



Early Detection and Conservative Management of Chronic Renal Failure

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A B S T R A C T

The incidence and prevalence of chronic renal failure (CRF) and renal replacement therapy (RRT) is increasing worldwide. Chronic kidney disease (CKD) is of an economic and organizational concern, since RRT consumes a considerable proportion of healthcare resources. CKD is more focused in medical fraternity due to early detection of renal failure before the fall in glomerular filtration rate (GFR) and rise in serum creatinine and the intervention to delay the progression of chronic renal failure.

Early detection and conservative treatment of CRF patients help in (A) Timely intervention to slow progression of CKD, (B) Management of complications, (C) Identification and management of comorbid conditions i.e. heart disease, and (D) Smooth transition to renal replacement therapy.

Treatments to delay progression are aimed at treating the primary disease and strictly controlling the systolic and diastolic blood pressure and proteinuria. The role of antihypertensive agents, statins, and the use of other maneuvers such as protein restriction and novel approaches are discussed herein. The treatment of complications of CKD like anemia, renal bone disease, malnutrition and neuropathy and co-morbidities like cardiovascular disease; helps in smooth transition to RRT.

To conclude, CKD should be detected in early phase, even before the significant fall in GFR. The timely intervention will retard the progression of CRF and will decrease the comorbidities.

INTRODUCTION

The incidence and prevalence of chronic renal failure (CRF) and renal replacement therapy (RRT) is increasing worldwide. In third national health and nutrition examination survey (NHANES) done from 1988 to 1994, 3% of US adult population was found to have elevated serum creatinine value.¹ Recently, Chronic kidney disease (CKD) is more focused in medical fraternity due to early detection of renal failure before the fall in glomerular filtration rate (GFR) and rise in serum creatinine and intervention to delay the progression of chronic renal failure. As well as being a large and growing clinical problem, chronic kidney disease (CKD) is of an economic and organizational concern, since RRT consumes a considerable proportion of healthcare resources. Several interventions to delay the progressive loss of renal function and/or to prevent the development of CVD are now available. Intervention in the conservative phase of CKD is likely to be more effective if performed as early as possible in the course of the disease.

CRF is characterized by persistently abnormal glomerular filtration rate (GFR). It represents an evolving process that is initiated by various course all with the common and results of

persistent and usually progressive damage of varying severity to the kidneys.

In 2000, National Kidney Foundation (NKF) kidney disease outcome quality initiative (K/DOQI) advisory board approved development of clinical practice guidelines to define CKD and to classify stages in the progression of CKD.² Despite the absence of process epidemiological data, we know there are a great many patients of in the conservative phase of CKD. The present article will give brief review of early detection and conservative treatment of CRF and intervention to retard the progression of CRF and prevention of the complications and comorbidities of CRF.

Early detection and conservative treatment of CRF patients help in

- a. Timely intervention to slow progression of CKD
- b. Management of complications, i.e. anaemia, bone disease, neuropathy, malnutrition
- c. Identification and management of comorbid conditions i.e. heart disease
- d. Smooth transition to renal replacement therapy

Table 1 : K-DOQI clinical action plan for patients with CKD

Stage	Description at increased risk	GFR (ml/min/m ²)	Action	Prevalence (%)
1	Kidney damage with normal or ↑GFR	>90	Diagnosis and treatment Treatment of comorbid conditions Slowing progression CVD risk reduction	3.3
2.	Kidney damage with mild ↓ GFR	60-89	Estimating progression	3
3.	Moderate ↓ GFR	30-59	Evaluating and treating complication	4.3
4.	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy	0.2
5.	Kidney failure	<15	Replacement (if uremia+ nt)	0.1

DEFINITION OF CKD² (Table-1)**Criteria**

- Kidney damage for >3 months, as defined by structural or functional abnormality as the kidney with or without decreased GFR, manifest by either.
 - Pathological abnormalities,
 - Markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests.
- GFR <60 ml/mt/1.73m² ≥ 3 months with or without kidney damage

DETECTION OF CHRONIC RENAL FAILURE**Assessment of risk and predisposing factors²⁻⁴**

All individuals should be evaluated during health encounters to determine whether they are at risk of having or of developing CKD. These risk factors include individuals with

- Persistent activity of underlying disease
- Common amplifiers of risk
 - Suboptimal control of hypertension
 - Proteinuria >1 g/day
 - Urinary tract obstruction/reflux/infection
 - Analgesics or other nephrotoxins
- Marked reduction in nephron number (congenital or acquired)
- Low birth weight-prenatal factors
- Other factors promoting increase in glomerular pressure/flow
 - High protein diet
 - Diabetes mellitus
 - Pregnancy
- Hyperlipidemia
- Chronic anemia
- Smoking, recreational drug use, and obesity
- Autoimmune disease and systemic infection
- Recovery from ARF
- Age >60 years
- Family history of kidney disease
- Reduces kidney mass (include kidney donors and transplant recipients)
- ACE gene polymorphism

- African American descent

CLINICAL EVALUATION OF PATIENTS AT INCREASED RISK OF CKD²**All patients**

- Measurement of blood pressure
- Serum creatinine to estimate GFR
- Protein to creatinine ratio, or albumin to creatinine ratio in a first morning or random untimed spot urine specimen
- Examination of the urine sediment or dipstick for RBC and WBC.

Selected patients, depending on risk factors

- Ultrasound imaging (in patients with symptoms of urinary tract obstruction, infection or stone or family history of polycystic kidney disease)
- Serum electrolytes (Na⁺, K⁺, Cl, and HCO₃)
- Urinary concentration or dilution (specific gravity or osmolality)
- Urinary acidification (pH)

LABORATORY EVALUATION OF PATIENTS WITH EARLY CRF**All patients need evaluation of**

- Serum creatinine to estimate GFR
- Protein/creatinine ratio or albumin to creatinine ratio in a first morning or random mentioned spot were specimen
- Examination of the sediment or dipstick for RBC and WBC
- Imaging of the kidneys by ultrasonogram
- Serum electrolytes (Na⁺, K⁺, Cl, HCO₃)

Estimation of GFR

- Cockcroft-Gault equation (Sr. creatinine wt, sex)
$$\text{Ccr(ml/min)} = \frac{(140 - \text{age}) \cdot \text{Weight (multiply 0.85 if female)}}{72 \cdot \text{serum creatinine}}$$
- Inulin clearance
- 24 hr endogenous creatinine clearance
- Radionuclide scan ^{99m}Tc DTPA
- Serum cystatin estimation

Table 2 : Showing comprehensive strategy for retarding progression of CRF

Intervention	Therapeutic goal
Specific renoprotective therapy ACE inhibitor or ARB treatment or both	Proteinuria < 0.5 g/day GFR decline < 2 ml/mt/year
Adjunctive cardiorenal protective therapy Additional antihypertensive therapy if needed	< 130/80 mmHg
Dietary protein restriction	0.6-0.8g/kg/day
Dietary salt restriction	3-5 g/day
Tight glycemetic control in diabetes	HbA1c < 6.5%
Reduce elevated calcium phosphorus product	Normal value < 55
Lipid lowering therapy	LDL-c < 100mg/dl
Antiplatelet therapy	Thrombosis prophylaxis
Correction of anemia	Hb > 12 g/dl
Smoking cessation	Abstinence
Weight control	Ideal body weight

CONSERVATIVE TREATMENT OF CRF

Interventions to retard progression of chronic renal disease (Table 2)

Treatment of underlying disease

Treatment of some causes retards progression to CRF e.g. antagonism of platelet-derived growth factor (PDGF) during acute phase of an animal model of mesangioproliferative nephritis prevented functional and morphologic changes of CRF from developing.

The DCCT trial demonstrated that even in patients who had microalbuminuria, the risk of developing greater degree of proteinuria was diminished by intensive blood sugar control.⁵ In UKPDS trial, in patients with type 2 diabetes, markers of kidney damage including microalbuminuria, proteinuria and elevation in serum creatinine were all attenuated by blood glucose control by several mechanisms.⁶ Even in established diabetic nephropathy euglycemia of 10 years following pancreatic transplantation has been shown to reverse histological renal lesion.⁷

In some animal models, more specific downstream therapy may be useful for well-established chronic disease. Example includes use of relaxin (which decreases macrophage infiltration and interstitial fibrosis independent of hemodynamic effects),⁸ vascular endothelial growth factor (VEGF)⁹ and aldosterone antagonist.¹⁰

Treatment of hypertension

The renal benefit of treatment depends to a significant extend on the underlying proteinuria. This was born out in modification of diet in renal disease (MDRD) study. Patients were randomized to groups with mean arterial pressure (MAP) goals of either 92 mmHg or 107 mmHg. The decline in GFR was found to be slower in more aggressively treated group overall, and benefit was in direct proportion to the severity of baseline proteinuria.¹¹

The UK prospective diabetes study (UKPDS) showed a linear relationship between blood pressure and microvascular disease in type 2 diabetics. This held true for average systolic BP at least as low as 114mmHg.¹² The Hypertension Optimal Treatment (HOT) study showed that treating the BP as low as 120/70 mmHg was not associated with any increase in cardiovascular events or mortality. In a subset of patients with diabetes, cardiovascular events and mortality were lowest in group assigned to a target diastolic BP 80mmHg or lower.¹³

In renal disease from type 1 diabetes together blood pressure control, independent of the use of ACE inhibitors, decreases proteinuria.¹⁴ A recent study from Steno Diabetes Centre showed that tight blood pressure control MAP 93 mmHg can decrease the GFR decline to that found with normal aging.¹⁵

Thus, to slowdown GFR decline, the goal for patients without diabetes with significant proteinuria involving at least 1g/d and for patients with diabetes is to lower the MAP to the low 90s. Based on MDRD data, Peterson et al suggested a MAP goal of 98mmHg a lower for patients with proteinuria involving between as 0.25 and 1 g/d.¹⁶

Treatment of proteinuria

ACE inhibitors

These drugs preferentially dilate the efferent arteriole, thereby hemodynamically decreasing glomerular hypertension and proteinuria. They also decrease proteinuria by preserving the integrity of component proteins of the slit diaphragm and by ameliorating podocyte foot process broadening.¹⁷ ACE inhibitors ameliorate monocyte/macrophage/infiltration, TGF-B expression fibroblast proliferation, differentiation in to myofibroblast and development of interstitial fibrosis.¹⁸

Clinical benefits have been found for diabetic¹⁹ and nondiabetic renal disease.²⁰ Adjustment for effect of systolic and diastolic blood pressure reduced but did not eliminate this benefit. Even in the presence of chronic renal insufficiency, ACE inhibitors can be used.^{20,21} The benefits are proportional to the extent of proteinuria. The preservation of GFR is directly proportional to the extent of lowering of proteinuria, which thus serves as a useful prognostic indicator.²¹

Angiotensin Receptor Blockers

Because ACE can be formed by non-ACE-dependent pathways and because of intolerance to ACE inhibitors in many patients, ARBs have been increasingly used to delay progression of CRF. They also have been found to normalize the glomerular nephrin deficiency and podocyte foot process broadening in diabetic animals.²² Animal studies suggest that the benefits are similar to those of ACE inhibitors. These agents diminish proteinuria and protect against renal function decline among patients with type 2 diabetes mellitus and nephropathy.^{23,24} No large-scale comparative studies have been published comparing ARBs and ACE inhibitors regarding progression of chronic renal failure. Small studies suggest comparable benefits in antiproteinuric effects and no differences in rate of progression were found in a study of diabetes mellitus at 1 year.²⁵

ACE inhibitors plus ARBs

Animal data indicate that the combination results in better reduction in better reduction of renal angiotensin II levels than either agents used alone.²⁶ Clinical studies have been conflicting as to whether a combination of both agents has additive antiproteinuric effects. Addition of ARBs to maximal ACE inhibitors may reduce renal TGF-B production despite the lack of salutary effects on proteinuria.²⁷ No large prospective studies on rate of progression using combination therapy are currently available.

Calcium Channel Blockers

Nondihydropyridines, appear to have some role at least in diabetic nephropathy.²⁸ Dihydropyridines do not have antiproteinuric effects.

Beta blockers

The large UKPDS-39 study found atenolol and captopril to be equivalent in limiting progression of albuminuria and azotemia over 4 years.⁶ Blocking the sympathetic nervous system may be beneficial independent of antihypertensive effect. In a multicenter prospective study of nondiabetic, African American with hypertensive renal disease, metoprolol was comparable with ramipril in reduction of proteinuria and in progression to end-stage renal disease.²⁹ However a composite end-point and the overall rate of GFR decline was worse with metoprolol, suggesting that ACE inhibitors should still be the preferred agents in this population.

Protein Restriction

The role of protein restriction remains controversial. Two relatively recent metaanalyses of low protein studies have been performed. In both, nondiabetic patients with chronic renal failure were shown in benefits from protein restriction.^{30,31} However it appears that the difference in the rate of decline of GFR is small. Pooling the results of 13 randomized controlled trials, Kasiske et al³¹ estimated a difference of only 0.53 ml/min/year among those assigned to protein restriction, which may not be clinically meaningful. For diabetic chronic renal disease the benefits seemed greater but the pooled number of patients was small, totaling only slightly over 100 in both meta-analyses.

It has been shown that a low protein diet decreases the filtered urine creatinine as well as urine creatinine secretion and affects the later more than the former. Such changes can occur independent of changes in the GFR.³² It also remains unclear whether there is benefit of combining a low protein diet with use of ACE inhibition.

For patients with advanced renal failure (GFR<25ml/min)who are not undergoing dialysis, the K-DOQI guidelines³³ currently recommended protein restriction to 0.6 g/kg/day but allowing for maximum up to 0.75 g/kg/day. While this avoids generation of nitrogenous metabolism and ameliorates uremic manifestation of outright benefit in delaying progression remains unproven.

Treatment of Hyperlipidemia/Use of Statins

Mostly, the use of statins are directed at lowering cholesterol,³⁴ although some work has also been published on the use triglyceride lowering agents.³⁵ Apart from lipid lowering effects, statins also downregulate TGF-B expression, interfere with

intracellular signaling pathways and prevent the activation of nuclear factor kB and substances downstream of TGF-B such as mitogen protein kinases and connective tissue growth factor.³⁶ These actions may ameliorate the progression of CRF. A recent metaanalyses of trials that were mostly based on statins showed a modest benefit in slowing down GFR decline.³⁴

Aldosterone Antagonism

In vitro in presence of angiotensin II, aldosterone further increases PAI-1 expression. This raises the possibilities that aldosterone antagonism may have additional benefits beyond those of A II antagonism. A recently reported case series of eight patients showed improvements in proteinuria by adding spironolactone to enalapril, though it is unclear if this occurred independently of blood pressure changes.³⁷

Erythropoietin

Erythropoietin can exert cytokine effect on the kidneys and regulate their survival and proliferation. Apart from amelioration of hypoxia, this may have a salutary effect in progression of renal failure.³⁸

Binding Protein Metabolites

Indoxyl sulfate is a protein metabolite that promotes the progression of glomerulosclerosis in animal studies. AST-120, an oral adsorbent that binds indole, decreases serum and urinary levels of indoxyl sulphate and also improves the rate of decline of GFR in patients with CRF.³⁹

Early Nephrology Referral

Late referral is associated with an increase in early morbidity. Specifically, early nephrology referral is associated with better predialysis care, and more appropriate choice of angioaccess for eventual hemodialysis. It has also been found to be cost-effective.⁴⁰

Other Modalities

The vasopeptidase inhibitor, omapatrilat, was recently shown to be as effective as ACE inhibitor in decreasing proteinuria and glomerulosclerosis. The active site of neutral endopeptidase and ACE are structurally similar.⁴¹

Peroxisome Proliferator activated γ receptor agonists

These are currently used to enhance the insulin sensitivity in type 2 diabetes mellitus. Salutary effects include amelioration of histologic changes in an animal model of this disease and non-diabetic glomerulosclerosis and improvement of microalbuminuria in diabetes.^{42,43}

Experimentally variable but often beneficial effects have been reported by blocking harmful cytokines and vasoactive substances such as platelet-derived growth factor, endothelin, TGF-B, and epidermal growth factor. Other studies have used cytokines such as relaxin, hepatocyte growth factor and bone morphogenic protein-7.⁴⁴⁻⁴⁶

Antibiotic agents have also produced encouraging results.⁴⁷

Dietary modifications

Soy protein and flaxseed have shown benefit in some animal models. The longest prospective study to date, a crossover trial involving 6 months each of soy protein or animal protein,

Table 3: Complications and additional interventions for patients with GFR <60 ml/min/1.73 m²

Clinical problem	Parameters in assessment	Possible additional parameters to access	Treatment
Anemia	Hemoglobin	If anemic <ul style="list-style-type: none"> Red blood cell indices Reticulocyte count Iron studies (serum iron, total binding capacity, percent transferrin saturation and ferritin) Test for occult blood in stool Medical evaluation for comorbid conditions 	Erythropoietin Dose-80-120 U/kg/wk SC 120-180 U/kg/wk IV Target –Hb-11-12 g/dl Hct-33-36% Transferrin saturation >20% and ferritin >100 ng/ml. Hypochromic RBC<10%. Iron status should be monitored monthly initially then 2-3 monthly.
Malnutrition	Weight Serum albumin Dietary history Subjective global assessment (SGA)	If malnourished <ul style="list-style-type: none"> 24-hour urine collection for urea nitrogen excretion Food recall/records for protein and total energy intake Medical evaluation for comorbid condition 	Intensive counseling Calorie (GFR<25ml/min) and <60 yrs age and not on dialysis-35Kcal/kg/d >60 yrs-30-35 Kcal/kg/d Protein-0.6g/kg/d(Max-0.75g/kg/d CRF with GFR<25 ml/mt and not on dialysis)
Bone disease	Serum PTH Serum calcium Serum phosphorus	If abnormal <ul style="list-style-type: none"> Consider vitamin D levels Consider bone X-rays Consider DEXA scan 	Target – iPTH (pg/ml) Stage 3 - 35-70 Stage 4 - 70-110 Stage 5 - 150-300
Neuropathy	Parasthesias Mental status abnormalities Sleep disturbances Restless legs	If symptomatic: <ul style="list-style-type: none"> Neurologic examination, including mental status Serum electrolytes Medical evaluation for comorbid conditions Consider nerve conduction velocity (NCV) Consider EEG/sleep studies 	Dialysis improves the symptoms. However NCV remains abnormal in 60-80% cases. Transplantation improves peripheral neuropathy
Reduced functioning and well-being	Standardized, self administered instruments such as Dartmouth COOP charts, QWB, DUKE/DUSO/SF-36, KDQOL	If abnormal <ul style="list-style-type: none"> Medical evaluation for comorbid conditions Self-management education Physical rehabilitation Mental health treatment Social support Vocational rehabilitation 	Assess functional status and well being. Reassessment if increased symptoms, complication of kidney disease start dialysis, change modalities. Counselling, peer support, education, physical therapy, vocational rehabilitation

DUKE-duke health profile, KDQOL-kidney disease quality of life, SF-36-medical outcomes study short form36, QWB-quality of well being scale.

Table 4: Frequency and target measurements of PTH, calcium, phosphorus by stages of CKD

CKD stages	GFR	PTH frequency	Calcium/phosphorus	Target PTH(pg/ml)	Target phosphorus (mg/dl)
3	30-59	12 monthly	12 monthly	35-70	2.7-4.6
4	15-29	3 monthly	3 monthly	70-110	2.7-4.6
5	<15 or dialysis	3 monthly	Monthly	150-300	3.5-5.5

failed to show any change on GFR. This topic has been recently reviewed.⁴⁸

Treatment of complications: (Table 3, 4)

NKF-DOQI guidelines define a decrease in GFR of 60-89 ml/min/m² as chronic kidney damage only if accompanied by a marker of kidney damage. Many complications begin to occur at GFR <60 ml/min/1.73m^{2.2} The important complications are anemia, bone disease, malnutrition, neuropathy, reduced functioning and well being. The following table shows complications, parameters

to assess and additional clinical intervention to prevent and treat the complications. The details are beyond the scope of this chapter.

Anemia

anemia is defined in terms of low hemoglobin and hematocrit. Anemia work up should be started if Hb and Hct level falls below 80% of the mean level for defined healthy i.e. Hct-33% for female and 36% for male. Erythropoietin is the treatment of choice. Adequate iron store should be ensured with target

transferring saturation >20% and ferritin level >100 ng/ml. However functional iron deficiency should be taken care.

Renal bone disease

High (PTH>200pg/ml), low (PTH<65pg/ml), and mixed turnover bone disease are encountered in CRF patients. Patients should be treated with 1.dietary phosphate restriction, 2. Phosphate binders like calcium carbonate, calcium acetate, aluminum containing phosphate binders, magnesium containing phosphate binders. Newer binders like Sevelamer hydrochloride (RenaGel) and Lanthanum carbonate can be used in patients at risk of hypercalcemia. 3. Vitamin D and its analogues 4.Calcimimetics. calcium and phosphate product should not exceed 55.

Treatment of Comorbidities; cardiovascular disease (CVD)

Patients with CKD are at increased risk of CVD, including coronary artery disease, cerebrovascular disease, peripheral vascular disease and heart failure. Both traditional and CKD (non-traditional) CVD risk factors may contribute to this increased risk.

Cardiovascular disease accounts for 40% to 50% of all deaths in the end-stage renal disease (ESRD) population and CVD mortality rates in ESRD patients are approximately 15 times higher than the general population. Forty percent of patients starting dialysis already have evidence of coronary heart disease (CHD) and only 15% are considered to have normal left ventricular structure and function by echocardiographic criteria. Data from the USRDS in 1997 show a 40% prevalence of either coronary artery disease or congestive heart failure in patients starting dialysis. Framingham Heart Study, the prevalence of various manifestations of cardiovascular disease were examined in participants with elevated serum creatinine (serum creatinine 1.5 to 3.0mg/dl and 1.4 to 3.0mg/dl in men and women, respectively). In men, CVD prevalence was 17.9% and in women, CVD prevalence was 20.4%. This contrasts with the CVD prevalence reported in the same study in men (13.9%) and women (9.3%) with normal serum creatinine level. Cardiovascular disease is the leading cause of death in patients with chronic kidney disease, regardless of stages of kidney disease.⁵¹ Early detection and timely intervention decreases the morbidity and mortality of the patients with CRF.

Smooth Transition from CRF to RRT

An intuitively critical component of the care of CRF patients is the timing of initiation of RRT. A proper conservative treatment of CRF, allows for timely intervention for vascular access placement, initiation of dialysis and renal transplantation. NKF-DOQI recommends for primary arteriovenous fistula at creatinine clearance <25 ml/min, creatinine level >4 mg/dl or within 1 year of anticipated need of dialysis. Dialysis AV graft should be placed at least 3 to 6 weeks prior to an anticipated need for hemodialysis.⁵² A retrospective analysis suggests that CKD patients who are transplanted before the start of dialysis have improved transplant survival as compared to those transplanted after receiving dialysis.⁵³

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