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4

Drug and Diabetic Nephropathy

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1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defect in insulin secretion, insulin action, or both. It is the leading cause of heart disease, adult blindness, and amputation of the lower extremities[1]. Diabetic patient suffer from a number of complications. Of these – hypertension, retinopathy, neuropathy, peripheral vascular disease – are most frequent ones and are responsible for considerable morbidity and mortality. Diabetic nephropathy (DN) is a chronic progressive kidney disease with high morbidity and mortality. There is a gradual loss of renal function ultimately leading to end stage renal disease (ESRD) where life is not sustainable without renal replacement therapy[2]. The course of DN is characterized by early elevation of arterial blood pressure, increasing albuminuria with gradual decline in glomerular filtration rate (GFR) of 10-12 ml.min-1.year-1[3,4,5]. The degree of albuminuria is closely related to the progression of DN[6]. Diabetic patients with nephrotic range proteinuria have the fastest decline in GFR[7] and the shortest survival time[8].

Proteinuria has been considered an indicator of glomerular disease severity[9]. The proposed effects of proteinuria on the kidney include increased severity of glomerulosclerosis, tubulointerstitial inflammation, and subsequent fibrosis, thereby contributing to progressive renal function loss. These facts have permitted the establishment of a "proteinuria hypothesis" that consists of three postulates: higher levels of proteinuria predict adverse clinical outcomes; reduction of proteinuria correlates with slowing of renal progression; and proteinuria is a surrogate end point and target of clinical interventions[10].

Key to the development of DN is the hyperglycemic state, which has been postulated to mediate its effect in several different ways. First, glucose in sustained high concentrations may be directly toxic to cells, altering cell growth and gene and protein expression and increasing extracellular matrix and growth factor production[11]. Second, glucose may induce its effects indirectly through the formation of metabolic derivatives such as oxidants and glycation products[12,13]. Formation of advanced glycation end-products (AGES) may damage cells because of modifications to extracellular matrix proteins and to cellular proteins[14].

The renin-angiotensin-aldosterone system (RAAS) is a coordinate cascade of proteins and peptide hormones, the principal effector of which is angiotensin II. In kidney it is regulated via a self-contained renin angiotensin system in a paracrine fashion[15]. Renin is an enzyme produced by the kidney in response to a number of factors including adrenergic activity (β_1-

receptor) and sodium depletion. Renin converts circulating glycoprotein, angiotensinogen, into the biologically a high potent vasoconstrictor angiotensin II[16].

Angiotensin II acts on the heart and the kidneys by binding to the G protein-coupled receptors type 1 and type 2. The angiotensin receptor type 1 mediates the more deleterious effects of angiotensin II – that is, vasoconstriction and cardiac and vessel hypertrophy[17].

In diabetes mellitus, local activation of the renin angiotensin system or increased intrarenal sensitivity to angiotensin II, especially angiotensin II receptor 1 occurs. Several studies have demonstrated that, in spite of normal or suppressed plasma renin activity, the intrarenal content of renin in increased. This increase can contribute to the progression of diabetic nephropathy via several hemodynamic, tubular and growth promoting actions[18].

Activation of the local renin angiotensin system also constricts the efferent more than the afferent arteriole. This glomerular hemodynamic change increases single nephron glomerular filtration rate in an attempt to maintain global glomerular filtration rate despite progressive loss of functioning nephrons in chronic kidney disease. However, if this change is sustained, it will likely result in glomerular injury and an accelerated loss of kidney function over time[19].

Angiotensin II 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. Angiotensin II 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 nepropathies[17].

A large number of studies established that progressive deterioration of renal function is the result of compensatory glomerular hemodynamic changes in response to nephron loss. In the widely used experimental model of renal mass reduction, the remaining nephrons undergo hypertrophy, reduced arterial resistance, and increased glomerular blood flow[20].

After nephron loss, the remaining nephrons develop glomerular capillary hypertension, and the single-nephron glomerular filtration rate (GFR) increase (hyperfiltration). These changes are thought to be adaptive in that they help to initially maintain the overall GFR. However, they have negative long-term effects and ultimately lead to renal insufficiency and ESRD.

Podocytes are glomerular epithelia cells for glomerular structure and function, surrounding glomerular capillaries and forming foot processes contributing to the filtration barrier and providing structural stabilization. The diabetic kidney abnormally regulates intraglomerular pressure with imbalance between afferent and efferent arteriolar vasodilatation leading to a 20 mmHg increase in glomerular pressure and allowing hypertension to be transmitted to the glomerulus[21].

Besides these glomerular hemodynamic effects, other studies have revealed several nonhemodynamic effects of angiotensin II that may also be important in renal disease progression. These findings have suggested that angiotensin II may alter permselective properties of the glomerular capillary barrier by mediating contraction of the foot processes, ultimately changing slit-diaphragm architecture and allowing proteins to escape more easily into the urinary space[22].

Nonhemodynamic effects of angiotensin II include increased production of reactive oxygen species; upregulation of cytokines, cell adhesion molecules, and profibrotic growth factors; induction of transforming growth factor-β (TGF-β) expression, increased synthesis of extracellular matrix proteins; stimulation of plasminogen activator inhibitor-1 production by endothelial and vascular smooth muscle cells; and macrophage activations and infiltrations[23].

There is increasing evidence that TGF-β is a major pro sclerotic mediator. Its production is stimulated by angiotensin II and by glucose directly. Preclinical studies have shown that TGF-β blockade prevents and also ameliorates DN[24,25].

In addition, to amplify some of the effects of angiotensin II, aldosterone may also directly contribute to endothelial dysfunction, aldosterone may also remodel human endothelium in vitro by increasing the size and stiffness of endothelial cells, which favors leakage through intracellular gaps[26].

In animal models, high intraglomerular capillary pressure impairs the size-selective function of the glomerular permeability barrier and causes protein ultrafiltration[27, 28]. The secondary process of reabsorption of filtered proteins can contribute to renal interstitial injury by activating intracellular events. Local recruitment of macrophages by tubular cells that are loaded with ultrafiltered plasma proteins may contribute to interstitial fibrosis by engaging matrix-producing interstitial myofibroblasts. Macrophages also regulate matrix accumulation via release of growth factors, such as TGF-β and platelet derived growth factor (PDGF). TGF-β stimulates the transformation of interstitial cells into myofibroblasts. In addition proximal tubular epithelial cells communicate with interstitial fibroblasts to promote fibrogenesis via paracrine release of TGF-β. In rats with remnant kidneys at day 14, after the onset of proteinuria, TGF-β mRNA was upregulated in proximal tubular cells in parallel with early accumulation of the peritubular interstitium, suggesting that interstitiall fibroblasts are the initial target of profibrogenic signals elicited by protein overreabsorption[29]. Treatment of these rats with an angiotensin converting enzyme inhibitor (ACEI) at the same time limited excess protein overload and interstitial inflammatory cell infiltration and abrogated the abnormal TGF-β 1 gene expression in tubular cells that in all likelihood was responsible of myofibroblasts in surrounding areas. ACEI exerts beneficial effects in the glomerulus primarily by preserving the permselective barrier to proteins[30], thereby limiting proteinuria and filtered protein-dependent inflammatory and fibrogenic signals. The ACEI also may act locally by preventing nonhemodynamic effects of angiotensin II via apical angiotensin receptors on tubular cells, including renal cell proliferation and TGF-β 1 expression[31].

In addition to albumin, transferring, and Immunoglobulin, glomerular proteinuria results in ultrafiltration of high molecular weight precursor forms or complexes of growth factor proteins such as insulin like growth factor 1, hepatocyte growth factor and TGF-β 1. Inflammatory and vasoactive substances formed in excessive amounts by proximal tubuli are secreted toward the basolateral compartment of the cell and give rise to a inflammatory reaction in the interstitium that consistently precedes renal scarring. These processes can be accelerated by cytokines released by tubular epithelial cells and by inflammatory cells that accumulate in the interstitium when proteinuria is present[32-36].

Both interstitial inflammation and progression of disease can be controlled by such drugs as ACEI, which strengthen the glomerular permeability barrier to proteins and thereby limit proteinuria and filtered protein-dependent inflammatory signals[37].

Lastly, the increased glomerular permeability may result in excess ultrafiltration of some complement protein fractions that may be directly toxic to proximal tubules and incite injury. In a subtotal nephrectomy model of renal insufficiency, C3 staining was associated with the appearance of interstitial infiltrated. Treatment with ACEI, which lowered proteinuria, also decreased C3 staining[38].

Recent studies utilizing transgenic rats with overexpression of the angiotensin II type 1 receptor in podocytes revealed that increased angiotensin receptor type 1 signaling in podocytes leads to structural podocyte damage and protein leakage[39]. To support this finding from a therapeutic point of view, recent studies showed that ACEI and angiotensin receptor blocker (ARB) induce redistribution of the molecules in the slit diaphragm, which determine leakage of protein through glomerular filtration barrier[40-42].

There are some data showing that some of the beneficial effects of the RAAS blockade may be related to anti-inflammatory properties of ACEI and ARB[43]. In a clinical study, Stevinkel et al found low plasma levels of tumor necrosis factor-α and C-reactive protein (CRP) in ESRD patients treated with ACEI[44]. The benefit seen with these drugs is beyond that which would be expected from their antihypertensive effects.

The disassociation between doses needed to inhibit local tissue actions of angiotensin II and circulatory concentrations directly involved in blood pressure regulation may be due to reduced tissue penetration or higher tissue concentration of angiotensin II or its receptor[45]. Increased RAAS activity and augmented angiotensin II receptor density in the diseased renal tissue together with reduced penetration of the drug may explain that higher doses are needed for complete RAAS blockade in the tissue responsible for antiproteinuric effects as compared to circulatory levels regulating systemic blood pressure[46].

Several underlying mechanisms may explain the blood pressure independent antiproteinuric effects of agents blocking the RAAS[47-50]. These include reduced intraglomerular hydraulic pressure independent of systemic blood pressure by vasodilatation preferentially of the post glomerular arterioles[51] and improved permselective properties of the glomerular membrane[52]. In addition, ARBs may prevent the occurrence of proteinuria by reducing the loss of glomerular nephrin[53] and by reducing renal levels of prosclerotic cytokines such as TGF-β and CTGF[54].

Doses of ACEI that exceed their maximal antihypertensive dose have not been examined adequately, because, ultrahigh doses of ACEI (doses above those approved for antihypertensive treatment according to the FDA and the European agency for the evaluation of medicinal products) was thought to be associated with serious side effects[55-57]. In contrast, ARB has tested over a wide range of doses, without showing an increase of side effects with ultrahigh doses. Various clinical studies support the notion that the dose of ARB is inversely related to proteinuria, independent of blood-pressure control[58-61].

2. Rationale for higher dose

ACEI and ARB have been shown to reduce proteinuria, blood pressure and thereby retarded deteriorating kidney function in diabetic subjects. Doses of ACEI and ARB currently employed in clinical practice and even in experimental protocols are based essentially on the observation of the maximal effects of these drugs on blood pressure.

"Conventional" doses of these drugs may be insufficient to completely neutralize the anomalous activation of the RAAS, thus helping to explain their failure to achieve complete renal protection[62].

So far reno protective therapy has been administered in doses extrapolated from the treatment of essential hypertension, with doses that may be suboptimal for reno protection. Studies of dose-related efficacy of ACEI or ARBs with dose titration based upon achieving the maximum antiproteinuric effect for reno protection have not been adequately performed[63].

The full reno- and cardiovascular protective potential of agents blocking the RAAS may not be reached in patients with diabetic renal disease when recommended doses of these agents are extrapolated from their blood pressure-lowering properties, which is currently the case for all ACEI and ARBs used for renoprotection. By exceeding currently recommended maximal dose, it has been demonstrated that within the recommended dose interval higher doses provide greater antiproteinuric effects than lower doses[64].

Recent trials investigating the ability of these agents to protect patients against target organ damage have now repeatedly shown that the higher doses were most effective, thus recommending more aggressive treatment in future[65].

The study of the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA-2) investigated the reversibility of kidney function changes after withdrawal of 2 years' antihypertensive treatment. They included 133 hypertensive type 2 diabetic patients with persistent microalbuminuria, randomized to double-masked treatment with either placebo, irbesartan 150 mg, or irbesartan 300 mg once daily for 2 years. Arterial blood pressure, overnight urinary albumin excretion rate, and glomerular filtration rate (GFR) were determined repeatedly. In IRMA-2 trial the benefit of protein reduction was maintained only in the group that was treated with the higher dose of Irbesartan 300mg/day[66].

A double-masked randomized crossover trial included 52 (41 males) hypertensive type 2 diabetic patients with microalbuminuria on ongoing antihypertensive medication. Following 2 months wash-out (baseline), patients were treated randomly with irbesartan 300, 600, and 900 mg once daily, each dose for 2 months. This study by Rossing et al., revealed that ultrahigh dosing of irbesartan [900mg O.D (3 times higher maximal recommended dose)] was generally safe and offers additional nephroprotection independent of changes in systemic blood pressure and glomerular filtration rate in comparison to the currently recommended dose of 300mg[46]. In another study conducted by Andrei Forclaz et al., assessed the blockade of the rennin-angiotensin system (RAS) achieved with 2 angiotensin antagonists given either alone at different doses or with an ACE inhibitor. First, 20 normotensive subjects were randomly assigned to 100 mg Losartan once daily or 80 mg Telmisartan once daily for 1 week; during another week, the same dose of losartan and telmisartan were combined with 20 mg Lisinopril once daily. Then, 10 subjects were randomly assigned to 200 mg losartan once daily and 160 mg of Telmisartan once daily for 1 week and 100 mg losartan twice daily and 80 mg telmisartan twice daily during the second week. This study stated that the blockade of the renin angiotensin system (RAS) being only partial with 100mg Losartan and 80mg Telmisartan[67]. Previous studies with ACEI and angiotensin II receptor antagonists have shown that increasing the dose once

daily has little effect on the peak inhibition but tends to prolong the duration of the inhibition. In accordance with this observation increasing the dose of Losartan to 200mg (2 times higher than maximal recommended dose) once daily and that of Telmisartan to 160mg once daily significantly improved the trough blockade[68,69,70]. Another study with a total of 23 hypertensive patients with type 2 diabetes and nephropathy was carried out with four treatment periods, each lasting 2 months. This study stated that, albuminuria was reduced significantly more by Candesartan 16 and 32mg (recommended maximal dose) as compared with 8mg daily, without differences between the two highest doses[45]. Study with 64mg (2 times maximal recommended dose) was more effective in reducing proteinuria in patients with chronic kidney disease than 16 and 32mg/day Candesartan[71]. Data from another study of 10 older patients with heavy proteinuria (>1.5 g/day) of different eitiology have suggested that additional reduction in proteinuria can be obtained by increasing the dose of Candesartan from 32 to 96mg (3 times maximal recommended dose) daily[72]. A recent short-term safety study of 12 patients with various forms of chronic renal diseases with severe proteinuria also demonstrated good tolerability of the ARB Candesartan in doses 5 times higher than currently approved maximum dose[58].

Vogt et al., conducted study with Lisinopril 10, 20, 30 and 40mg/day (2 times higher the usual dose) in 12 (8 of whom were finally selected for the study) nondiabetic proteinuric patients. The eligible patients entered the run-in phase in which previous medication was replaced for the highest recommended daily dose irbesartan 300 mg combined with the diuretic hydrochlorothiazide 12.5 mg once daily. Then, patients with proteinuria >1 g/d and serum potassium concentration <5.5 mmol/L entered the phase of dose titration. In this phase, lisinopril was added in increasing daily doses to a maximum of 40 mg. All periods of treatment (run-in and up-titration) lasted at least 6 weeks. Their study concluded that, dose titration induced further reduction of residual proteinuria[73]. Fujihara et al., concluded that the renal protection afforded by ARB in renal ablation was dose dependent and maximal protection may require doses several fold higher than those currently employed. In rat model, treatment with Losartan at a dose 10 fold higher than dose 50mg/kg/day and 50 fold higher than those usually employed in experimental studies, arrested the progression of both glomerulosclerosis and interstitial expansion. This dose dependence of Losartan is likely to be observed in human as well, since clinical studies showed that the human responses can be predicted with reasonable accuracy from animal experiments[62]. The effects of different dosage of ramipril, from a minimum of 5mg/day to a maximum of 20 mg/day (4 times the recommended maximum dosage) were evaluated on the level of proteinuria. Although the higher dosage had no additional effect on blood pressure, urinary protein excretion rates were further reduced[37].

In a study by Ruggenenti P, uptitration of lisinopril from 10 to 40 mg was done in 28 patients with nondiabetic chronic nephropathies. These patients entered 4-week lisinopril uptitration periods (from 10, to 20, 30, and 40 mg/d), followed by a 6-week backtitration period to lisinopril 10 mg/d and 4-week recovery period (lisinopril withdrawal). Maximum lisinopril doses significantly and safely reduced proteinuria, serum total, LDL cholesterol, and triglycerides without substantially affecting serum HDL and renal hemodynamics[74]. More recently in a preliminary report, Schjoedt et al.[75] studied 56 patients with type 1 diabetes and nephropathy, who in a double masked crossover trial received 20, 40 or 60 mg/day of lisinopril. The 40 mg/day dose provided a great antiproteinuric effect than 20 mg/day but 60 mg/day did not afford further renoprotection.

Tang et al., in their study on 75 patients with chronic heart failure with low Enalapril (5 mg) dose and high dose (40 mg) over six months and found that there was not any significant reduction in systolic and diastolic blood pressure between the two dose groups. They also measured serum aldosterone and angiotensin II levels in their study and they observed that these renin system hormones weren't adequately suppressed even with the higher dose[76].

Most studies that showed effective reduction of blood pressure and proteinuria included mostly normotensive and/ or microalbuminuric group of patients. In the study conducted by Adrienne et al.,[77] the antiproteinuric effects of losartan in 147 normotensive patients with type 2 diabetes and microalbuminuria was assessed. The losartan dose was 50 mg during the first 5 weeks and 100 mg during the subsequent 5 weeks. A significant 25% relative reduction in the albumin excretion rate occurred after 5 weeks of the 50 mg losartan dose, with further improvement over the subsequent 5 weeks with the 100 mg dose. Losartan was safe and well tolerated in these normotensive patients.

Lacouriciere et al.,[78] in their studies after using Losartan and Enalapril found significantly decreased blood pressure in hypetensive type 2 diabetics with early nephropathy. The study was a one-year prospective, double blind trial with losartan and enalapril administered alone or in combination with hydrochlorothiazide and other antihypertensive agents. Arterial Blood Pressure and renal and biochemical parameters were measured at baseline and after 12, 28, and 52 weeks of active treatment. 92 hypertensive type 2 diabetics with early nephropathy completed the study.

It may be possible that advanced renal failure patients with proteinuria may not respond to increasing doses of Enalapril. Similar findings were also seen by Jensen et al.,[79]. They conducted study with normal to high Enalapril dose (5 to 40 mg) including macroproteinuric patients with advanced renal insufficiency of variable etiologies. They found that at study end blood pressure and proteinuria didn't change significantly in both dose groups.

Anderson et al.,[63] in their study with 50 consecutive hypertensive type 1 diabetic patients with diabetic nephropathy received increasing doses of losartan 50, 100, and 150 mg once daily in three periods each lasting 2 months. Using Losartan from 50 to 150 mg among macroproteinuric patients with normal renal function found that maximum antiproteinuric effect was at 100 mg dose without any adverse effect at 150 mg. No significant benefit of increasing dose from 100 to 150 mg was observed in their study groups.

Huo et al.,[80] undertook a study with Losartan starting with 50 mg and then increasing to 200 mg in a total 360 proteinuric nephropathy patients for a period of 3 years and found significant reduction in blood pressure and proteinuria. But in their study, to control blood pressure, concomitant antihypertensive drugs were used in their patients. It may be possible that antihypertensive drugs in Hou's study reduced blood pressure significantly which influenced the proteinuria reduction to a significant level unlike ours.

Woo et al.,[81] carried out a study in nondiabetic proteinuric subjects with renal dysfunction using 10 mg Enalapril and 100 mg Losartan. 41 patients with biopsy-proven IgAN entered a control trial, with 21 in the treatment group and 20 in the control group. Patients in the treatment group received ACEI/ATRA or both with 3 monthly increases in dosage. They found that blood pressure or proteinuria was reduced only in 30% to 50 % patients. The non responder patients were those who had heavy proteinuria (>2 g/day) and more

advanced renal dysfunction (serum creatinine > 2.5 mg/dl). Study results indicate that combination of heavy proteinuria with advanced renal impairment may be less or non responsive to angiotensin converting enzyme inhibitors or angiotensin receptor blocker even at higher doses.

Rocca et al.,[82] in 45 chronic heart failure patients showed increasing dose of Enalapril from 5 to 40 mg reduced blood pressure more and cough was more common on highest than lowest dose. The dosage was changed three times to treat all patients with lower, higher, and finally, the initial dosage for 4 weeks each. Within patient comparison revealed that serum potassium and creatinine were higher on the highest than the lowest dose. The patient's included in that trial were suffering from chronic heart failure and were primarily non diabetic and non proteinuric patients. It is possible that these patients are more susceptible to adverse effect with increasing doses of angiotensin converting enzyme inhibitor.

Brenner et al.,[83] conducted a study with a total 1513 patients having hypertension, type 2 DM and nephropathy (S. cr 1.3-3 mg/dl) for a mean of 3.4 years. A total of 327 patients in the losartan group reached the primary end point, as compared with 359 in the placebo group. Their study established that losartan, along with conventional antihypertensive treatment as needed, conferred strong renal protection in these patients. The risk of the primary end point a composite of doubling of the S. creatinine concentration, ESRD was reduced by 25% & 28% respectively with losartan but had no effect on the rate of death. The level of proteinuria declined by 35% with losartan.

3. Safety monitoring

Enalapril was well tolerated even at 40mg (maximal recommended dose) once daily dose, as compared with 5mg once daily dose. In fact, there were more reported adverse events and death (requiring withdrawal from the trial) in the low-dose group than in the high-dose group. As seen in previous studies, a large proportion of patients with advanced chronic heart failure could receive up to very high doses of Lisinopril (medium-dose 12.5 or 15.0 mg once daily for 2 to 4 weeks and then randomized to high 35.0 or 32.5 mg once daily or low-dose 5.0 or 2.5 mg once daily) and Enalapril without significantly more adverse effects[84,85]. Losartan could be administered at an extremely high dose without any perceptible toxic effect. In rat model, treated with 500mg/kg/day, had no hypotension and plasma K^+ concentration was not higher[63]. In the trial with lisinopril (where a total of 3164 patients were assigned randomly with either low dose of 2.5 to 5.0 mg daily lisinopril in 1596 patients or high doses of 32.5 to 35 mg daily lisinopril to 1568 patients for 39 to 58 months), increase in serum creatinine in the high-dose group (35mg/day) was slightly greater than in the low-dose group (5mg/day), but the number of patients with major increase in serum creatinine (>1mg/dl) was not different[86]. There was a therapy with Candesartan 8, 16, 32mg (maximal recommended dose) in a total of 23 hypertensive patients with type 2 diabetes and nephropathy with four treatment periods, each lasting for 2 months. The therapy was well tolerated without associated adverse events. A slight increase in serum K^+ was found, but no incidence of hyperkalamia and hypotension was observed in these patients[45]. No serious adverse event was reported in relation to the ultrahigh dose (64mg i.e.2 times maximal recommended dose) of candesartan. This confirmed previous studies observing no dose-response curves of serious adverse effect of increasing dose of ARB[70].

In a pilot study, 12 patients (10 males; age = 57± 14 years) with a history of diabetic or non-diabetic chronic kidney disease received candesartan in an 8-week open-label trial in which drug was titrated to a targeted dosage of 160 mg/day (5 times above the currently approved maximum dose) and remained at that dosage for the subsequent 4 weeks. Candesartan was well tolerated with no serious drug-related adverse events reported. Serum creatinine concentrations throughout the study were not different from baseline levels. Plasma potassium concentrations at 160 mg/day candesartan were similar to those at baseline. The results of this pilot study suggest that supramaximal doses of ARBs are safe and well tolerated in patients with chronic kidney disease, while reducing both blood pressure and proteinuria[58].

In Irbesartan Diabetic Nephropathy Trial (IDNT), Irbesartan (titrated to 300mg/day i.e. maximal recommended dose) slowed the deterioration of renal function by decreasing risk of doubling of serum creatinine, development of end stage renal disease, or death by 20%. Fewer patients receiving Irbesartan had a doubling of their serum creatinine concentration than placebo[87].

Treatment with Irbesartan was carried out in 52 (41 males) hypertensive type 2 diabetic patients with microalbuminuria. Following 2 months of wash-out (baseline), patients were treated randomly with irbesartan 300, 600, and 900mg/day (3 times higher maximal recommended dose), each dose for 2 months. The therapy induced an increase in plasma K^+ and these changes were only marginally greater when exceeding the currently recommended dose of Irbesartan. None of the patients developed hyperkalemia[46].

In RENAAL (Reduction of Endpoints in NIDDM with the AngiotensinII II Antagonist Losartan) study, 50 consecutive hypertensive type 1 diabetic patients with diabetic nephropathy received increasing dose of losartan, 50, 100, and 150 mg once daily in three periods each lasting 2 months. Losartan 50mg to 100mg reduced the primary end point (doubling of baseline serum creatinine, end stage renal disease, or death). Potassium, sodium, and cholesterol, including HDL-cholesterol, remained unchanged at 50, 100 and 150mg/day with Losartan. Levels of uric acid in serum did not exceed the upper normal range in this study[63].

Serum K^+ and serum creatinine were slightly, higher at high [40mg/day (4 times the recommended dose)] than at low (10mg/day) enalapril levels. Most patients show an only mild increase in serum creatinine, and ACEI therapy did not have to be discontinued in these patients. An increase in enalapril dose did not lead to hyperkalemia. Serious adverse events (i.e. worsening of chronic heart failure, anuria and serious arrhythmia) tended to be more common after downward than after upward titration of enalapril[82]. In the ValHeft (Valsartan in Heart Failure) trial, patients received 160mg valsartan twice daily without any serious adverse effect[88]. In a study by Hou et al. , the incidence of cough was significantly higher in the benazepril arm as compared to losartan arm, but it did not seem to be dosage related. Hyperkalemia occurred in eight (4.4%) patients in the benazepril arm and eight (4.4%) patients in the losartan arm. Of these 16 patients, six were successfully treated with dietary modification, concomitant diuretic therapy, and optimized acid-base balance. The remaining 10 patients withdrew from the study[80]. In the study with ultrahigh dose of Irbesartan (900 mg) total 58 patients having hypertension, type 2 diabetes mellitus with microalbuminuria (persistent Urinary Albumin Excretion between 30 & 300 mg/24hours) on ongoing antihypertensive (wash out done) were included. 4 patients were excluded due to

adverse clinical events, which were not considered related to the study medication. 1 patient discontinued the study after 2 weeks on Irbesartan 900 mg before any clinical examination was performed due to complaints of dizziness & general discomfort. Among 52 patients completing the study, 7 patients complained of mild & transient dizziness, 1 patient during 300 mg, 3 patients during 600 mg & 3 during 900 mg. There was a significant increase in plasma K^+ of 0.3 mmol/L during treatment with irbesartan 300 & 600 mg & by 0.4 mmol/L during treatment with 900 mg. However, none of the patients included in the study developed hyperkalemia (plasma K^+> 5.5 mmol/L). Plasma hemoglobin decreased significantly from 8.7 mmo/L at baseline to 8.2 mmol/L during treatment with 300 & 600 mg & to 8.1 mmol/L during irbesartan 900 mg[46].

4. Dual blockage of RAAS with ACEIs and ARBs

An insufficient response to ACE inhibition might be explained by the incomplete blockade of the RAS obtained with ACE inhibitors, which are unable to block completely the formation of angiotensin II (Ang II), because some generation of Ang II is produced via other non-ACE pathways[89]. Furthermore, Ang II levels return to normal values after chronic therapy with ACE inhibition, the so-called "ACE escape phenomenon"[90].

The demonstration of local angiotensin II (Ang II) synthesis in numerous tissues and organs has led to the concept of local or tissue-based RAASs that are independent of but can interact with the traditional circulating RAAS[91]. These local RAASs appear to act in a paracrine/autocrine manner to regulate organ function and are involved in pathologic events associated with end-organ damage. The kidney contains all the elements of the RAAS, and intrarenal formation of Ang II independent of the circulating RAAS was first demonstrated more than 30 years ago[92].

Local AngII in the kidney has multiple roles contributing in hypertension and kidney damage. It enhances capillary filtration pressure, directly by efferent arterial vasoconstriction and indirectly through TGF-β1 (transforming growth factor beta1) mediated impaired afferent arteriole autoregulation[93]. AngII decreases the synthesis of negatively charged proteoglycans and suppresses nephrin transcription[94, 95], which results in podocyte apoptosis. Through VEGF (vascular endothelial growth factor) and TGF-β1, induces synthesis of the α3 chain of collagen type IV, the principal ingredient of the glomerular basement membrane[96], stimulates upregulation of adhesion molecules such as vascular cellular adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and integrins, allowing circulating immune cells to adhere on capillaries. Ang II induces nuclear factor Kβ (NF-κB) –mediated transcription of chemokines, including monocyte chemoattractant protein-1 (MCP-1), RANTES, and others, resulting in renal tissue infiltration with leukocytes and also induces plasminogen activator inhibitor-1 (PAI-1) and tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) which inhibits metalloproteinases resulting in accumulation of extracellular matrix. Through all these mechanisms, AngII induces proteinuria, inflammation, growth effects, apoptosis and fibrosis[97].

Chymase-dependent Ang II formation may be at least partly responsible for 'ACE escape'. This term refers to the observation that, in a high proportion of patients chronically treated with ACE inhibitors, Ang II levels gradually return to baseline after an initial decline. This increase in Ang II formation in the presence of ACE inhibitors is likely due to a compensatory increase in plasma renin activity (PRA) caused by disruption of the feedback loop by which

AngII normally inhibits renin release[98]. Under these circumstances, Ang II can be formed from Ang I by alternative, ACE-independent pathways, such as chymase, which has been shown to be upregulated in diabetic and hypertension-related nephropathies[99].

ACE-I inhibits the angiotensin-converting enzyme (ACE), thereby reducing the synthesis of Ag II. In addition, it inhibits the degradation of bradykinin, a vasodilator that stimulates nitric oxide, prostaglandin E2, prostacyclin and cyclic guanosine monophosphate production. This might confer additional renal protection, beyond that achieved by the inhibition of Ag II. However, with prolonged ACE-I therapy, the Ag II level can increase through an escape mechanism via peripheral chymase action[89,99]. ARB, on the other hand, acts directly on the Ag II type 1 receptor (AT 1) and thus blocks all the known actions of Ag II. In addition, by blocking AT 1, it provides unopposed stimulation of the Ag II type 2 receptor (AT 2) in the kidney. Stimulation of the AT 2 receptor has been associated with increased nitric oxide production, increased natriuresis as well as growth inhibitory effects[100]. In order to take advantage of the distinct properties of both these medications, a number of studies have explored the possibility of dual blockade of the RAAS with ACE-I and ARB.

In the search of new alternatives that could improve the antiproteinuric and nephroprotective effects of RAS blockers, we believe that the association of ACE inhibitors and ARB might prove useful. ARB produces a complete blockade of the RAS and stimulates the vasodilating and non-proliferative actions of Ang II via the AT2 receptor[101]. Furthermore, ACE inhibitors, but not ARB, inhibit the metabolism of kinins, which increases the levels of bradykinin, also a potent vasodilator[102].

Recently, some authors have reported a superior effect of the combination of ACE inhibition and ARB on microalbuminuria and on clinical proteinuria in patients with primary nephropathies[103-105], and in type 1 and type 2 diabetic patients[106, 107].

The rationale for combined therapy with ACE inhibitors and ARB is based on the different mechanism of these two drugs in the RAS blockade. Both drugs inhibit the action of Ang II. It is known that Ang II plays a pivotal role in the pathophysiological course of renal disease progression. ACE inhibition could not completely inhibit the generation of Ang II, which may be produced via other non-ACE pathways[89]. In contrast, ARB completely abolishes the action of Ang II through blockading theAT1 receptor, producing an accumulation of Ang II that stimulates the vasodilatory and antiproliferative actions of Ang II mediated through the AT2 receptor[101]. On the other hand, ACE inhibitors but not ARB, decreases degradation of bradykinin, which is a potent vasodilator[102].

A recent meta-analysis by Jennings et al reported a greater reduction in proteinuria with combination therapy when compared with ACE-I alone[108]. The response to treatment with ACE-I and ARB may differ among different races[109].

Mogensen et al studied 197 hypertensive patients with type 2 DM and microproteinuria, and found that combination therapy with once daily candesartan 16 mg and lisinopril 20 mg was more effective in reducing BP and albuminuria than monotherapy with either drug alone[106].

Cetinkaya et al found that a combination of enalapril 10 mg daily and losartan 50 mg daily decreased both the proteinuria and MAP by a greater extent when compared with the administration of either drug alone[110].

In two separate randomised double-blind crossover studies, Rossing et al found a further reduction in albuminuria when candesartan 16 mg was added to the pre-existing ACE-I therapy in hypertensive type 2 diabetic patients. In the first study involving 18 type 2 diabetic patients who were taking the recommended doses of ACE-I, corresponding to 20 mg of enalapril/lisinopril once daily or 100 mg of captopril daily, the administration of candesartan 16 mg daily for two months induced a 25% reduction in albuminuria, together with a 10 mmHg reduction in 24-hour systolic BP[111]. In the second study involving 20 type 2 diabetic patients on a maximal recommended dose of ACE-I (enalapril/lisinopril 40 mg daily or captopril 150 mg daily), there was a further 28% significant reduction in albuminuria, and a modest but non-significant reduction in BP after two months of being administered candesartan at 16 mg daily[112]. On the other hand, the addition of Losartan 50 mg daily for one month did not improve proteinuria in 16 obese, hypertensive patients (12 with diabetic nephropathy) with moderately advanced renal failure and heavy proteinuria (mean urinary protein 3.8 g/day)[113]. A Korean group also reported no beneficial effect on proteinuria when candesartan was added to ramipril therapy in type 2 diabetic patients with nephropathy despite the positive anti-proteinuric effect seen in patients with IgA nephropathy following the same regimen[114, 115].

Dual blockade of RAAS at different steps with ACEI and ARB would be an attractive alternative.

In meta-analysis, Doulton et al demonstrated that combination therapy provided a further 30%- 39% drop in proteinuria compared to monotherapy[116] and in MacKinnon et al resulted in a significant decline in proteinuria both in diabetic and nondiabetic patients with a slight but significant increase in potassium, and an insignificant drop in GFR[117].

The IMPROVE (Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events) study has shown no further benefit on albuminuria reduction in patients treated with combination therapy despite the fact that BP reduction was slightly better in the combination group. Subgroup analyses showed the largest reduction in albuminuria occurred in patients with overt nephropathy but it did not reach statistical significance[118].

In contrast to these studies, the VALERIA (Valsartan in Combination With Lisinopril Versus the Respective High Dose Monotherapies in Hypertensive Patients With Microalbuminuria) trial demonstrated that combination therapy was more effective in reducing microalbuminuria despite the fact that patients received the maximal recommended doses of lisinopril or valsartan as monotherapy[119].

5. Direct renin inhibition

Aliskiren is the first orally active Direct Renin Inhibitor (DRI) to receive regulatory approval for hypertension. By inhibiting the enzymatic conversion by renin of Angiotensinogen to Angiotensin I, DRIs inhibit the initial and rate-limiting step in the RAAS cascade, thus reducing the product ion of al l downstream products derived from Angiotensin[120, 121]. Furthermore, in both clinical studies[122] and in experimental animals[123], aliskiren reduces plasma and/or urinary excretion of aldosterone. The role of aldosterone in endothelial dysfunction, inflammation, proteinuria and fibrosis is well known[97].

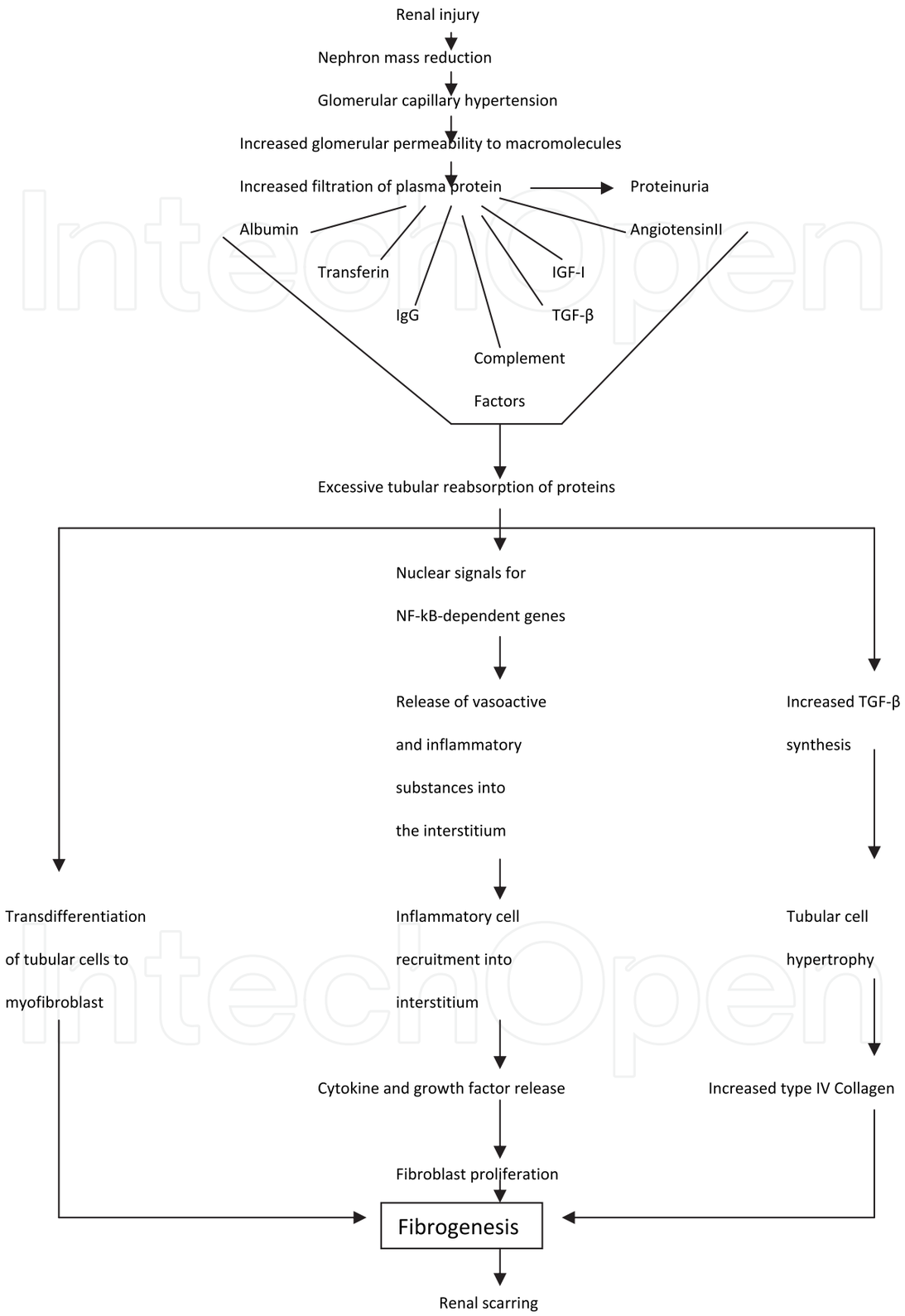

Fig. 1. Effect of increased glomerular permeability to proteins on progressive renal injury

The mechanisms by which aliskiren may impart renoprotection are still under investigation. However, a number of possible mechanisms can be envisioned. First, aliskiren not only inhibits renin but also inhibits the activity of prorenin[124] following its non-proteolytic activation upon binding to the (pro)renin receptor[125]. This may be of particular importance in diabetes in which prorenin levels are elevated and may contribute to local Ang II formation[126]. Second, aliskiren blocks the circulating RAAS and lowers blood pressure[127]. Hypertension is one of the most common comorbidities in CKD and its control is essential in reducing further renal damage and cardiovascular risk in CKD patients[128]. Third, aliskiren blocks the intrarenal RAAS and lowers renal Ang I and Ang II levels[129], thus reducing the deleterious renal effects of Ang II[97] (fig. 1). Finally, aliskiren has been shown to reduce the renal expression of the (pro)renin receptor in an animal model of diabetes[124]. If the (pro)renin receptor plays a role in CKD, downregulation of this receptor may reduce the Ang II-independent effects of (pro)renin receptor activation on renal fibrotic pathways[130] (Fig. 3).

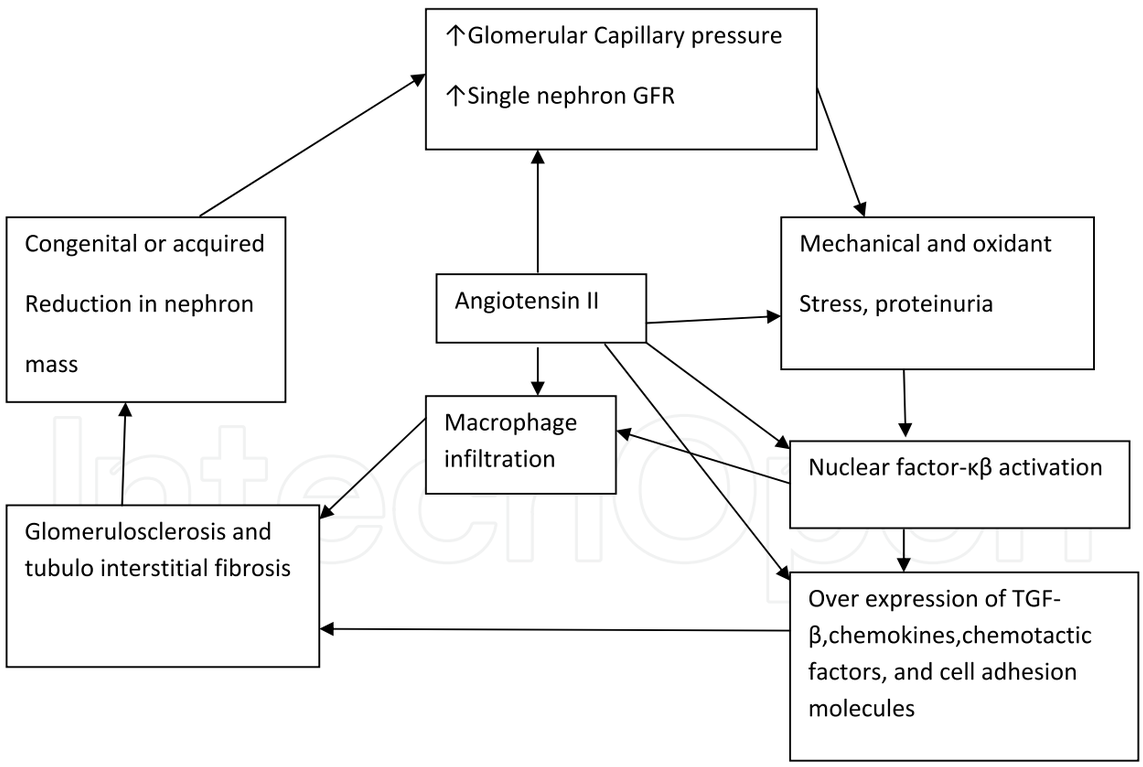

Fig. 2. Final common pathway for progression of chronic renal disease

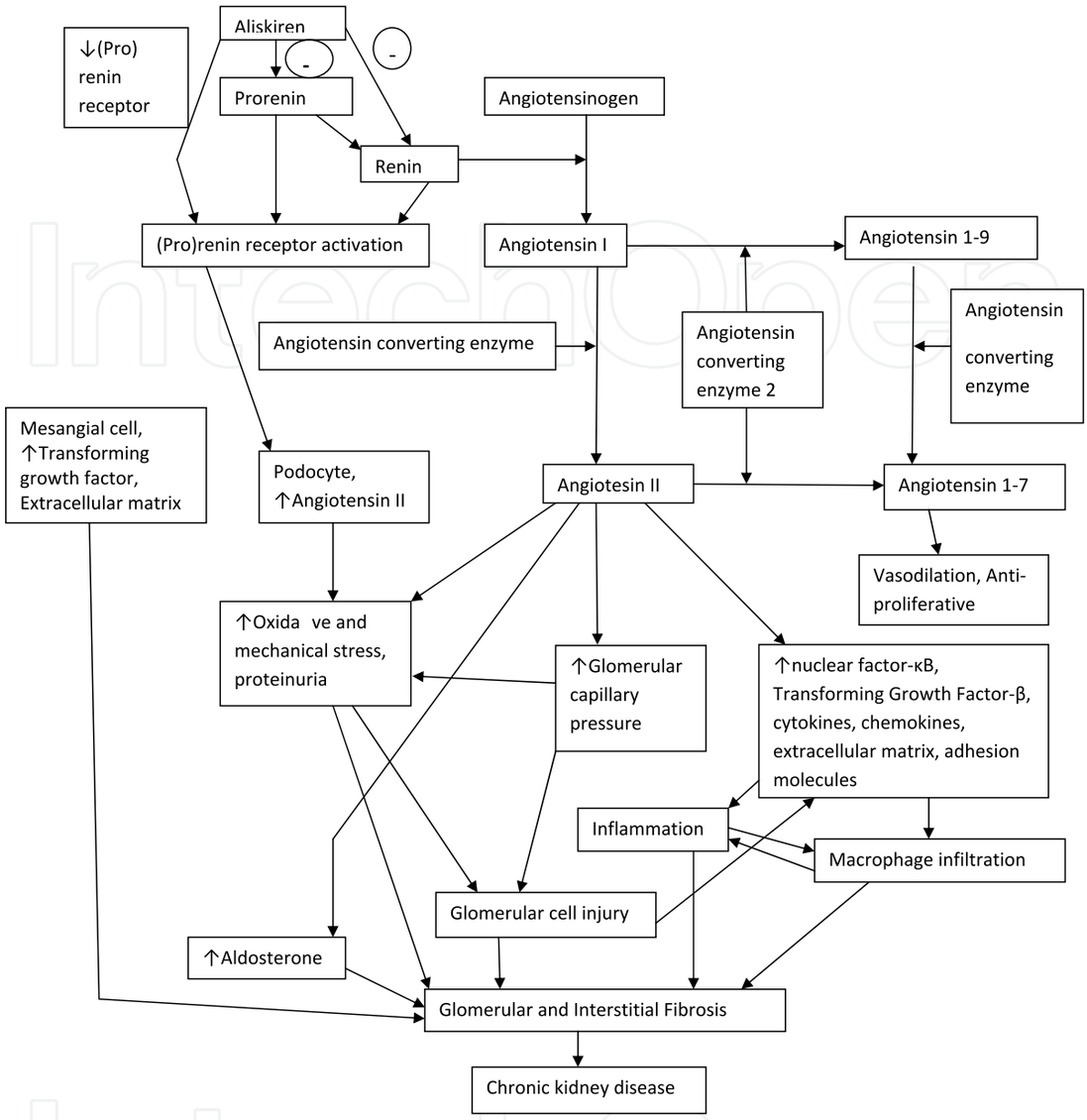

Fig. 3. Multiple role of the Renin angiotensin aldosterone system in the pathogenesis of chronic kidney disease

In patients who have vascular disease or high risk diabetes without heart failure, angiotensin-converting-enzyme inhibitors reduce mortality and morbidity from cardiovascular causes, but the role of angiotensin-receptor blockers in such patients is unknown. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) was carried out for the comparative study between ramipril, telmisartan and the combination of both in patients with vascular disease or high risk diabetes. After a 3 week, single-blind run-in period, patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipri per day, 8542 assigned to receive 80 mg telmisartan per day, and 8502 assigned to receive both drugs (combination therapy). Telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit[131].

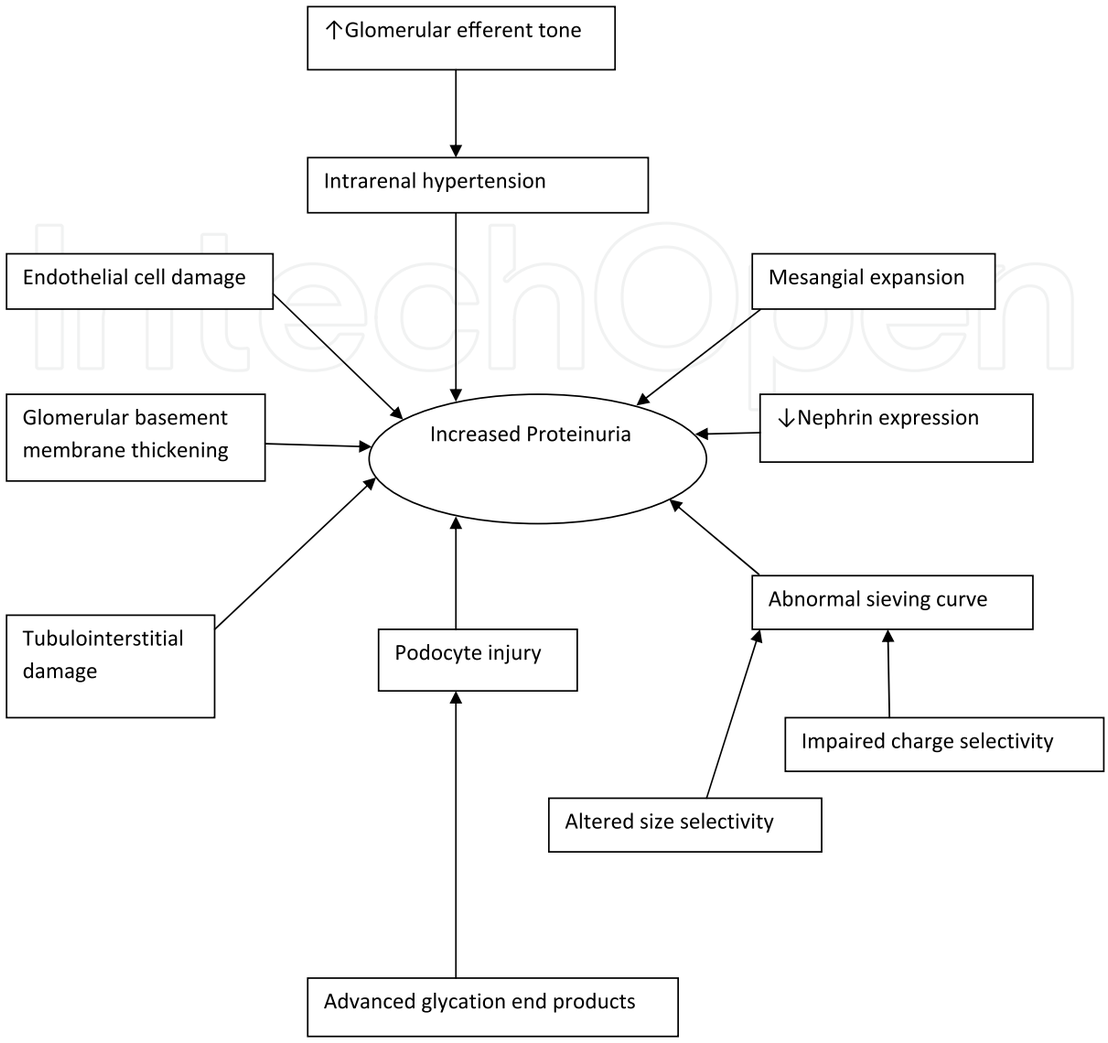

Fig. 4. Mechanism of proteinuria in diabetic nephropathy

Stage	Glomerular Filtration Rate	Urinary albumin excretion (mg/d)	Blood pressure	Years after diagnosis
i. Hyperfiltration	Supernormal	<30	Normal	0
ii. Microalbuminuria	High normal To normal	30-300	Rising	5-15
iii. Proteinuria	Normal To decreasing	>300	Elevated	10-20
iv. Progressive nephropathy	Decreasing	Increasing	Elevated	15-20
v. End stage renal disease	<15ml/min	Nephrotic	Elevated	20-30

Table 1. Stages of Diabetic Nephropathy

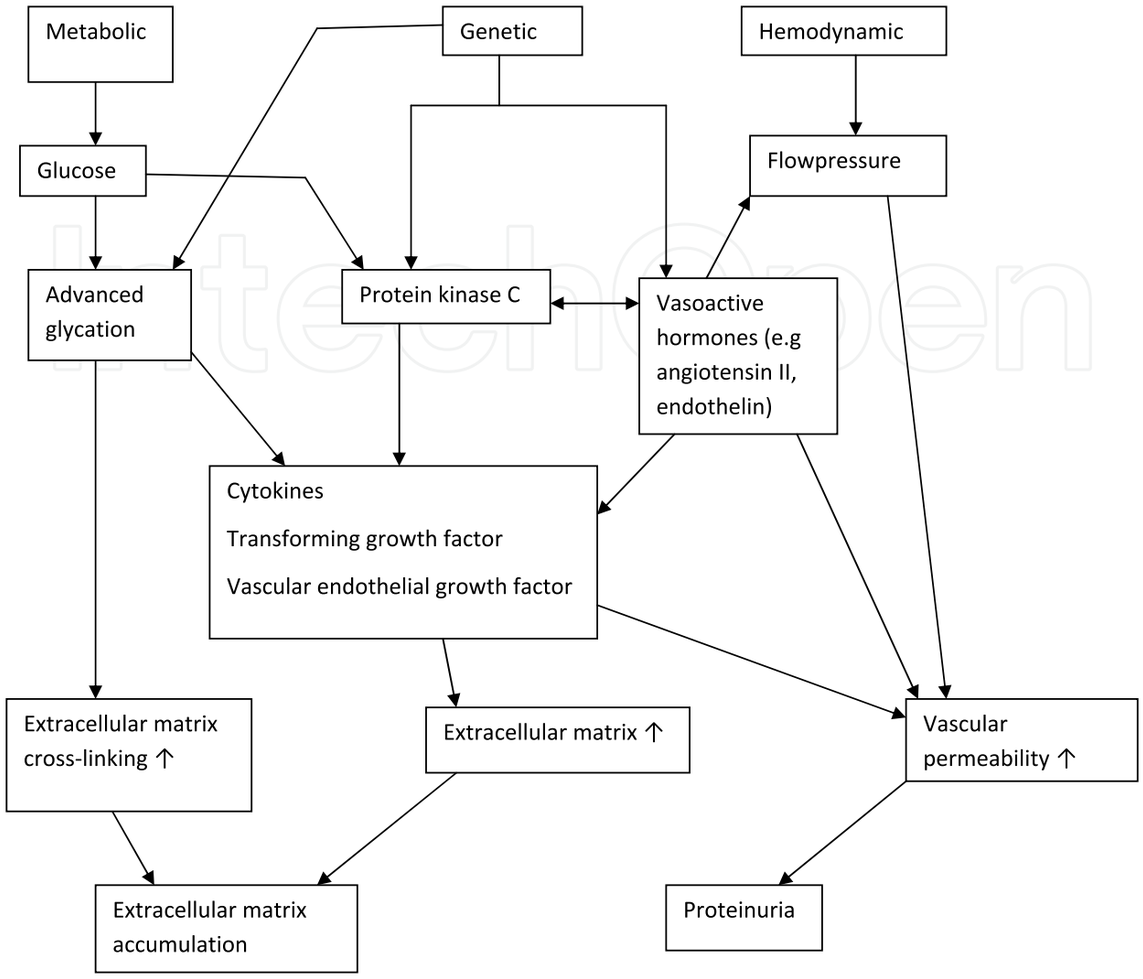

Fig. 5. Pathogenesis of Diabetic nephropathy

6. Conclusion

ACE inhibitors and ARBs, as monotherapy or in combination, have evolved as accepted first-line agents for delaying the progression of diabetic nephropathy. Currently, recommendations favor ACE inhibitors for type 1 and ARBs or ACE inhibitors for type 2 diabetes as a result of large, controlled clinical trials. Therapeutic goals should be addressed not only for BP reduction, but in diminishing albuminuria as well. In subjects with microalbuminuria, the dose of ARBs or ACE inhibitors should be titrated by the clinician until normoalbuminuria is induced, even if supramaximal doses or a combination of ARBs and ACE inhibitors are necessary. There is evidence that achieving reduction in both microalbuminuria and in heavy proteinuria at greater doses than those used to control BP may be required using monotherapy or a combination of these RAS blockers[132].

Different studies showed that higher doses of angiotensin converting enzyme inhibitors and angiotensin receptor blocker are safer and beneficial. Rationale to use higher doses of angiotensin converting enzyme inhibitors or angiotensin receptor blocker is not only to reduce proteinuria and or to control blood pressure. Additional beneficial effects are

observed at higher doses other than renal systems. Losartan showed cardio protection by cardiac remodeling, vascular remodeling, atherosclerosis, endothelial function, inhibition of thrombus formation and platelet aggregation, reduction of risk factor for stroke in addition to renal effects[133].

Higher drug doses can reduce nephrotoxic components like TGF β[134], connective tissue growth factor[135], inflammatory mediators like cytokines[63] etc. It is evident that, these drugs, even when do not reduce proteinuria or blood pressure significantly, may provide the additional renoprotection with higher doses.

Dual blockade of the RAS provides superior short-term renoprotection independent of systemic blood pressure changes in comparison with maximally recommended doses of ACEI in patients with type 2 diabetes as well as nephropathy.

The ability of these two therapeutic agents to synergistically antagonize the RAAS can also be explained by their complimentary mechanisms of action. For example, ACE inhibition leads to a prolonged half-life of bradykinin, a potent vasodilator believed to be renoprotective. ARBs do not increase the half-life of bradykinin. They can further ablate the damaging effects resulting from the production of angiotensin II by non-ACE pathways, which is not completely blocked by an ACEI. Thus, it seems plausible that combining these two agents could more effectively oppose the RAAS than either agent alone[136].

7. References

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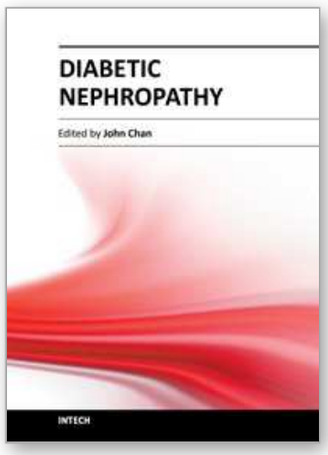

Diabetic Nephropathy

Edited by Dr. John Chan

ISBN 978-953-51-0543-5
Hard cover, 166 pages
Publisher InTech
Published online 20, April, 2012
Published in print edition April, 2012

Internationally renowned experts have provided data on their own studies, and discuss the relative usefulness of their work in relation to diabetic nephropathy. The first section describes the novel role of intrarenal renin-angiotensin-aldosterone system (RAAS) and oxidative stress in the development of diabetic nephropathy and discusses the current and novel pharmacological interventions in the treatment of diabetic nephropathy. The second section discusses other important contributors outside of the RAAS in the pathogenesis of diabetic nephropathy including AGE/RAGE, epithelial-mesenchymal-transition (EMT) and immune cytokines. Features: Provides novel information on various pathophysiological determinants in the development of diabetic nephropathy Provides novel information on various pharmacological interventions of diabetic nephropathy

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Rozina Rani (2012). Drug and Diabetic Nephropathy, Diabetic Nephropathy, Dr. John Chan (Ed.), ISBN: 978-953-51-0543-5, InTech, Available from: http://www.intechopen.com/books/diabetic-nephropathy/drug-and-diabetic-nephropathy

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