissue by up to 40% (Meer *et al,* 2010). On a group level, dietary sodium restriction and diuretic therapy were equally effective in enhancing the antialbuminuric response to the ARB losartan (Hiddo *et al,* 2011). At an individual level, in a poor responder to ARB therapy the antialbuminuric response is significantly improve further by the addition of a low sodium diet, whereas in a good responder to ARB therapy the antialbuminuric response did not improve further by the addition of a low sodium diet (Hiddo *et al,* 2011). Antiproteinuric therapy should different between the different non-diabetic glomerulopathies. However, it has been reported that angiotensin II inhibition is efficient for diverse proteinuric diseases

including IgA nephropathy, membranous nephropathy, and HIV-associated nephropathy (Meer *et al*, 2010).

CONCLUSION

The renin–angiotensin system (RAS) plays an important role in the control of blood pressure, hypertension, in the cardiac hypertrophy, heart failure, advanced liver disease, atherosclerosis, and renal artery stenosis. Renin is the main enzyme of RAS and it is act upon the main substrate of RAS-Angiotensinogen. Renin inhibitors such as β- Blockers, Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), Direct Renin Inhibitors are used for the RAS inhibition and ultimately proven important for the study of prevention of several renal diseases and cardiovascular diseases. Several drugs such as vitamin D receptor activators, endothelin antagonists, Angiotensin II antagonists, Aldosterone antagonists, or monocyte chemotactic protein-1 antagonists are also used in controlling blood pressure, endothelial dysfunction and heart failure. Aliskiren, Captopril, Enalapril, and other inhibitors have proved a valuable therapeutic approach in different diseases.

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