

Original Research Article


The role of ACE inhibitors in retarding the progression of non diabetic chronic kidney disease by controlling blood pressure and proteinuria

E.A. Ashok Kumar^{1*}, P. Jijiya Bai²

¹Professor, Department of Medicine, MNR Medical College and Hospital, Fasalwadi, Sanga Reddy, Medak, Telangana, India

²Professor, Department of Pathology, MNR Medical College and Hospital, Fasalwadi, Sanga Reddy, Medak, Telangana, India

*Corresponding author email: ashokedla@gmail.com

	International Archives of Integrated Medicine, Vol. 3, Issue 4, April, 2016. Copy right © 2016, IAIM, All Rights Reserved. Available online at http://iaimjournal.com/ ISSN: 2394-0026 (P) ISSN: 2394-0034 (O)	
	Received on: 15-03-2016	Accepted on: 22-03-2016
	Source of support: Nil	Conflict of interest: None declared.
How to cite this article: E.A. Ashok Kumar, P. Jijiya Bai. The role of ACE inhibitors in retarding the progression of non diabetic chronic kidney disease by controlling blood pressure and proteinuria. IAIM, 2016; 3(4): 37-52.		

Abstract

Lowering of blood pressure itself lowers urinary protein excretion rate and slows rate of GFR decline in chronic renal disease. There are data that suggests that ACE inhibitors improve glomerular barrier size selective function in experimental and human renal disease by directly lowering the mean dimensions of large unselective pores. A reduction in urinary protein excretion correlates with improved renal function and survival in non diabetic and diabetic renal disease. The initial reduction in rate of excretion inversely correlates with long term preservation of renal function in patient without diabetes treated with angiotensin converting enzyme inhibitors. In this study of 97 patients, the results showed that antihypertensive regimens of ace inhibitors group were more effective than non ace inhibitor in slowing progression of non diabetic chronic kidney disease. The presence of proteinuria in non diabetic chronic kidney disease is a strong indication for treatment with ace inhibitors. A brief epidemiology and pathophysiology is also discussed to understand the role of hypertension and proteinuria in chronic kidney disease.

Key words

ACE inhibitors, Chronic kidney disease, Blood pressure, Proteinuria.

Introduction

Chronic kidney disease (CKD) is a major public health problem all over the world. The incidence and prevalence of kidney failure is rising. By 2010, it is estimated that the prevalence will be greater than 650000 [1]. The prevalence of earlier stages of CKD is even higher. Unfortunately CKD is under diagnosed and undertreated resulting in losing opportunity for prevention [2-4]. Hypertension and proteinuria occur in most patients with CKD and are the risk factor for faster progression of kidney disease. In most forms of proteinuric CKD, glomerular filtration rate (GFR) continues to decline even when the initial insult has been removed [5, 6]. The chronic kidney disease progression occurs in general through focal nephron loss irrespective of etiology. Glomerular capillary hypertension is often maintained by angiotensin dependent mechanism both through increasing systolic blood pressure and via specific effects on glomerular hemodynamics.

Angiotensin II can cause tissue remodelling but can also contribute directly to CKD by stimulating expression of TGF-beta an important mediator of extracellular matrix deposition and fibrosis in kidney. Proteinuria is an independent risk factor for progression of renal disease. The proteinuria or microalbuminuria serves as a marker of glomerular capillary hypertension. Hypertension has important role and exacerbate pre-existing renal disease. Normalization of systolic blood pressure limits renal disease progression. In nearly all studies, the renoprotective properties of angiotensin converting enzyme (ACE) inhibitors were accompanied by a decrease in rate of urinary protein excretion [7, 8]. The ACE inhibitors have beneficial effects on the permeability and size selective function of glomerulus, these effects would lead to limited ultrafiltration of macromolecules and proteins [9-11].

ACE inhibitors are more effective than conventional antihypertensive drugs at delaying

the progression of renal disease in diabetic [12-22], and non diabetic patients [23].

Epidemiology

The worldwide rise in the number of patients with CKD is reflected in the increasing number of people with end stage renal disease (ESRD) treated by renal replacement therapy - dialysis or transplantation [24]. In the UK, the annual incidence of ESRD has doubled over the past decade to reach about 100 new patients per million of population [25], well below the European average (about 135 per million) and rates in the USA [26].

The incidence is expected to continue to rise at an annual rate of around 5–8%. Two factors are important. The first is the ageing of the population; the incidence of ESRD is higher in elderly people than in the general population. The second factor is the global epidemic of type 2 diabetes mellitus; the number of people with diabetes worldwide is predicted to double within the next 20 years [27]. This increase will be most notable in less developed countries, where the number of diabetic patients could rise from 99 million to 286 million by 2025 [27], with an expected parallel epidemic of diabetic nephropathy.

About 90% of treated ESRD patients come from more developed countries that can still afford the cost of renal replacement therapy [28]. The annual expenditure on ESRD is estimated to increase [26]. Dialysis alone takes up most of health-care budgets with only a small proportion of the population needing treatment. There is a clear and direct relation between the gross national product and the availability of renal replacement therapy, with less developed countries unable to meet the increasing demand [28].

The number of patients with ESRD probably underestimates the entire burden of CKD because the numbers with earlier stages of disease (stages 1 to 4) are likely to exceed by as much as 50 times those reaching ESRD (stage 5)

[29]. The prevalence of CKD increases to 50–60% when at-risk individuals are screened [30]. Clearly, the early identification of such individuals and the prevention of progressive CKD are likely to be key factors in alleviating the future burden of end-stage renal disease and the associated mortality.

Pathophysiology

Hypertension is both a cause and a complication of chronic kidney disease and should be carefully controlled in all patients. Evaluation and treatment of other complications of microalbuminuria, decreased GFR, such as anemia, malnutrition, bone disease, neuropathy, and decreased quality of life, should be undertaken. Renal replacement therapy should begin when GFR declines to less than 15 mL/min per 1.73 m² (stage 5). The clinical action plan for each stage should include actions begun in preceding stages.

Pathophysiology of progressive nephropathies

In patients with renal diseases characterized by proteinuria, the initial insult to the kidney is usually followed by a progressive decline in the glomerular filtration rate. This decline has been thought to be due to changes in renal hemodynamics initiated by the loss of nephrons [31]. When renal mass is reduced in rats, the remaining nephrons undergo sudden hypertrophy, with a concomitant lowering of arteriolar resistance and an increase in glomerular plasma flow [32, 33]. Afferent arteriolar tone decreases more than efferent arteriolar tone, and therefore, the hydraulic pressure in glomerular capillaries rises [34] and the amount of filtrate formed by each nephron increases. These changes increase the filtration capacity of the remaining nephrons, thus minimizing the functional consequences of nephron loss, but they are ultimately detrimental [35].

Therapies that attenuate these adaptive changes limit the decline in the glomerular filtration rate and minimize structural damage. For example, angiotensin converting enzyme (ACE) inhibitors,

which reduce intra glomerular capillary pressure more effectively than other antihypertensive drugs, consistently protected rats with reduced renal mass [36, 37] or diabetes mellitus [38, 39] from progressive renal injury.

Why should hemodynamic changes - specifically, glomerular hypertension - lead to progressive renal injury? One possible explanation is that the high glomerular capillary pressure enlarges the radius of the pores in the glomerular membrane by a mechanism that is mediated at least in part by angiotensin II [40, 41]. This enlargement impairs the size-selective function of the membrane so that the protein content of the glomerular filtrate increases, which in turn increases the endocytosis of protein by tubular epithelial cells, ultimately resulting in a nephrogenic effect [42]. A vicious circle is then established in which changes in renal hemodynamics due to the loss of nephrons lead first to proteinuria and then to the loss of more nephrons.

Proteins filtered by the glomerulus cause injury of the tubulointerstitium, leading to parenchymal damage and, ultimately, renal scarring and insufficiency.

Excessive reabsorption of protein as a consequence of increased glomerular permeability results in the accumulation of proteins in proximal tubular cells and may trigger the activation of genes encoding endothelin, chemokines, and cytokines that are either dependent on Nuclear Factor *κ*B (NF κ B) or independent of this factor. Excessive synthesis of these or other vasoactive and inflammatory substances contributes to the proliferation of fibroblasts and interstitial inflammation, ultimately leading to increased synthesis of extracellular matrix and renal scarring. Moreover, the increase in the synthesis of angiotensin II by the kidney as a result of injury leads to an increase in the expression of the gene for Transforming Growth Factor β 1 (TGF β 1) in tubular cells, eventually inducing hypertrophy of

these cells and increasing the synthesis of type IV collagen (fibrogenesis).

Protein-Dependent Interstitial Inflammation in Nephropathies

The evidence has accumulated that in humans with nephropathy; more severe proteinuria means more rapid progression of disease [43-46]. Among patients with non-diabetic proteinuric renal diseases, those with higher rates of urinary protein excretion had more rapid progression of renal disease, independent of its specific cause [43]. The occurrence of proteinuria in 10 to 30 percent of patients with chronic hypertension or diabetes after 10 to 15 years of normal renal function invariably predicts a subsequent decline in the glomerular filtration rate [47, 48]. The base-line urinary protein excretion was the best single predictor of disease progression and end-stage renal disease in nondiabetic proteinuric nephropathies [49].

Renin Angiotensin Aldosterone system

Angiotensin II (AT II) mediated hypertension can cause tissue remodelling, and can also contribute directly to chronic kidney disease by stimulating expression of TGF-BETA an important mediator of extracellular matrix deposition and fibrosis [50]. Angiotensin II triggers several signal transduction pathways through its interaction with the Angiotensin I (AT I) receptor, resulting in cell proliferation, growth, and tissue remodelling [51-53]. In the kidney, this may manifest as mesangial production and glomerulosclerosis [51-54]. But In addition, angiotensin II stimulates production of aldosterone by its action on zona glomerulosa of adrenal cortex. Aldosterone may cause cardiac and renal fibrosis independent of its effects on blood pressure. The heptapeptide angiotensin III (AT III) also stimulates aldosterone production.

Two major classes of receptor for angiotensin II are AT I and AT II; AT1 may exist as two sub types alpha and beta. Most of the effect of angiotensin II and III are mediated by AT I receptor. In addition, many tissues have a local renin angiotensin systems and the ability to

produce angiotensin II. These tissues include uterus, placenta, vascular tissue, heart, brain, adrenal cortex, kidney [55].

Angiotensin converting enzyme inhibitor

In general ACE inhibitors maintain GFR, increase effective renal plasma flow (ERPF), and decrease Renal Vascular Resistance (RVR) in patient who have essential hypertension with normal renal function. Urinary protein excretion is decreased. In patient with impaired GFR (<80 ml/min/1.73m²) marked improvement in renal function (GFR and ERPF) may occur. These changes may be sustained up to 3 years [56].

ACE inhibitors may reverse the pathophysiological process of essential hypertensive renal disease by attenuating the intra renal effects of angiotensin II. An initial decrease in GFR may be observed after starting therapy related to alterations in the hemodynamic determinants of GFR [57]. Such changes in GFR are reversible. Urinary protein excretion is usually decreased [58, 59]. The decrease in proteinuria is unrelated to changes in systemic blood pressure, GFR, ERPF or filtration fraction.

The anti-proteinuric effect of ACE inhibitor has been attributed to

- A decrease in glomerular capillary hydraulic pressure,
- An increase in basement membrane barrier permselectivity.
- A decrease in mesangial uptake and clearance of macromolecules [60, 61].

To the degree, the proteinuria reflects the glomerular injury; ACE inhibitor may have the potential to retard the progression of renal disease (as reflected by a reduction in the degree of proteinuria) independent of antihypertensive effect.

Reno protective effects

ACE inhibitors have a renoprotective effect. In patients with micro albuminuric, it decreases progression to overt proteinuria. In patients with

overt proteinuria (>500 mg/day), the degree of proteinuria is decreased where as in those with renal insufficiency (serum creatinine) >1.5 mg/dl) progression of renal insufficiency is slowed [62].

In comparison with other antihypertensive agents in patients with non diabetic nephropathies, ACE inhibitors appear to superior in reducing proteinuria when comparable effect on blood pressure is achieved [63, 64]. The renoprotective effects of ACE inhibitors may be explained by other mechanism of decreasing intra glomerular pressure and limiting macromolecule and protein passage into proximal tubule [65, 66].

Aim

- To evaluate the effect of ACE inhibitors in blood pressure control and proteinuria in non diabetic chronic renal disease.
- To determine the levels of blood pressure and urine protein excretion associated with the lowest risk for the progression of chronic kidney disease with and without ACE inhibitors.

Material and methods

Study design

It was a randomized, controlled trial, comparing the efficacy of anti hypertensive regimen with or without ACE inhibitors (where nifedipine was given) for patients with non diabetic kidney disease. The study group was followed for 12 months duration.

Patients

A total number of 97 patients between the age group of 18 to 70 years were studied, those attending Medical and Nephrology Department according to the following inclusion and exclusion criteria.

Inclusion criteria

- Hypertension
- Decreased Kidney function (defined as increased serum creatinine conc. >1.6 mg/dl in men: >1.4 mg/dl in women).
- Normal kidney size.

Exclusion criteria

- Acute renal failure
- Treatment with immunosuppression medication
- Clinically significant congestive heart failure
- Obstructive uropathy
- Renal artery stenosis
- Active systemic disease
- Type I diabetes mellitus
- History of transplantation
- History of allergy to ACE inhibitors
- Pregnancy

All patients gave informed consent. Patients enrolled were of 18 to 70 years age group. A total of 97 patients fulfilled the inclusion criteria, 77 patient were in ACE inhibitor group and 20 patients were in control group without ACE inhibitors (were given nifedipine).

Definition and ascertainment of blood pressure and 24 hour urine protein excretion

Visit was defined as any contact with patient during whole study related information was recorded or clinical variables were measured. Blood pressure and urine protein excretion levels at follow-up visits were defined as current levels. Blood pressure was measured using a mercury sphygmomanometer. Systolic and diastolic blood pressures were measured after 5-10 min of rest in supine position. Urine protein excretion was taken as total urine protein excretion in a 24 hour urine sample.

Primary outcome

Kidney disease progression was defined as combined end point of a two fold increase (doubling) in serum creatinine concentration from baseline values. Kidney failure- defined as titration of long-term dialysis therapy.

Follow up

All patients were followed up for a period of 12 months (1 year). At least once in 2 months for first six months and once in 3 months for next 6 months. At each visit blood pressure, urine

proteins estimation and serum creatinine were measured. The values recorded at the beginning of each time segment was defined as the current level, and used for that segment. If a blood pressure or urine protein measurement was not recorded for a particular visit, values from the previous visits were carried forward.

Study drugs

ACE inhibitors were used in this study which was given orally. Control group patients were given Nifedipine for the control of blood pressure. Concurrent medication was considered necessary for the patient's welfare and which did not interfere with the ACE inhibitors, was given.

Laboratory assessment

The laboratory investigation was carried at baseline and during follow-up periodically as discussed above. All the basic necessary investigations were done at baseline.

Withdrawal/ dropout

Patients were withdrawn from the study if serum creatinine doubles from baseline value or who require dialysis.

Data analysis

Assessment of efficacy was based on measurement of blood pressure levels and 24 hour urinary protein estimation related to kidney disease progression when ACE inhibitors were used and compare it with non ACE inhibitor group (nifedipine).

Results

A total of 97 patients were taken up for the study. 77 patients who met the inclusion criteria were included in ACE inhibitor group and 20 in non ACE inhibitor group. Out of 77 patients of ACE inhibitor group, 6 patient dropped out of study as they developed progression of kidney disease, one patient was noncompliant another patient lost to follow up. After the exclusion of dropouts there were 69 patients in ACE inhibitor group and 20 in Non ACE inhibitor group.

Baseline characteristics were compared between two groups and at follow up at 12 month.

Age

Most of the patients were in the age group ranging from 28 to 57 years. (**Table - 1**)

Sex distribution

There were 52 (75.4 %) males and 17 (24.6 %) females in ACE inhibitors group, the ratio being 3:1. There were 12 (60%) males and 8 (40%) females in Non ACE inhibitor group, the ratio being 3:2. (**Table – 2, Table - 3**)

Table – 1: Age distribution.

Age group (years)	No. of patients in ACE I	No. of patients in Non ACE I
18-27	10	1
28-37	17	10
38-47	18	6
48-57	17	3
58-67	7	0

Table – 2: Sex wise distribution in ACE I group.

Sex	No. of patients
Male	52
Female	17

Table – 3: Sex wise distribution in non ACE I group.

Sex	No. of patients
Male	12
Female	8

Blood pressure

The blood pressure was staged according to JNC VII guide lines.

Systolic blood pressure

ACE I group

Most of the patient were in stage I 35 (50.7%) and stage II 31 (44.9%) at base line. At the end of 12 month of treatment with ACE I most of the patient were in pre-hypertensive stage 38 (55%) and stage I 28 (40%). (**Table - 4**)

Non ACE I group

In Non ACE I group, most of the patients were in stage I (75%) and stage II (15%) at base line. At the end of 12 months of treatment with Non ACE I (nifedipine) most of the patients were in stage I (65%) and pre-hypertension stage (35%). (Table - 5)

Table – 4: Systolic blood pressure in ACE I group.

SBP (mmHg)	No. of patients base line	No. of patients at 12 months
<120	0	3
120-139	35	38
140-159	31	28
>160	3	0

Table – 5: Systolic blood pressure in non ACE I group.

SBP (mmHg)	No. of patients base line	No. of patients at 12 months
<120	0	0
120-139	2	7
140-159	15	13
>160	3	0

Diastolic blood pressure

ACE I group

In ACE inhibitors group most of the patient were in stage I (43.4%) and stage II (43.4%) at base line. At the end of 12 month of treatment with ACE I most of the patient were in pre-hypertensive stage (68.1%). (Table - 6)

Non ACE I group

In Non ACE I group, most of the patients were in stage-I (55%) and stage II (20%) at base line. At the end of 12 months of treatment with Non ACE I (nifedipine) most of the patients were in stage I (70%). (Table - 7)

Table – 6: Diastolic blood pressure in ACE I group.

DBP (mmHg)	No. of patients base line	No. of patients at 12 months
<80	4	0
80-89	5	47
90-99	30	18
>100	30	4

Table – 7: Diastolic blood pressure in non ACE I group.

DBP (mmHg)	No. of patients base line	No. of patients at 12 months
<80	0	0
80-89	5	5
90-99	11	14
>100	4	1

Serum creatinine

ACE I group

At base line the number of patient with serum creatinine 2.0 to 2.4 mg% were 36 (52.1%). At the end of 12 month of treatment with ACE inhibitor there were only 13 (18.8%). In this group there were significant number of patient (i.e. 23) whose serum creatinine levels were decreased. (Table - 8)

Non ACE I group

At base line there were 9 (45%) with serum creatinine levels of 2.0 to 2.4 mg%. At the end of 12 month of treatment with Non ACE I (Nifedipine) there were 4 patients remaining with same creatinine levels. There is relatively little change in number of patient whose serum creatinine is decreased when compared to ACE I group. (Table - 9)

Table – 8: Serum creatinine in ACE I group.

Serum creatinine (mg%)	No. of patients base line	No. of patients at 12 months
1.0-1.4	1	3
1.5-1.9	30	53
2.0-2.4	36	13
2.5-2.9	2	0

Table – 9: Serum creatinine in non ACE I group.

Serum creatinine (mg%)	No. of patients base line	No. of patients at 12 months
1.0-1.4	1	1
1.5-1.9	8	12
2.0-2.4	9	4
2.5-2.9	3	3

24 hours urinary protein

ACE I group

At base line 69 patients were having more than 0.5 gm/day of proteinuria. At the end of 12 months after treatment with ACE I there were 30 patient having more proteinuria ranging above 0.5 gm/day. But there were 37 patients whose proteinuria decreased less than 0.5 gm/day. This was very significant outcome. (Table - 10)

Non ACE I group

At baseline 18 patients were having more than 0.5gm/day proteinuria and 2 patients were having less than 0.5 gm/day. At the end of 12 month treatment with Non ACE I (nifedipine) 18 patients were having more than 0.5 gm/day proteinuria and 2 patients were having less than 0.5 gm/day. This showed there was no change at all. (Table - 11)

Table – 10: 24 hours urinary protein in ACE I group.

24 hour urinary protein (gm/d)	No. of patients base line	No. of patients at 12 months
0.1-0.4	0	37
0.5-0.9	35	30
1.0-1.4	24	1
1.5-1.9	7	1
2.0-2.4	2	0
2.5-2.9	1	0

Table – 11: 24 hours urinary protein in non ACE I group.

24 hour urinary protein (gm/d)	No. of patients base line	No. of patients at 12 months
0.1-0.4	2	2
0.5-0.9	9	10
1.0-1.4	7	7
1.5-1.9	2	1
2.0-2.4	0	0
2.5-2.9	0	0

Mean systolic blood pressure during follow up of patients was as per Table – 12 and mean diastolic blood pressure during follow up of patients was as per Table – 13.

The mean 24 hour urinary protein in ACE I group at baseline was 1.02 gm/day and at end of 12 month was 0.48 gm/day the difference was 0.54 gm/day. At base line the mean 24 hour urinary protein in Non ACE I group was 0.98 gm/day and at end of 12 month was 0.89 gm/day the difference was 0.09 gm/day. There was significant decrease in proteinuria in ACE I group compared to Non ACE I group. (Table - 14)

The mean serum creatinine at base line was 1.96 mg% and at 12 month was 1.69 mg% the difference is 0.27 mg% whereas in Non ACE I group at baseline is 2.06 mg% and at 12 month was 1.93 mg% the difference is 0.13 mg% (Table - 15). There was relatively significant decrease in serum creatinine in ACE I group when compare to Non ACE I group. (Table - 15)

Relation of 24 hour urinary protein and serum creatinine

In ACE I group with decrease of mean 24 hour urinary proteinuria at 12 month there was relative decrease in mean serum creatinine, where as in Non ACE I group there was relatively no change in mean 24 hour urinary proteinuria at 12 month, the mean serum creatinine showed little change which was not significant. (Table - 16)

Discussion

The renoprotective properties of ACE inhibitors were accompanied by a decrease in rate of urinary protein excretion [7, 8]. Some studies given the evidence that filtered proteins have an intrinsic renal toxicity [67, 68].

Patients with baseline proteinuria of less than 3 gm/24 hour had a slow rate of renal function deterioration whereas patients with baseline proteinuria of 3 gm/24 hour or more had a rapid decline in GFR. The early reduction in urinary protein excretion rate was associated with a slower rate of GFR decline in subsequent follow up in diabetic [69] and non diabetic [70] renal disease.

Table – 12: Mean systolic blood pressure during follow up of patients.

Follow up at No. of months	0	2	4	6	9	12
SBP in ACE I (mmHg)	155.4	145.4	142.4	136.8	130.2	127.8
SBP in non ACEI (mmHg)	146.1	145.3	142.5	136.8	136.2	136.2

Table – 13: Mean diastolic blood pressure during follow up.

Follow up at No. of months	0	2	4	6	9	12
DBP in ACE I (mmHg)	94.3	89.8	87.8	85.5	84.4	83.7
DBP in non ACE I (mmHg)	90.1	91.8	90.5	88	88	88

Table – 14: Mean 24 hours urinary protein during follow up.

Follow up at No. of months	0	2	4	6	9	12
24 hours urinary protein in ACE I (gm/d)	1.02	0.86	0.78	0.66	0.56	0.48
24 hours urinary protein in non ACE I (gm/d)	0.98	0.96	0.94	0.93	0.92	0.89

Table – 15: Mean serum creatinine during follow up.

Follow up at No. of months	0	2	4	6	9	12
Serum creatinine in ACE I (mg%)	1.96	1.93	1.88	1.82	1.74	1.69
Serum creatinine in non ACE I (mg%)	2.06	2.05	2.01	1.99	1.98	1.93

Table – 16: Mean serum creatinine vs 24 hours urinary protein.

	Base line	End of 12 months
Serum creatinine in ACE I (mg%)	1.96	1.69
Serum creatinine in non ACE I (mg%)	2.06	1.93
24 hours urinary protein in ACE I(gm/d)	1.02	0.48
24 hours urinary protein in non ACE I (gm/d)	0.98	0.89

The lowering of blood pressure itself lowers urinary protein excretion rate and slows rate of GFR decline in chronic renal disease [71-74]. There were data that suggests that ACE inhibitors improve glomerular barrier size selective function in human renal disease by directly lowering the mean dimensions of large unselective pores [10]. Therefore the renoprotective properties of ACE inhibitors may depend on the traffic of proteins and their consequent toxicity [67, 68].

Results of the REIN strarum 2 long term follow up study [75] showed that no more events (progression to end stage renal disease) arose in

patients treated with ACE inhibitors than in those with advanced renal failure and heavy proteinuria after 36 month of treatment with ramipril. The same authors have reported that this occurrence could arise in patients with daily baseline proteinuria of less than 3 gm after 48 months follow up [76]. These findings suggested that patients who survive the initial periods of treatment with ACE inhibitors have almost total remission of chronic renal disease.

Proteinuria has been shown to have a causal role in progression of renal dysfunction in various renal diseases [77]. A reduction in urinary protein excretion correlates with improved renal

function and survival in non diabetic and diabetic renal disease [72, 73, 78]. The initial reduction in rate of excretion inversely correlates with long term preservation of renal function in patient without diabetes treated with angiotensin converting enzyme inhibitors [74].

No severe adverse reaction was reported in any of treatment groups during follow up. The effectiveness of ACE inhibitors in the treatment of diabetic renal disease is widely acknowledged [79]. As in diabetic renal disease ACE inhibitor decrease blood pressure and urinary protein excretion, slow the increase in serum creatinine and reduce the incidence of ESRD.

The beneficial of ACE inhibitor is strong in patient with greater proteinuria at the onset of therapy. Others have speculated that the benefit of ACE inhibitor in slowing the progression of renal disease may be related to inhibition of the effects of angiotensin II on intra renal hemodynamics or on growth factors and fibrosis [80, 81]. The analyses showed a strong beneficial effect in patient with urinary protein excretion greater than approximately 0.5 gm/d.

This study showed that antihypertensive regimens of ACE inhibitors group are more effective than Non ACE inhibitor in slowing progression of non-diabetic chronic kidney disease [82-84]. Therefore we conclude that ACE inhibitor should be the antihypertensive agents of first choice in non-diabetic renal disease as well as in diabetic renal disease. The presence of proteinuria in chronic kidney disease is a strong indication for treatment with ACE inhibitors.

In non-diabetic chronic nephropathies enhanced glomerular traffic of plasma proteins is toxic to the kidney [85]. And also support the hypothesis that in long term reduced proteinuria is protective [86, 87].

The current practice of avoiding ACE inhibitor in severe renal failure to prevent further renal impairment and hyperkalemia is no longer justified [88].

In animals with experimentally induced renal disease, drugs that inhibit angiotensin converting enzyme reduce glomerular capillary pressure, inhibit cellular growth and reduce glomerular capillary permeability to protein, thus reducing proteinuria and preventing development of glomerulosclerosis [89, 90].

Findings of Jafer and colleagues meta analysis confirm that both higher systolic blood pressure and protein excretion level reflects pathophysiologic forces that lead to adverse outcome. The findings suggest that hypertensive patients with chronic kidney disease and higher levels of protein excretion merit more aggressive management than to those with lower level of protein excretion [74].

Although sensitive analysis showed that kidney disease progression was more strongly related to earlier rather than later values of blood pressure, reverse causality was not excluded and bidirectional effects between blood pressure levels and renal failure with follow up urine protein levels less than 2.0 gm/d and systolic blood pressure levels of 110 to 129 mmHg. JNC-7 recommends aggressive treatment of hypertension to target blood pressure values less than 130/80 mmHg in patients with chronic kidney disease.

The present study analyses the current level of urine protein excretion rather than the baseline level. The current level may be more appropriate measure of clinical decision making because it reflects the patient current clinical status including the anti-proteinuric effect of antihypertensive agent [91].

Our results showed that antihypertensive regimen that included ACE inhibitor were more effective in slowing the progression of kidney disease than non ACE inhibitor group.

Conclusion

The result of this study suggested that ACE inhibitors are more useful in reducing proteinuria

with the control of blood pressure, in non diabetic chronic kidney disease, when compared to Non ACE inhibitor. Timely recognition and proper control of proteinuria at an early stage with the use of ACE inhibitor in chronic kidney disease will retard the progression of disease and prevent the development of complications. This study concludes that, ACE inhibitor should be the first line of drugs in controlling blood pressure and proteinuria in non diabetic chronic kidney disease as in diabetic kidney disease.

References

1. U.S. Renal Data System. USRDS 2000 Annual Data Report. Bethesda. MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Health: 2000.
2. McClellan WM, Knight DF, Karp H, Brown WW. Early detection and treatment of renal disease in hospitalized diabetic and hypertensive patients: important differences between practice and published guidelines. *Am J Kidney Dis.*, 1997; 29: 368-75.
3. Obrador GT, Ruthazer R, Arora P, Kausz AT, Pereira BJ. Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. *J Am Soc Nephrol.*, 1999; 10: 1793-800.
4. Coresh J, Wei GL, McQuillean G, Brancati FL, Levey AS, Jones C, et al. Prevalence of high blood pressure and elevated serum creatinine level in the United States: Findings from third National Health and Nutrition examination survey (1988-1994). *Arch Intern Med.*, 2001; 161: 1207-16.
5. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med.*, 1982; 307: 652-659.
6. Hostetter TH, Olson JL, Rennke HG, Venkatachalam MA, Brenner BM. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. *Am J Physiol.*, 1981; 241: F85-93.
7. Kasiske BL, Kalil RSN, Ma JZ, Liao M. Effects of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med.*, 1993; 118: 129-38.
8. Weidmann P, Schneider M, Bohlen L. Therapeutic efficacy of different antihypertensive drugs in human diabetic nephropathy: An updated meta analysis. *Nephrol Dial Transplant*, 1995; 10: 39-45.
9. Morelli E, Loon N., Meyer T, et al. Effects of converting-enzyme inhibition on barrier function in diabetic glomerulopathy. *Diabetes*, 1990; 39: 76-82.
10. Remuzzi A, Reuggenti P, Mosconi L, Pata V, Remuzzi G. Effect of low dose enalapril on glomerular size selectivity in human diabetic nephropathy. *J Nephrol.*, 1993; 6: 36-43.
11. Remuzzi A, Puntorieri S, Battaglia C, Bertani T, Remuzzi G. Angiotensin converting-enzyme inhibition ameliorates glomerular filtration of macromolecules and water and lessens glomerular injury in the rat. *J Clin Invest.*, 1990; 85: 541-49.
12. United States Renal Data System. Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases; 1999.
13. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.*, 1993; 329: 1456-62.

14. Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group. *JAMA*, 1994; 271: 275-9.
15. Parving HH, Hommel E, Smidt UM. Protection of kidney function and decrease in albuminuria by captopril in insulin dependent diabetics with nephropathy. *BMJ*, 1988; 297: 1086-91.
16. Laffel LM, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. North American Microalbuminuria Study Group. *Am J Med.*, 1995; 99: 497-504.
17. Björck S, Mulec H, Johnsen SA, Norde'n G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. *BMJ*, 1992; 304: 339-43.
18. Burszty'n M, Kobrin I, Fidel J, Ben-Ishay D. Improved kidney function with cilazapril in hypertensive type II diabetics with chronic renal failure. *J Cardiovasc Pharmacol.*, 1991; 18: 337-41.
19. Golan L, Birkmeyer JD, Welch HG. The cost-effectiveness of treating all patients with type 2 diabetes with angiotensin-converting enzyme inhibitors. *Ann Intern Med.*, 1999; 131: 660-7.
20. Mosconi L, Ruggenti P, Perna A, Mecca G, Remuzzi G. Nitrendipine and enalapril improve albuminuria and glomerular filtration rate in non-insulin dependent diabetes. *Kidney Int Suppl.*, 1996; 55: S91-3.
21. Ravid M, Brosh D, Levi Z, Bar-Day'an Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med.*, 1998; 128: 982-8.
22. Bakris GL, Weir MR, DeQuattro V, McMahon FG. Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. *Kidney Int.*, 1998; 54: 1283-9.
23. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitor on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. *Ann Intern Med.*, 1997; 127: 337-45.
24. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. *J Am Soc Nephrol.*, 2002; 13: 37-40.
25. The Renal Association. UK Renal Registry. The Sixth annual report. Available at: www.renalreg.com/home.htm (accessed Dec 22, 2004).
26. United States Renal Data System. Annual data report: incidence and prevalence of ESRD (2003). *Am J Kidney Dis.*, 2003; 42(suppl 5): S37-173.
27. King H, Auburt RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care*, 1998; 21: 1414-31.
28. De Vecchi AF, Dratwa M, Wiedmann ME. Healthcare systems and end-stage renal disease: an international review - costs and reimbursement of ESRD therapies. *N Engl J Med.*, 1999; 14: 31-41.
29. Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis.*, 2003; 41: 1-12.
30. Brown WW, Peters RM, Ohmit SE, et al. Early detection of kidney disease in

- community settings: the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis.*, 2003; 42: 22-35.
31. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med.*, 1982; 307: 652-659.
32. Hayslett JP. Functional adaptation to reduction in renal mass. *Physiol Rev.*, 1979; 59: 137-164.
33. Johnson HA, Vera Roman JM. Compensatory renal enlargement: hypertrophy versus hyperplasia. *Am J Pathol.*, 1966; 49: 1-13.
34. Anderson S, Meyer TW, Brenner BM. The role of hemodynamic factors in the initiation and progression of renal disease. *J Urol.*, 1985; 133: 363-368.
35. Chanutin A, Ferris EB Jr. Experimental renal insufficiency produced by partial nephrectomy: control diet. *Arch Intern Med.*, 1932; 49: 767-787.
36. Anderson S, Meyer TW, Rennke HG, Brenner BM. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. *J Clin Invest.*, 1985; 76: 612-619.
37. Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest.*, 1986; 77: 1993-2000.
38. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest.*, 1986; 77: 1925-1930.
39. Anderson S, Rennke HG, Garcia DL, Brenner BM. Short and long term effects of antihypertensive therapy in the diabetic rat. *Kidney Int.*, 1989; 36: 526-536.
40. Lapinski R, Perico N, Remuzzi A, Sangalli F, Benigni A, Remuzzi G. Angiotensin II modulates glomerular capillary permselectivity in rat isolated perfused kidney. *J Am Soc Nephrol.*, 1996; 7: 653-660.
41. Bohrer MP, Deen WM, Robertson CR, Brenner BM. Mechanism of angiotensin II-induced proteinuria in the rat. *Am J Physiol.*, 1977; 233: F13-F21.
42. Remuzzi G, Bertani T. Is glomerulosclerosis a consequence of altered glomerular permeability to macromolecules? *Kidney Int.*, 1990; 38: 384-394.
43. Mallick NP, Short CD, Hunt LP. How far since Ellis? The Manchester Study of glomerular disease. *Nephron*, 1987; 46: 113-124.
44. Wehrmann M, Bohle A, Bogenschutz O, et al. Long-term prognosis of chronic idiopathic membranous glomerulonephritis: an analysis of 334 cases with particular regard to tubulointerstitial changes. *Clin Nephrol.*, 1989; 31: 67-76.
45. Risdon RA, Sloper JC, De Wardener HE. Relationship between renal function and histological changes found in renal-biopsy specimens from patients with persistent glomerular nephritis. *Lancet*, 1968; 2: 363-366.
46. Rossing P, Hommel E, Smidt UM, Parving H. Impact of arterial blood pressure and albuminuria on the progression of diabetic nephropathy in IDDM patients. *Diabetes*, 1993; 42: 715-719.
47. Ruilope LM, Alcazar JM, Hernandez E, Moreno F, Martinez MA, Rodicio JL. Does an adequate control of blood pressure protect the kidney in essential hypertension? *J Hypertens.*, 1990; 8: 525-531.
48. Mogensen CE, Christensen CK, Beck-Nielsen H. Early changes in kidney function, blood pressure and the stages in

- diabetic nephropathy. In: Keen H, Legrain M, eds. Prevention and treatment of diabetic nephropathy. Boston: MTP Press, 1983, p. 57-83.
49. Ruggenti P, Perna A, Mosconi L, et al. Proteinuria predicts end-stage renal failure in non-diabetic chronic nephropathies. *Kidney Int Suppl.*, 1997; 63: S-54.
50. Border WA, Noble NA. Interactions of transforming growth factor-beta and angiotensin II in renal fibrosis. *Hypertension*, 1999; 12(suppl): 205S-213S.
51. Hostetter T, Rosenberg M, Ibrahim H, Juknevicus I. Aldosterone in progressive renal disease. *Semin Nephrol.*, 2001; 21: 573-579.
52. Weir MR, Dzau VJ. The angiotensin-aldosterone system: a specific target for hypertension management. *Am J Hypertens.*, 1991; 4(suppl): 2635-269S.
53. Siragy HM. The role of the AT2 receptor in hypertension. *Am J Hypertens.*, 2000; 13(suppl): 62S-67S.
54. Dzau VJ, Gibbons GH, Pratt RE. Molecular mechanisms of vascular rennin-angiotensin system in myointimal hyperplasia. *Hypertension*, 1991; 18: 100-105.
55. Simon G, Morioka S, Synder DK, Cohn JN. Increased renal plasma flow in long-term enalapril treatment of hypertension. *Clin Pharmacol Ther.*, 1983; 34: 459-465.
56. Larochelle P., Gutkowska J, Schiffrin E, et al. Effect of enalapril on renin, angiotensin converting enzyme activity, aldosterone and prostaglandins in patients with hypertension. *Clin invent Med.*, 1985; 8: 197- 201.
57. Reams GP, Bauer JH. Long-term effects of enalapril monotherapy and enalapril/hydrochlorothiazide combination therapy on blood pressure, renal function, and body fluid composition. *J Clin Hypertens.*, 1986; 2: 55-63.
58. Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D. Reduction of proteinuria by angiotensin converting enzyme inhibition. *Contrib Nephrol.*, 1990; 83: 160-165.
59. Heeg JE, de Jong PE, Stelwagen T, et al. Mechanism of the antiproteinuric effect of angiotensin-converting enzyme inhibition. *Contrib Nephrol.*, 1990; 83: 160-165.
60. De Zeeuw D, Heeg JE, Stelwagen T, et al. Mechanism of the antiproteinuric effect of angiotensin-converting enzyme inhibition. *Contrib Nephrol.*, 1990; 83: 160-165.
61. Hegg JE, de Jong PE, van der Hem GK, et al. Angiotensin II does not acutely reverse the reduction of proteinuria by long-term ACE inhibition. *Kidney Int.*, 1991; 40: 734-741.
62. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.*, 1993; 329: 1456-1462.
63. Apperloo AJ, de Zeeuw D, Sluiter HE, de Jong PE. Differential effects of analapril and atenolol on proteinuria and renal haemody-namics in non-diabetic renal disease. *BMJ*, 1991; 303: 821-824.
64. Gansevoort RT, Sluiter WJ, Hemmelder MH, et al. Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials. *Nephrol Dial Transplant.*, 1995; 10: 1963-1974.
65. Woo KT, Lau YK, Wong KS, Chiang GS. ACEI/ATRA therapy decreases proteinuria by improving glomerular permselectivity in IGA nephritis. *Kidney Int.*, 2000; 58: 2485-2491.
66. Morelli E, Loon N., Meyer T, et al. Effects of converting-enzyme inhibition on barrier function in diabetic glomerulopathy. *Diabetes*, 1990; 39: 76-82.
67. Remuzzi G. Abnormal protein traffic through the glomurular barrier induces

- proximal tubular dysfunction and causes renal injury. *Curr Opin Nephrol Hypertens.*, 1995; 4: 339-42.
68. Hirschberg R. Bioactivity of glomerular ultrafiltrate during heavy proteinuria may contribute to renal tubulo-interstitial lesions: evidence for a role for insulin-like growth factor I. *J Clin Invest.*, 1996; 98: 116-124.
69. Rossing P., Hommel E, Smidt UM, Parving H-H. Reduction in albuminuria predicts diminished progression in diabetic nephropathy. *Kidney Int.*, 1994; 45(suppl 45): S145-49.
70. Apperloo AJ, de Zeeuw D, de Jong PE. The initial antiproteinuric effect of antihypertensive treatment predicts the effect of treatment on long term renal function outcome. *J Am Soc Nephrol.*, 1992; 3: 279.
71. Petterson JC, Adler S, Buktart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. *Ann Intern Med.*, 1995; 123: 754-62.
72. The GISEN Group. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet*, 1997; 349: 1857-63.
73. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE – inhibition in non-diabetic nephropathics with non-nephrotic proteinuria. *Lancet*, 1999; 354: 359-64.
74. Jafar TH, Schmit CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease : a meta-analysis of patient-level data. *Ann Intern Med.*, 2001; 135: 73-87.
75. Ruggenenti P, Perna A, Gherardi G, et al. Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet*, 1998; 352: 1252-56.
76. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE – inhibition in non-diabetic nephropathics with non-nephrotic proteinuria. *Lancet*, 1999; 354: 359-64.
77. Locatelli F, Marcelli D, Cornelli M., et al. Proteinuria and blood pressure as causal components of progression to end-stage renal failure. *Nephrol Dial Transplant*, 1996; 11: 461-67.
78. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med.*, 1993; 329: 1456-62.
79. American Diabetes Association: clinical practice recommendations 1997. *Diabetes Care*, 1997; 20 Suppl 1: S1-70.
80. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med.*, 1996; 334: 939-45.
81. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, nondiabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). *Lancet*, 1997; 349: 1857-63.
82. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N Engl J Med.*, 1982; 307: 652-9.
83. Hunsicker L, Levey A. Progression of chronic renal disease. Mechanisms, risk factors, and testing of interventions. In: Jacobson HR, Striker GE, Klahr S, eds. *The Principles and Practice of*

- Nephrology, 2nd edition, St. Louis: Mosby; 1995.
84. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. *Ann Intern Med.*, 1997; 127: 337-45.
85. Remuzzi G, Bertani T. The pathophysiology of progressive nephropathics. *N Engl J Med.*, 1998; 339: 1448-56.
86. Apperloo AJ, de Zeeuw D, de Jong PE. Short-term antiproteinuric response to antihypertensive treatment predicts long-term GFR decline in patients with non-diabetic renal disease. *Kidney Int.*, 1994; 45(suppl 45): S174-78.
87. Rossing P., Hommel E, Smidt UM, Parving H-H. Reduction in albuminuria predicts diminished progression in diabetic nephropathy. *Kidney Int.*, 1994; 45(suppl 45): S145-49.
88. Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med.*, 1996; 334: 939-45.
89. Anderson S, Rennke HG, Brenner BM. Therapeutic advantage of converting enzyme inhibitors in arresting progressive renal disease associated with systemic hypertension in the rat. *J Clin Invest.*, 1986; 77: 1993-2000.
90. Jackson B., Johnson CI. The contribution of systemic hypertension to progression of chronic renal failure in the rat remnant kidney: effect of treatment with an angiotensin converting enzyme inhibitor or a calcium inhibitor. *J Hypertens.*, 1988; 6: 495-501.
91. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, Marcantoni C, et al. Proteinuria as a Modifiable risk factor for the progression of non-diabetic renal disease. *Kidney Int.*, 2000; 60: 1131-40.