

MINI REVIEW

Renin Angiotensin Aldosterone System (RAAS): Its biology and drug targets for treating diabetic nephropathy

Maryam Zain^{1,2} and Fazli Rabbi Awan^{1,2*}

¹Diabetes and Cardio-Metabolic Disorders (D&C-MD) Laboratory, Health Biotechnology Division, National Institute for Biotechnology and Genetic Engineering (NIBGE), Jhang Road, Faisalabad, Pakistan

²Pakistan Institute of Engineering and Applied Sciences (PIEAS), Nilore, Islamabad, Pakistan

Abstract: Diabetes mellitus is a multifactorial disorder of hyperglycemia caused by a combination of biochemical, molecular and genetic factors, which leads to the dysfunction of various organs including kidneys. Diabetic nephropathy (DN) is one of the microvascular complications of diabetes that results due to poor glycemic control. Several molecular and biochemical pathways have been implicated in the pathogenesis of DN. Of these, the Renin Angiotensin Aldosterone System (RAAS) is considered as a key pathway. RAAS involves various subsystems which contribute to the development of DN. Mutations in several genes of the RAAS pathway have been associated with the development of DN. These genes or their products present them as therapeutic targets for potent drugs to control or prevent DN, and development of new drugs for targeting the RAAS. Drugs in use for DN are mainly the Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptors Blockers (ARB) and renin inhibitors which play important roles in reducing DN. Hence, the present review is focused on the pathophysiology and genetic factors for DN by exploring the RAAS pathway and emphasizing the benefits of blocking this pathway to control and prevent DN.

Keywords: Angiotensin, ACE, aldosterone, diabetic nephropathy, renin.

INTRODUCTION

Diabetes mellitus is a metabolic disorder of defect in the insulin production, action or both, which results in high glucose levels in the blood that leads to excessive excretion of glucose in the urine. There are two main types of diabetes; type 1 and type 2 diabetes, both of these conditions have hyperglycemia in spite of different underlying etiologies. As a result of uncontrolled diabetes several vital organs are also affected mainly kidneys, eyes, heart, liver, as well as peripheral nervous system (PNS) due to long term damage, disorder and failure of these organs. The impaired function of these organs owing to the associated complications pose major health problem and ultimately leads to organ failure and finally death (ADA, 2008). One of the major microvascular complications of diabetes is the diabetic nephropathy (DN), which is the damage to kidneys as a result of excess glucose in blood. It accounts for 25-40% of the diabetics, hence it is important to understand its underlying genetics and pathophysiological basis (Granier *et al.*, 2008).

The DN is characterized by various changes in the kidney functions due to excess glucose which leads to the End Stage Renal Disease (ESRD). Initially, clinical symptoms are persistent proteinuria, albuminuria, hypertension, hyperlipidemia, oedema and reduced glomerular filtration rate (GFR). Moreover, there is also an increased

production of glycated proteins (Locatelli *et al.*, 2003). The microalbuminuria (30-300mg/24hrs) is followed by macroalbuminuria (≥ 300 mg/24hrs) which reflects damage to kidneys (Bain and Chowdhury, 2000, Maharjan *et al.*, 2010) due to impaired filtration from damaged nephrons of kidneys. Some of the biochemical parameters are also raised than their normal levels such as urea (normal ranges: 10-50 mg/dL), creatinine (normal ranges: 0.6-1.3 mg/dL) that is because of the impaired filtration from the kidneys. ESRD is the advance stage of diabetic nephropathy which is defined by the decrease in GFR values because of filtration defects in the kidney. The GFR is considered to be the best measure of overall kidney function in health and disease and its values are interpreted according to age, sex and body size as these factors considerably influence GFR. The normal ranges of GFR in young adults are approximately 120 ml/min/1.73m². It continues to decline with the passage of time as the age is a major factor, so 70% of the people above age of 60 years have GFR less than 60 ml/min/1.73m². The ESRD is the stage when GFR of a person declines to 15 ml/min/1.73m² and the person is on dialysis or needs kidney transplantation (Levey *et al.*, 2003).

In addition to this, many physiological changes to the kidney components also occur as hypertrophy of glomeruli, thickening of the basement membrane of kidneys which results in the glomerular hyperfiltration

*Corresponding author: e-mail: awan.fr@gmail.com

(Ziyadeh, 1993). In the later stages, the microalbuminuria is caused and also favored by glomerulosclerosis in which the glomerulus of kidneys are affected and scar like appearance of glomerulus occurs which damages the filtration capacity of the kidneys and results in the decrease of GFR (Remuzzi *et al.*, 1993, Levey *et al.*, 2003).

In the development of DN different pathways are involved such as Renin Angiotensin Aldosterone System (RAAS) pathway, aldose reductase – polyol pathway, diacylglycerol- protein kinase C pathway, advanced glycation end products (AGE) - hexosamine pathway, oxidative stress pathway, dopaminergic pathway and some cytokine related pathways which contribute to the development of DN as reviewed in earlier papers (Prasad *et al.*, 2006, Granier *et al.*, 2008, Bain and Chowdhury, 2000). Study of these and related pathways is important to identify changes in the metabolites, proteins and genetic mutations involved in DN. The present review is focused on the dissection of molecular genetics pathway mainly Renin Angiotensin Aldosterone System (RAAS) and effects of drugs to control this pathway.

Renin angiotensin physiology

Renin Angiotensin Aldosterone System (RAAS) acts as a circulating system that regulates blood pressure (Corvol and Jeunemaitre, 1997). This system plays a crucial role

in regulating the sodium metabolism, vascular tone, blood pressure, renal hemodynamic and vascular modeling. Genetic variants of RAAS have been extensively studied on the basis of physiological and biochemical functions. The development of hypertension in diabetes is also due to the effects of RAAS activation as shown in fig. 1 (Stas *et al.*, 2004).

Components of the RAAS pathway

There are various components of this pathway which play important roles in the normal functioning of this system. Each of these components plays an important role in controlling the blood pressure and maintaining the normal kidney functions of the body. This system involves the components as Renin, Angiotensinogen, Angiotensin II, Angiotensin Converting Enzyme (ACE), and Aldosterone Synthase (CYP11B2: Cytochrome P450, family 11, subfamily B, polypeptide 2). A brief overview of each of these components is given in the following sections.

Renin

Renin is a protein of 340 amino acids long and has a molecular weight of 37 kDa. The renin gene is located on the long arm of chromosome 1 (1q32) and this gene is 12kb long, which contains 8 introns (Hobart *et al.*, 1984). Renin mediates extracellular volume that includes blood plasma, lymph and interstitial fluids and is involved in arterial vasoconstriction and blood pressure, and

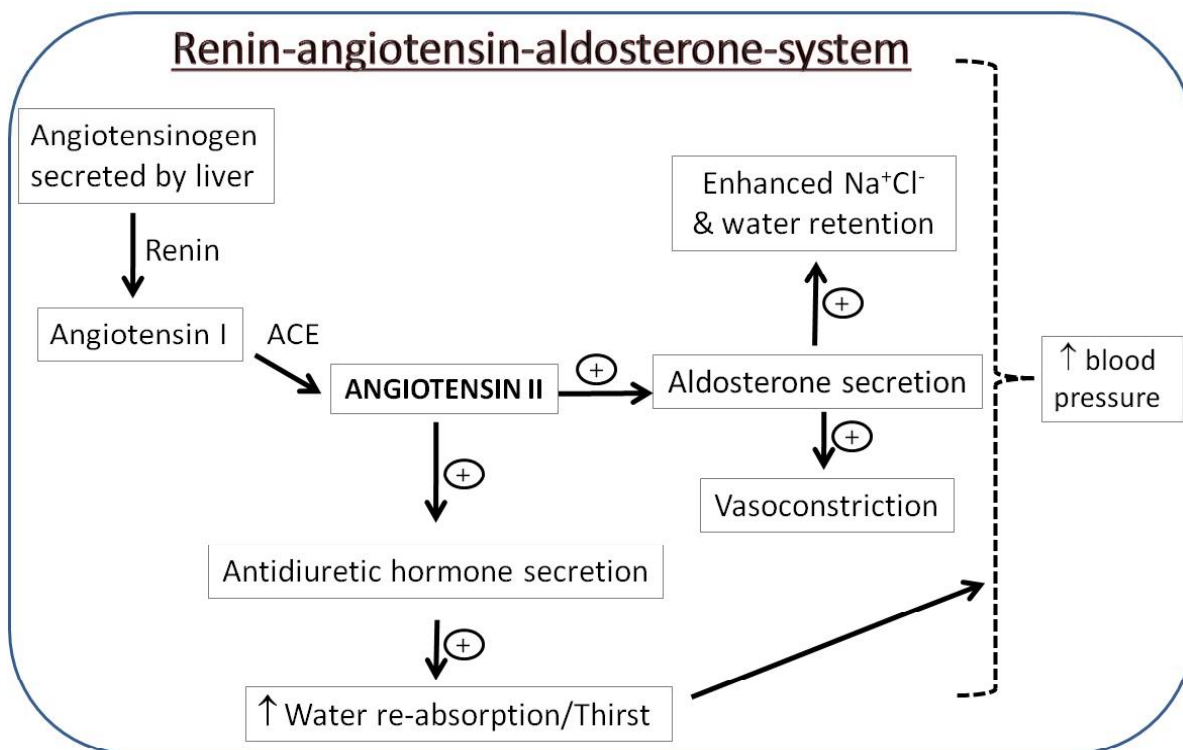


Fig. 1: Regulation of blood pressure by renin-angiotensin aldosterone system (RAAS).

ACE: Angiotensin converting enzyme, ⊕ shows increase. Concepts of this figure are adapted from this paper (Ruggenenti *et al.*, 2010)

cardiovascular homeostasis (Pratt *et al.*, 1988). It is secreted by the kidneys in response to the following actions:

- i) When the arterial blood pressure is decreased, renin is released to maintain the arteriolar pressure and blood pressure.
- ii) In response to the sodium chloride level decrease in the ultra filtrate of nephrons.
- iii) Sympathetic nervous system which is involved in the regulation of blood pressure also causes the release of renin.

The renin is circulated in the blood stream and cuts down the liver secreted angiotensinogen into angiotensin I, which is further cleaved off by endothelial bound enzyme ACE into angiotensin II which acts on the adrenal glands and secretes aldosterone. Aldosterone acts on the distal tubules and collecting ducts of the kidneys to increase the re-absorption of sodium and water leading to the increase in blood volume and blood pressure which also results in cardiac complications (Thomas *et al.*, 2001). This pathway is explained in fig. 1.

Angiotensinogen

Angiotensinogen is the precursor of angiotensin peptide mainly produced and released into the circulation by the liver. Structurally, this peptide belongs to the family of inhibitors of serine proteases (serpins). Angiotensinogen is a glycoprotein of 452 amino acids produced in the liver as well as the other organs as heart, kidneys, vessels and adipose tissues, which circulates as an active biological peptide. Angiotensinogen is converted to the Angiotensin I by the action of renin.

Angiotensin II

Angiotensin II appears as the central effector peptide of the RAAS pathway with its physiological role in the regulation of salt and water homeostasis, renal function and blood pressure maintenance. When blood pressure is decreased, angiotensin II (a peptide vasoconstrictor) causes the increase in sodium re-absorption which ultimately restores blood pressure. Angiotensin II also causes vasoconstriction by noradrenalin secretion (Luther and Brown, 2011). Angiotensin I is converted to angiotensin II by the removal of two C-terminal residues by the ACE enzyme. This enzyme is found in various parts of the body but it is abundantly present in the lungs due to high density of capillary beds over there (Erdos, 1990).

Angiotensin converting enzyme (ACE)

Angiotensin-converting enzyme (ACE) is located at the epithelial and endothelial cells of different organs including the kidneys, heart, lungs and endothelial vessel cells (Erdos, 1990, Marre, 1996). Diabetes is one of the pathological conditions in which ACE levels were reported to increase and this has been known for many years (Lieberman and Sastre, 1980). Various studies have

been conducted in which associations have been found between the ACE gene polymorphism (Insertion/Deletion, I/D) with several diseases ranging from chronic coronary heart disease and high blood pressure to retinal and renal disease (Marre *et al.*, 1994, Marre *et al.*, 1997).

Aldosterone synthase / Cytochrome P450, family 11, subfamily B, polypeptide 2 (CYP11B2)

Aldosterone synthase, a key enzyme in the biosynthesis of aldosterone, is part of the superfamily of cytochrome P450. Aldosterone synthase is an enzyme complex localized at the mitochondrial inner membrane (White and Slutsker, 1995). Aldosterone is secreted from the adrenal cortex of the kidney and is involved in the conservation of sodium, secretion of potassium, increase in the water retention, and as a result increases in blood pressure. There are several studies which showed that mutation in the aldosterone synthase gene is responsible for hypertension and diabetes as it is involved in the regulation of blood pressure. Many anti-hypertensive drugs have been studied e.g. spironolactone, ramipril, enalapril which are used in controlling the blood pressure by blocking its secretion and thus controlling the disease condition (Luther and Brown, 2011).

Role of RAAS pathway genes polymorphism in the development of diabetic nephropathy

The RAAS pathway genes polymorphisms play important roles in the disease progression. The ACE (I/D), AGT (M235T), CYP11B2 (T/C) are well studied polymorphisms with reference to diabetic nephropathy. A brief overview of these polymorphisms in the development of proteinuria and diabetic nephropathy is given below.

The distribution of ACE (I/D) has been studied in type 2 diabetics and nephropathy patients by various investigators (Rigat *et al.*, 1992, Marre *et al.*, 1994). The ACE gene is located on the human chromosome 17 and it contains a 279 bp ins/del polymorphism in the intron 16. The ACE polymorphism is considered to be a best known polymorphism in diabetic nephropathy along with Angiotensinogen M235T polymorphism (Gallego *et al.*, 2008, Jeunemaitre *et al.*, 1992). It has been shown in the meta-analysis study that ACE is the most studied polymorphism (Ng *et al.*, 2005). The II genotype of ACE was found to show a better response in relation to the ACE inhibitor drugs (Ruggenti *et al.*, 2008). Some studies showed the association of ACE I/D polymorphism with coronary heart disease (Min *et al.*, 2009), while other studies reported no such associations with the cardiovascular and renal complications (Gomez-Angelats *et al.*, 2000, Sagar-Malik *et al.*, 2000). Plasma ACE levels were also found to be higher in the type 2 diabetic patients having nephropathy as compared to the normal subjects (Marre *et al.*, 1994).

Table 1: Summary of clinical studies targeting RAAS Pathway in diabetic nephropathy

RAAS Inhibitor	Target Organ / Clinical parameter investigated	No. of patients	Study Duration	Therapeutic or physiological effects/ Disease outcome from therapy	Reference
NG-Nitro-L-Arginine-Methyl-Ester & Losartan	Kidneys & GFR	23	3 d	Improved renal hemodynamics	(Montanari <i>et al.</i> , 2013)
Ramipril, Telmisartan	Kidneys & CV	9628	56 m	Protection from CV & renal events	(Mann <i>et al.</i> , 2013)
Aliskiren	Kidneys & UAER	138	12 w	Antiproteinuric effect for kidneys	(Fogari <i>et al.</i> , 2013)
Irbesartan, Lisinopril	Kidneys	133	32 m	Improvement in DN	(Fernandez Juarez <i>et al.</i> , 2013)
Aliskiren, Losartan	p-Aldosterone & LVH	465	36 w	Protection for LVH & ↓ in p-aldosterone	(Vardeny <i>et al.</i> , 2012)
Telmisartan, Aliskiren, eplerenone	Chronic kidney disease & HTN	18	8 w	↓ albuminuria & antiproteinuric	(Tylicki <i>et al.</i> , 2012)
Aliskiren, ARBs & ACEi	Angiodema	17	365 d	Improvement in angiodema	(Toh <i>et al.</i> , 2012)
Aliskiren	Kidney & proteinuria	25	12 m	Antiproteinuric	(Tang <i>et al.</i> , 2012)
Losartan, ARBs	Kidney, CV & HTN	60	6 w	Antihypertensive & antiproteinuric	(Slagman <i>et al.</i> , 2012)
N acetyl cysteine, Losartan	Kidneys	70	2 m	↓ Proteinuria	(Rasi Hashemi <i>et al.</i> , 2012)
Aliskiren, Losartan	Kidneys & HTN	599	6 m	↓ UACR	(Persson <i>et al.</i> , 2012)
Aliskiren	HTN, UAER	8561	32.9 m	Renal, HTN & CV protective effect	(Parving <i>et al.</i> , 2012)
Losartan	Insulin mediated vasodilation	17	12 w	Improvement in glucose mediated insulin uptake	(Lteif <i>et al.</i> , 2012)
ARBs effect	Sodium/creatinine ratio, renal & CV events	1177	1 d	Improvement in CV & renal events	(Lambers Heerspink <i>et al.</i> , 2012)
ACEI/ARB plus statin plus beta-blocker	Polypathological effect	1260	12 m	survival & functional improvement	(Galindo-Ocana <i>et al.</i> , 2012)
ACEs & ARBs	LVH, DN or microalbuminuria	2895	6 m	↓ in LVH, DN & microalbuminuria	(Barrios <i>et al.</i> , 2012)
Valsartan	HTN & UAER	391	26 w	↓ in HTN & UAER	(Weir <i>et al.</i> , 2011)
Valsartan	UACR & hsCRP	153	6 m	Anti inflammatory, ↓ in UACR & CRP	(Shishido <i>et al.</i> , 2011)
Atorvastatin	GFR	60	2.1 y	Reduction in GFR	(Rutter <i>et al.</i> , 2011)
RAA blocking drugs	HTN & microalbuminuria	211	3 m	↓ in HTN & microalbuminuria	(Robles <i>et al.</i> , 2011)
Atrasentan	Renal outcomes & albuminuria	89	8 w	Improvement in renal outcomes & albuminuria	(Kohan <i>et al.</i> , 2011)
Captopril, irbesartan, aliskiren	BP, aldosterone levels, plasma angiotensin II	43	2 w	↓ in BP, aldosterone & angiotensin II levels	(Hollenberg <i>et al.</i> , 2011)

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RAAS Inhibitor	Target Organ / Clinical parameter investigated	No. of patients	Study Duration	Therapeutic or physiological effects/ Disease outcome from therapy	Reference
Rosuvastatin	Albuminuria, serum cystatin, inflammation, lipid levels & eGFR	91	24 w	↓ in albuminuria, serum cystatin, inflammation, lipid levels & eGFR	(Abe <i>et al.</i> , 2011)
Valsartan	BP & UAER	391	4 w	↓ in BP & UAER	(Weir <i>et al.</i> , 2010)
Lisinopril	SBP, UACR, serum potassium	81	-	↓ in BP, UACR, hyperkalemea	(Van Buren <i>et al.</i> , 2010)
Enalapril, losartan,	Urinary albumin excretion, HTN	34	8 w	↓ in UAER & HTN	(Tan <i>et al.</i> , 2010)
Atorvastatin	Proteinuria, BP, serum creatinine,	14	8 w	Improvement in tubular damage, ↓ in proteinuria & BP	(Renke <i>et al.</i> , 2010)
Aliskiren	UAER, GFR, BP	26	2 m	↓ in SBP & GFR, no ↓ in albuminuria	(Persson <i>et al.</i> , 2010)
Valsartan & amlodipine	HTN with glucose intolerance	1150	3 y	↓ of HTN & glucose intolerance	(Matsushita <i>et al.</i> , 2010)
Candesartan cilexetil / HCT	microalbuminuria, BP, glucose & lipid parameters	4110	12 w	↓ microalbuminuria, BP, glucose & lipid parameters	(Ketelhut and Bramlage, 2010)
Ramipril	Vistafin level, flow mediated dilatation, endothelial dysfunction, Insulin resistance & inflammation	62	2 m	↓ in vistafin, flow mediated dilatation, endothelial dysfunction, Insulin resistance & inflammation	(Eyiletan <i>et al.</i> , 2010)
Ramipril	Serum PTX3, hsCRP, & albumin levels, albuminuria & flow mediated dilation	81	12 w	↓ serum PTX3, hsCRP, & albumin levels, albuminuria & flow mediated dilation	(Yilmaz <i>et al.</i> , 2009)
Losartan, HCT	Urinary KIM	34	6 w	↑ in KIM1 value & ↓ in proteinuria	(Waanders <i>et al.</i> , 2009)
Valsartan, losartan, HCT	Effect of sodium intake in patients	32	24 w	↑ salt intake causes the ↓ in BP in patients with ARBs	(Uzu <i>et al.</i> , 2009)
Aliskiren	CV & renal morbidity & mortality	8600	48 m	↓ in CV & renal morbidity & mortality	(Parving <i>et al.</i> , 2009)
Enalapril, telmisartan	Proteinuria, GFR, serum potassium	80	24 w	↓ in proteinuria & other renal events	(Krairitichai and Chaisuvannarat, 2009)
RAAS blocker	BP, GFR, hyperkalemia	46	45 d	↓ in BP, GFR, & hyperkalemia	(Khosla <i>et al.</i> , 2009)
Spirolactone	Antifibrotic effect	30	6 m	↓ in proteinuria & urinary TGF-β1 excretion	(Guney <i>et al.</i> , 2009)
Losartan, lisinopril	GFR, ESRD, antiproteinuric effect, mortality	1850	1 y	↓ in GFR, ESRD, antiproteinuric effect, mortality	(Fried <i>et al.</i> , 2009)

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Table continue...

RAAS Inhibitor	Target Organ / Clinical parameter investigated	No. of patients	Study Duration	Therapeutic or physiological effects/ Disease outcome from therapy	Reference
Telmisartan & HCT	Sodium chloride supplementation & antialbuminuria	32	4 w	Albuminuric effect can be stopped by ↓ salt & telmisartan	(Ekinici <i>et al.</i> , 2009)
Losartan & HCT	↓ sodium effect on proteinuria & BP	34	6 w	Losartan & HCT ↓ BP & proteinuria	(Vogt <i>et al.</i> , 2008)
Valsartan or amlodipine	Microalbuminuria	137	24 w	↓ microalbuminuria	(Uzu <i>et al.</i> , 2008)
Candesartan	Insulin response, BP	12	3 m	↑ insulin response & ↓ in BP	(Suzuki <i>et al.</i> , 2008)
Aliskiren & losartan	Renal outcomes & BP	599	6 m	Renoprotective effect & ↓ in BP	(Parving <i>et al.</i> , 2008)
RAS inhibitor, Azelnidipine, nifedipine-CR	Renoprotective effect & inhibition of oxidative stress	38	16 w	↓ in BP, inflammation & oxidative stresses	(Ogawa <i>et al.</i> , 2008)
ACEi, calcium channel & beta blockers	Anti hypertensive effect	50	3-9 y	ACEi have ↑ anti hypertensive effect than other drugs	(Jarmuzewska <i>et al.</i> , 2008)
Telmisartan & valsartan	Renoprotective effect, inflammatory parameters, HTN	885	12 m	Renoprotection & ↓ in inflammatory parameters & HTN	(Galle <i>et al.</i> , 2008)
ACEi, thiazide diuretics & calcium channel blockers	BP & albuminuria	332	1 y	↓ in BP & albuminuria	(Bakris <i>et al.</i> , 2008)
Candesartan, valsartan	Aldosterone contribution in renal injury	95	15 m	Aldosterone blocking prevented renal injury in HTN patients	(Yoneda <i>et al.</i> , 2007)
Irbesartan, HCT	BP, CV & metabolic risk factors	14,200	9 m	Improvement in BP, metabolic & CV risk factors	(Kintscher <i>et al.</i> , 2007)
ACEi & ARB	Effect of RAS blockade on serum potassium	62	3 m	RAS blockade is not linked with risk of hyperkalemea	(Han <i>et al.</i> , 2007)
Losartan	SBP & albuminuria	1428	6 m	↓ in SBP & albuminuria	(Eijkelkamp <i>et al.</i> , 2007)
Ramipril, candesartan	Proteinuria & urinary TGF excretion	21	16 w	Blockade of RAS was effective for proteinuria & urinary TGF	(Song <i>et al.</i> , 2006)
Spirolactone	Albumiuria, GFR & BP	25	2 m	↓ in albuminuria, BP & GFR	(Schjoedt <i>et al.</i> , 2006)
Losartan	Albumiuria	96	2.8 y	Losartan gives renal protection patients	(Kurokawa <i>et al.</i> , 2006)
Telmisartan & enalapril	GFR & mortality rate	250	5 y	↓ in GFR & mortality	(Barnett, 2006)

ACEi: Angiotensin Converting Enzyme Inhibitor(s), ARB: Angiotensin Receptor Blocker(s), BP: Blood Pressure, CV: cardiovascular, CVD: cardiovascular disorder, d: day(s), DN: diabetic nephropathy, eGFR: estimated glomerular filtration rate, ESRD: End Stage Renal Disease, GFR: Glomerular Filtration Rate, HCT: Hydrochlorothiazide, hsCRP: high-sensitive C-reactive peptide, HTN: Hypertension, KIM: kidney injury molecule, LVH: Left ventricular hypertrophy, m: month(s), p-Aldosterone : plasma Aldosterone, RAAS: Renin Angiotensin Aldosterone System, SBP: Systolic Blood Pressure, TGF: Transforming Growth Factor, UACR: Urinary albumin to creatinine ratio, UAER: Urinary Albumin Excretion Rate, w: week(s), y: year(s)

The *AGT* gene is located on chromosome 1q42-q43, encodes glycoprotein of 485 amino acids (55 kDa) secreted by the liver has also been studied with reference to blood pressure and diabetic nephropathy. The *AGT* gene contains five exons spread over 11.67 kb contain 2184 base pairs of coding sequence. The M235T polymorphism in *AGT* is responsible for the substitution of a methionine to threonine is associated with circulating levels of AGT. It was reported that the T allele is associated with 10-20% increase in the concentration of plasma angiotensinogen (Jeunemaitre *et al.*, 1992). Moreover, this polymorphism is associated with hypertension (Caulfield *et al.*, 1994, Kim *et al.*, 1995, Kiema *et al.*, 1996, Borecki *et al.*, 1997, Jeunemaitre *et al.*, 1997). Conversely, there are some studies which found no association of *AGT* (M235T) polymorphism with diabetic nephropathy and hypertension (Tarnow *et al.*, 1996, Doria *et al.*, 1996).

The *CYP11B2* gene consists of 9 exons and is located on chromosome 8, region q22 (Taymans *et al.*, 1998). The variant -344 T>C polymorphism of gene *CYP11B2* for aldosterone synthase has also been studied with reference to the cardiovascular risk factors (Davies and Kenyon, 2003). It is linked to malfunctions in the secretion of aldosterone resulting in hypertension (White and Slutsker, 1995, Brand *et al.*, 1998). Similarly the results of some other groups also confirmed the association of T allele with the hypertension and diabetes, metabolic syndrome, pulmonary oedema, blood pressure and cardiovascular complications (Wang *et al.*, 1999, Russo *et al.*, 2007, Srivastava *et al.*, 2012, Baird *et al.*, 2007).

Prevention of DN by pharmacological intervention at molecular targets in RAAS pathway

The chronic activation of RAAS is the main cause of nephropathy, hypertension and cardiovascular diseases. Many clinical trials have demonstrated that by blocking the RAAS pathway (table 1), it decreases morbidity and mortality from hypertension, myocardial infarction, heart failure, complications of atherosclerosis as well as diabetes (Zaman *et al.*, 2002).

ACE inhibitors

ACE is a target for inactivation by ACE inhibitor (ACEi) drugs, which are responsible for the decrease in blood pressure. Drugs used as ACEi are major drugs against hypertension and cardiovascular problems (Hershon, 2011). Various types of ACE inhibitor drugs are available for example, enalapril, ramipril, captopril, benzapril etc in combination with renin inhibitors as aliskiren, and angiotensin receptor blockers (ARBs) as telmisartin and valsartan are used as illustrated in fig. 2 (Yusuf *et al.*, 2000, Zaman *et al.*, 2002, Stohr and Marx, 2012) and summarized in table 1 for clinical studies. According to some studies, the combination of therapies as renin inhibitors and the new ARBs along with ACEi helps in

better control of hypertension and diabetes problems (Lazich and Bakris, 2011). In patients with DD genotype of *ACE* and overt nephropathy the anti-renin therapy was found to be useful, while in males having the non-diabetic proteinuric nephropathies, the ACEi therapy was found to be effective (Ruggenti *et al.*, 2008). The ACEi have also been shown to play a role in delaying the disease progression as diabetes and renal failure etc (Stohr and Marx, 2012). However, according to some groups there are limitations in the use of these therapies (Holdiness *et al.*, 2011).

Angiotensin Receptor Blockers (ARBs)

Angiotensin Receptor Blockers (ARBs) are also reported as very useful in controlling the hypertension. The mechanism of their action is that they block the Angiotensin II type 1 receptor (AT1R). The AT1R blockade causes the increase of the Angiotensin II which binds to the Angiotensin type 2 receptor (AT2R) and it results in the decrease of the blood pressure and also reduced renal interstitial fibrosis (Siragy *et al.*, 1999). Combination therapy of ARBs and ACEi has been proved in some of the studies to be more beneficial and useful in terms of reducing the hypertension, proteinuria, blood pressure and cardiovascular complications (Jacobsen *et al.*, 2004, Rossing *et al.*, 2003, Mogensen *et al.*, 2000, Jacobsen *et al.*, 2003).

Direct renin inhibitors

Recently a direct renin blocker has been identified that blocks the RAAS pathway and is found to be more useful than ACEi and ARBs as shown in fig. 2. Aliskiren drug renoprotective therapy has been found in patients with diabetic and non-diabetic nephropathies (Horky, 2010). One study using the aliskiren for the treatment of the diabetes in patients which have the proteinuria showed that aliskiren, in addition to optimizing the blood pressure treatment in hypertension, it also reduced the mean urinary albumin to creatinine ratio in patients who were suffering from the type 2 diabetes as well as kidney problems (Parving *et al.*, 2008). So, a number of therapeutic trials have shown that when the pharmacologically blocking agents block the RAAS pathway, it reduces the risk of progression of diabetes by 20% to 25% (Yusuf *et al.*, 2000, Lindholm *et al.*, 2002, Holdiness *et al.*, 2011, Stohr and Marx, 2012, Lazich and Bakris, 2011) and it also helps in preventing the kidney and heart diseases (Luther and Brown, 2011). The blockage of RAAS pathway at different levels by the use of various inhibitor drugs (as shown in fig.2) have been reported to be useful in controlling blood pressure as well as the nephropathy and cardiovascular problems.

Therefore, the uses of ACEi alone or in combination as well as renin inhibitors not only play key roles in controlling blood pressure but also in delaying the progression of disease as diabetes, cardiovascular complications and kidney problems.

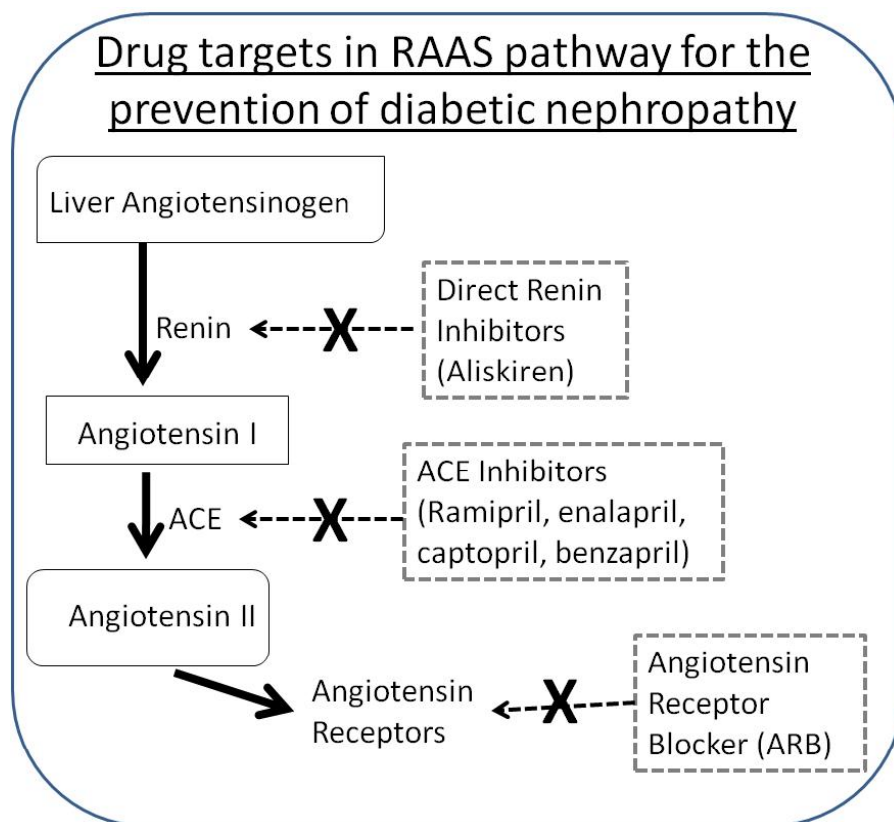


Fig. 2: Prevention of diabetic nephropathy by pharmacological interventions on molecular targets in the RAAS pathway.

Concepts of this figure are adapted from this paper (Ruggenenti *et al.*, 2010)

Summary of clinical studies of diabetic nephropathy based on RAAS pathway targets

Owing to the central importance of RAAS pathway in the regulation of blood pressure and its association with renal and cardiovascular disease, several clinical studies have been reported on this aspect. Some of the important clinical studies are summarized in table 1 with important features of the study like information of the type of RAAS inhibitor(s) used, their target action for the clinical parameter, and number and duration of study. Then a summary of the therapeutic or physiological response or disease outcome resulted from these studies has been shown along with relevant reference of the study (table 1).

CONCLUSION

Diabetes mellitus is a multifactorial disorder and the involvement of the kidney problems in the diabetic patients is a major cause of illness and death in these patients. RAAS pathway plays a major role in the pathogenesis of the diabetic nephropathy. To date, many clinical trials have been conducted to control this grave complication of diabetic nephropathy by blocking the RAAS pathway, although the complete blockade is not achieved yet. Hence, there is need to develop more potent

drugs for specific actions on these molecular targets. And more studies should be conducted at the molecular and genetic levels to find better ways in order to prevent the deleterious effects of RAAS pathway and protection from the diabetic kidney disease.

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