Early Diagnosis of CKD and Its Prevention

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Abstract
Chronic kidney disease is associated with increased mortality and morbidity especially due to cardiovascular disease and imposes a huge economic burden to the family and health care delivery system. In both developing and developed countries, diabetes mellitus and hypertension are the leading causes of CKD. While dialysis and transplantation are excellent options for end stage kidney disease, they are costly. Renal transplant is again limited by organ shortage. The better strategy to tackle CKD will be early identification of the disease and adopt measures to slow its progression to ESRD. A comprehensive approach to the prevention of CKD and retarding its progression is outlined. ©

INTRODUCTION
Chronic Kidney Disease (CKD) is emerging as a Public Health problem in both developed and developing countries. Besides causing premature mortality and morbidity and lowering quality of life it is a disease, which imposes a huge economic burden on not only the patients and their families but also on the health care system and society. It is a disease associated with multiple comorbid conditions – especially cardiovascular disease (CVD). The incidence of CVD in CKD is 10 to 30 times more than in those without kidney disease. The size of the dialysis population is expanding at a rate of 7% per year. The aggregate cost of treating ESRD in the coming decade will exceed $1 trillion. Renal transplantation is limited by organ shortage. One important reason for the existing alarming state of the disease is that it has been underdiagnosed and undertreated. One in 20 in our population has more than 1.4 mgs/dl of serum creatinine. The benefits of diagnosing early kidney disease extends beyond the kidney itself. Appropriate management of the comorbid conditions reduces not only the overall and cardiovascular mortality but improves the quality of life itself, reduces the economic burden and provides adequate time for the psychological, medical and economic preparation for renal replacement therapy (RRT). Glomerulonephritis and chronic interstitial nephritis which appeared to be the common causes of CKD in developing countries earlier is now replaced by diseases like diabetes mellitus (DM) 41% and hypertension (HT) 23%. India, the second most populous country has the most diabetics in the world. It is high time that we revise our strategies in the management of CKD and focus our attention on the prevention of CKD. Early diagnosis of CKD and its prevention involves measures to 1) screen for CKD 2) evaluate and estimate the progression of CKD and 3) measures to prevent the progression of CKD. This involves early identification of patients at risk for CKD. Patients with diabetes, hypertension, subjects above the age of 60 years, close relatives of patients with nephropathy caused by diabetes, hypertension and glomerulonephritis should be primary targets for screening to detect clinically silent kidney disease.

SCREENING FOR EARLY EVIDENCE OF CHRONIC KIDNEY DISEASE (CKD)
The simplest screening test for CKD is the detection of proteinuria and microscopic hematuria through standard dipstick testing. The presence of albumin in the urine predicts both cardiovascular and non cardiovascular morbidity as it reflects a generalized endothelial dysfunction. Estimation of the glomerular filtration rate (GFR) is the best overall indicator of the level of kidney function. Estimates of GFR can be made using the modification of diet in renal disease (MDRD) formula or the Cockroft- Gault equation. However there is a need to validate these formulas based on ethnicities in different parts of the world. Serum creatinine alone should not be used to assess the level of kidney function.

RISK FACTORS FOR PROGRESSION OF CKD
The risk factors for progression of kidney disease include (i) persistent activity of the disease responsible for CKD, example SLE, PAN, and other primary or secondary glomerular disease; (ii) suboptimal prevention and treatment of DM and HT; (iii) persistent proteinuria; (iv) high protein intake in the diet; (v)
urinary tract infection, reflux nephropathy or systemic infection; (vi) marked reduction in nephron number, either congenital or acquired; (vii) anemia; (viii) hyperlipidemia; (ix) cigarette smoking; and (x) obesity (metabolic syndrome).

Thus all patients with CKD should be screened for traditional risk factors—smoking history, blood pressure measurement, body weight, body mass index, fasting blood glucose, fasting lipid profile, serum uric acid level and 12 lead electrocardiogram. Though standard formulas are available to estimate the GFR, a 24 hour urine sample is advisable in individuals on a vegetarian diet and those with reduced muscle mass (amputation, gross malnutrition).

**MECHANISM OF PROGRESSION OF CKD**

Quite early, what we see as renal failure is only a tip of the iceberg. With decrease in glomerular filtration rate (GFR) below about one-half of the normal, further loss of function occurs even if the original disease becomes inactive. Surviving nephrons undergo adaptation in structure and function that raise single nephron GFR to meet excretory demands. These hemodynamic adaptations leading to glomerular HT and hyperfiltration initiate and perpetuate glomerular injury, causing detrimental effects of acquired nephron loss. Inborn deficits in total number of nephrons in association with low birth weight contribute to HT, glomerulosclerosis and CKD.4

Among a variety of measures that slow progression of experimental renal disease, alleviation of glomerular capillary hypertension has been found to be the common denominator. Due to nephron loss and thus raising the single nephron GFR leads to hyperfiltration if dietary protein intake is not controlled. Dietary protein restriction reduces glomerular pressure and ameliorates glomerular injury, causing detrimental effects of acquired nephron loss.5 Inborn deficits in total number of nephrons in association with low birth weight contribute to HT, glomerulosclerosis and CKD.4

Dietary protein restriction

Brenner’s experimental models showed that dietary protein restriction abrogates the adaptive rise in glomerular pressure and slows the tendency to renal disease progression. The National Institute of Health Modification of Diet in Renal Disease (NIH-MDRD) trial.5 Although ambiguous in early stages, subsequent sub-group analysis by Levey et al provided clear evidence of benefit from dietary protein restrictions. The meta analysis of 10 randomized controlled studies of the effects of protein restriction on the progression of diabetic and non-diabetic renal disease by Pedrini et al determined that the overall relative risk of renal failure or death was indeed reduced with protein restriction as compared with non-restricted protein intake.8,9 The benefits are obvious that GFR between 12.5 and 55 ml/mt. slows the progression of fall in GFR by 0.5 ml/mt/year. Protein restriction should be initiated in the early stage itself when the GFR is 60 ml/mt. The recommended protein intake is 0.8 g/kg/day when GFR is 25 to 55 ml/mt and 0.6 g/kg/day if less than 25 ml/mt. More than 50% of the calculated protein should be of high biological value. A meta-analysis of five small studies of diabetics showed that the relative risk of progression in protein restricted patients was
either ACE inhibitor or placebo, achieved similar control of blood pressure. Among patients with proteinuria of at least 3 gms/day at baseline, a significantly lower rate of GFR was seen after 2 years in patients receiving ramipril (−0.44 vs. −0.81 ml/min/month with non-ACE conventional therapy). In the extension phase of the study, patients who received placebo were switched to ACE inhibitors, and those already on ACE inhibitors continued the treatment. Consistent with the findings of the first 2-year phase of the study, ramipril treatment enjoyed a significant reduction in the rate of decline of GFR, while patients continuing on the ACE inhibitor enjoyed a further rate in the reduction of GFR decline to levels similar to those with non-ACE inhibitors. In 36 to 54 months of follow-up, no patients in the latter group reached the ESRD, and a small number actually experienced a rise in GFR. In Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) trial,11 Machio et al studies 583 patients with renal disease of diverse etiologies to treatment with benazepril or placebo. After 3 years of follow-up, the study found a 53% of reduction with ACE inhibitors in the combined risk of doubling of the baseline serum creatinine or need for dialysis.

In the AIPRI data study based on 11 randomized ACE inhibitors versus placebo-treatment trials, Jafar et al concluded that ACEIs are more effective than other antihypertensive treatment in slowing renal progression and reducing proteinuria.12 Significantly lower values were seen with ACEIs for several outcome measures including level of proteinuria and incidence of ESRD. A similar conclusion emerged from the AASK trial in hypertensive African Americans, in which ramipril proved more renoprotective than that of the comparator drugs, amlopidine or metaprolol.13

Most diabetic patients who develop ESRD suffer from Type II diabetes, reflecting its approximately 20-fold greater prevalence over type 1 diabetes. Type 2 diabetic patients develop glomerular hyperfiltration, proteinuria and progressive decline in GFR, much as in type 1 diabetes. Since 1995, ARBs have also been available to inhibit the RAS by blocking angiotensin II subtype 1 (AT1) receptors. Thus, whereas ACEIs depress ACE-dependent angiotensin II production, ARBs block the effects of angiotensin II from any source at the receptor level. The alternative pathway of angiotensin II production can be by chymase, cathepsin, tPA and PAI-1. Two large prospective randomized trials showed that the interruption of the RAS with ARBs in type 2 diabetic patients with overt nephropathy delays the progression of renal disease. The Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT)14 evaluated the effects of the ARB, irbesartan on renal versus the effects of conventional therapy amlopidine or placebo group, in 1715 subjects. The primary composite end point of the study was doubling of baseline serum creatinine, ESRD or death from any cause. For subjects receiving

Control of Hypertension

Hypertension in CKD results in left ventricular hypertrophy, cardiac dilatation, heart failure, ischemic coronary changes, worsening of atherosclerosis and contributes to increased cardiovascular morbidity and mortality. Both systolic and diastolic blood pressures are important. High systolic pressures increase the myocardial work, while low diastolic pressure reduces myocardial circulation and increase the myocardial ischemia. A pulse pressure of more than 50 mmHg is a marker of increased cardiovascular morbidity. The target BP is below 130/80 mmHg in all patients with CKD. It should be less than 120/75 mmHg in proteinuric renal disease.11

Use of ACEI and ARB

The antihypertensive drug of choice in CKD is ACEI, ARB or their combination, besides adding on long acting channel blockers or beta blockers and diuretics wherever it is indicated.

ACE inhibitors retard the development of glomerular lesions of experimental diabetic nephropathy. This motivated several small clinical studies performed to assess the effects of antihypertensive treatment in general and ACE inhibitors in particular on the rate of progression of diabetic nephropathy. When captopril was compared with placebo in 407 diabetic nephropathies, patients with proteinuria > 500 mgs/day on captopril treatment were associated with a 50% reduction in the combined risk of ESRD or death.1 This was in Type I diabetes nephropathy. In the more recent Ramipril Efficacy in Nephropathy (REIN) study, 352 patients with non-diabetic renal disease, randomly assigned to receive either ACE inhibitor or placebo, achieved similar control

Reduction of Proteinuria

Proteinuria has been considered as a marker of glomerular barrier integrity and the massive proteinuria indicates glomerular disease severity. Besides, proteinuria also contributes to progressive renal injury. Proteinuria stimulates protein uptake by proximal tubular cells through megalin and cubulin dependant transport processes. Increased protein traffic causes tubular cell dysfunction through various mechanisms, including complement-dependant pathways and generation of oxidative stress, catalysed by iron containing proteins. Excessive endocytosis of proteins induces local production of pro-inflammatory and pro-fibrogenic cytokines. Proteinuria also activates the local tubular renin angiotensin system (RAS). The REIN study demonstrated that higher baseline proteinuria was associated with more rapid decline in GFR.10 The MDRD study demonstrated that reduction in proteinuria; independent of blood pressure was associated with slower progression of renal disease.

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irbesartan, the adjusted relative risk of reaching the primary composite end point was 20% lower than for those receiving amlodipine. There was no significant difference between placebo and amlodipine for the primary composite end point. The relative risk of ESRD in the irbesartan group was 17% lower than that of placebo group and 24% lower than that in the amlodipine group. Proteinuria was reduced an average of 23% in the irbesartan arm, compared with 6% and 10% in the amlodipine and placebo arms respectively. The more favourable renal outcomes were in excess of effects directly attributable to blood pressure control.

The Reduction of End Points in NIDDM with ACEI losartan (RENAAL) study was undertaken to determine whether ARB, losartan reduces the number of patients with type 2 diabetes doubling in serum creatinine, ESRD or death, as compared with placebo-treated subjects. The primary and secondary end points of the study were similar to those of IDNT study but treatment was of longer average duration in the RENAAL study (3.6 vs. 2.6 years). Losartan lowered the risk of doubling of serum creatinine by 25%, ESRD by 28% and death by 20% when compared to placebo. Proteinuria declined by 35% in the losartan arm and increased slightly in the placebo group. Besides renoprotective effects of ACE inhibitor treatment, the Heart Outcomes Prevention Evaluation (HOPE) and Losartan Intervention for End Point Reduction in Hypertension Study (LIFE) trials reported substantial reduction in all cause mortality cardiac and stroke events in patients receiving ramipril or losartan respectively. Cardiovascular Disease (CVD) is the single largest cause of morbidity and mortality among patients with even mild CKD. The HOPE and LIFE trials provide a further compelling argument for use of drugs that interrupt patients with kidney diseases.

One important advantage of ARBs over ACE inhibitors is their more favourable side effects profile as ARBs are seldom associated with cough that may occur in up to 40% of patients receiving ACE inhibitors. Finally, the differing effects of ACEIs and ARBs on the RAS imply that in combination, they may have additive or even synergistic effects, and early evidence appears to support this contention. In the largest combination trial, the COOPERATE trial involving 336 patients with non-diabetic renal disease treated for 3 years with maximally effective doses of ACEI, trandolapril or the ARB, losartan, alone or in combination, the combination clearly was more effective in lowering the progression and urinary protein excretion than either drug alone.

**Tight Glycemic Control**

The pathophysiology of diabetic nephropathy centers on hyperglycemia. Hyperglycemia induces the polyol pathway, activates protein kinase C, increases advanced glycation end products (AGE) leading to cytokine release. It induces mitochondrial superoxide production and increases the oxidative stress. The inflammatory and oxidative processes alter lipoprotein metabolism and results in a highly atherogenic environment. A tight glycemic control will halt these effects. Tight glycemic control aims at fasting blood sugar < 100 mg/dl, 2 hours post prandial sugar < 130 mg/dl and Hb A1c < 6.5 %. The tight glycemic control will be an ideal mode to prevent secondary prevention of progression of kidney injury in diabetics. It will also be useful in tertiary prevention.

**Correction of Anemia in CKD**

Renal anemia starts early in the course of renal disease due to decreased production of erythropoietin. The resultant hypoxia stimulates progression of renal interstitial fibrosis and compromise post glomerular capillary circulation. The hemodynamic effects of anemia are a burden on the heart and vascular system already affected by uremia and hypertension. It results in mal-adaptive left ventricular growth, cardiac failure, exacerbation of coronary ischemia and death. Current guidelines target a hemoglobin level > 12 gm/dl and a hematocrit > 36% to prevent the continuing onslaught on the heart, and vascular system. In the nutritionally deprived population like ours and with the associated causes of gastrointestinal bleeding or other blood loss, iron supplementation may be required besides erythropoietin administration. Blood transfusions are preferably avoided for the known problems of transmitting infections. Sensitisation to foreign antigens could interfere with donor selection while preparing for renal transplant. Correction of anemia also gives an overall sense of well-being to the patient and improves the quality of life, an important factor in management of any chronic kidney disease.

**Management of Hyperlipidemia:**

CKD is commonly associated with abnormalities of plasma lipids, elevated levels of triglycerides, VLDL and LDL and reduced levels of HDL. This is probably secondary to the reduced lipoprotein lipase activity evident with GFR < 50 ml/m. Besides increasing the cardiovascular morbidity and mortality, these lipid abnormalities might accelerate the progression of renal disease by stimulation of mesangial cell proliferation, cytokine expression, extra-cellular matrix synthesis and oxidation of LDL to form reactive oxygen species. The MDRD study revealed low serum HDL to be an independent predictor of a more rapid decline in GFR.

The aim of treatment is to keep LDL cholesterol < 100 mg/dl. Statins have revolutionized the therapy by their effects not only on lowering LDL and increasing HDL but also with their benefits extending beyond lipid control. They are anticytokine and block NF-kb activation. Their anti-inflammatory effect retards renal disease progression. They reduce peripheral arterial
resistance and enable better control of hypertension. They also reduce the severity of proteinuria.\textsuperscript{21}

**Treatment of the Underlying Disease**

Often the diagnosis of CKD shifts the focus of the treating physician to the supportive measures, reducing the aggressiveness to treat the underlying, usually glomerular disease. In diseases like SLE, immunosuppressive therapy even in the presence of renal failure may be rewarding with reversal of renal failure. The advent of newer effective immunosuppressives like mycophenolate mofetil has enabled better management of glomerular diseases, not responsive to steroids or cyclophosphamide, e.g. MGN, FGS, resistant MCN and IgA Nephropathy.

**Treatment of Infection**

CKD itself is a chronic inflammatory state with reduced renal clearance of cytokines, accumulation of AGE and persistent infection aggravated by the co-existing malnutrition. Early identification of infection, adequate and appropriate management with attention on the dosing modifications required according to the severity of CKD will prevent worsening of the kidney failure.

**Relief of Obstruction**

Enlarged prostate in the old, urethral strictures in middle age, post urethral valves in the young are some examples wherein correction of the obstructive cause will improve renal function or prevent worsening of the renal disease due to continued insult by backpressure effect and increased risk of infection.

**Lifestyle Modifications and Treatment of Obesity**

Life Style Modification is an essential step towards renoprotection and should be recommended to all patients with CKD. Weight reduction is no longer for cosmetic purpose. Obesity perse causes proteinuric microalbuminuria, secondary focal segmental glomerulosclerosis due to hyperfiltration and volume overload and results in progression of renal failure.\textsuperscript{22} Weight reduction should be aimed to their ideal weight and a BMI < 23. Dietary salt intake should also be modified. Regular exercises, adequate nutrition and a healthy positive outlook enable better reserve for braving the illness and retard the onslaught.

Smoking should be completely stopped. It causes constriction in the renal vascular bed, accelerates atherosclerosis, induces progression of renal disease and also causes systemic hypertension.\textsuperscript{23}

**Early Referral to Nephrologist**

Early referral to nephrologist provides the opportunity to identify the reversible causes of renal function deterioration and to implement Renoprotective measures. It also enables patients and their families to receive sufficient information and education about the disease and the options for treatment. Predialysis education assists the patients in the choice of dialysis modality, preparatory creation of permanent vascular access, improves their compliance to the treatment plan, reduces hospitalizations and promotes psychological well being too. Patients with serum creatinine > 1.5 mg/dl, creatinine clearance less than 60ml/min/1.73m\textsuperscript{2} should be referred for specialist management. Earlier referral is indicated in hypertensives diabetics and in patients with significant proteinuria more than 1 g/day.

**A COMPREHENSIVE STRATEGY FOR RENOPROTECTION IN PATIENTS WITH CKD**

There is a strong case for prescribing ACEIs, ARBs or both in any patient with kidney disease in doses sufficient to achieve reduced proteinuria to less than 0.5gm/day and to show by at least twice yearly checks that some reliable estimate that GFR is falling by no more than 2 ml/mt/year. Besides, these adjunctive treatments should be given to prevent the cardiovascular disease that exists in all patients with kidney disease. These include additional antihypertensive drugs to target the blood pressure of < 130/80 mmHg. We should also recommend protein restriction, salt restriction, tight glycemic control in diabetics, statins, aspirin, erythropoietin and measures to reduce calcium phosphorus products, excess body weight, tobacco use, exposure to nephro-toxic drugs including many herbal remedies and dietary supplements. This aggressive and comprehensive strategy may add to the costs of the treatment, but it will translate into reduced morbidity and mortality from cardiovascular disease and fewer patients may need expensive renal replacement therapy. There are many newer drugs in the pipeline to add to the effects of ACEIs and ARBs. One such is the vaso-peptidase inhibitor (VPIs). Recently, one such dual ACE inhibitor Omapatrilat has been introduced which reduces high grade proteinuria, reduces the blood pressure and gives rise to great reno-protection, particularly when it is combined with ACEI. Many other
drugs such as renin inhibitors, endothelium receptor blockers, are in the phase III trials. Stem cell therapy is yet another field in which the destroyed nephrons can be replaced by new nephrons and thus the renal function can be restored towards the normal side, which will be available in the next few years.

Successful management of CKD and its prevention demands a multidisciplinary approach. A comprehensive effort will require patient education, professional education, and the involvement of payers (Medicare, Medicaid, and the health insurance industry). The involvement or cooperation of business, the community, and government will be required at local, state and national levels. More research efforts will be needed to measure and track the CKD burden, identify populations at risk, and target program efforts.

REFERENCES

Announcement


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