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CURRENT APPROACHES IN THE MANAGEMENT OF CHRONIC KIDNEY DISEASE: A REVIEW

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ABSTRACT

Chronic kidney disease (CKD) is a progressive loss in renal function over a period of months to years. The risk factors for CKD include mainly hypertension and diabetes. CKD may also be identified when it leads to one of its recognized complications, such as cardiovascular disease or anemia. It is differentiated from acute kidney disease in that the reduction in kidney function must be present for more than 3 months. Chronic kidney disease causes fluid and waste products retention in the body mainly urea and creatinine and thus leading to uremic syndrome. Treatment of chronic kidney disease consists of dealing promptly with any potentially reversible cause and delaying the progressive deterioration of renal function with conservative measures. As these measures fail, the only effective forms of treatment in ESRD are dialysis and renal transplantation. Unfortunately in many cases the cause of CKD is untreatable and progresses to ESRD despite adequate treatment.

KEYWORDS: Chronic Kidney Disease, End Stage Renal Disease, Renal transplantation, Maintenance dialysis, Conservative management.

INTRODUCTION

According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI)[1] guidelines (2002), Chronic Kidney Disease is defined as:

1. Kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifested by either:
- Pathological abnormalities or
- Markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests.

2. GFR < 60 ml/min/1.73 m^2 for ≥ 3 months with or without kidney damage.

Common causes of CKD[2]

- Diabetic Nephropathy
- Hypertensive Nephropathy
- Chronic Glomerulonephritis.
- Chronic Tubulointerstitial Nephritis (Chronic Pyelonephritis and Drugs/Toxic agents induced nephropathy).
- Vasculitis Syndrome.
- Autosomal Dominant Polycystic Kidney Disease.
- Obstructive Nephropathy.

Pathophysiology of Chronic Kidney Disease[3]

The pathophysiology of CKD involves two sets of mechanisms of damage. Firstly, initiating mechanisms specific to underlying etiology (such as genetically determined abnormalities in kidney development or integrity, immune complex deposition or toxin exposure) and secondly, progressive mechanisms, involving hyperfiltration and hypertrophy of remaining viable nephrons, which occurs as a consequence following long-term reduction of renal mass, irrespective of underlying etiology. The manifestations can be divided in three spheres of dysfunction:

(1) Those consequent to accumulation of toxic products that are normally excreted by kidney, including urea, creatinine and other categories of nitrogenous excretory products such as guanidino compounds, urates and hippurates, products of nucleic acid metabolism, polyamines, phenols, myoinositol, benzoates and indoles.

(2) Those consequent to the loss of other renal functions, such as fluid and electrolyte homeostasis and hormone regulation resulting in anemia, malnutrition and abnormal metabolism of carbohydrates, fats and proteins.

(3) Progressive systemic inflammation and its vascular and nutritional consequences.

Management of Chronic Kidney Disease

Treatment of chronic kidney disease consists of dealing promptly with any potentially reversible cause and delaying the progressive deterioration of renal function with conservative measures. When these measures are no longer able to keep the patient at work and leading normal life the patient has entered the stage of End Stage Renal Disease (ESRD). The only effective forms of treatment in ESRD are dialysis and renal transplantations.

It is foremost important to identify the potentially reversible causes of CKD (Table 1).

Table 1: Reversible causes of CKD

1. Infections such as urinary tract infection 2. Anaemia 3. Malnutrition 4. Urinary tract obstruction such as stone, tumour, benign prostatic hyperplasia. 5. Proteinuria	6. Dehydration 7. Nephrotoxic drugs 8. Hypertension 9. Hypokalemia 10. Hyperuricaemia

Unfortunately in many cases the cause of CKD is untreatable and progresses to ESRD despite good care. So, newer treatment modalities are being searched which can halt the progression and delay the development of ESRD.

Aims of therapy

1. To retard the progression of CKD to ESRD.
2. To control hypertension and DM.
3. To reduce proteinuria.
4. To maintain calcium and phosphorus homeostasis.
5. To avoid nephrotoxic drugs.
6. To cure anaemia.
7. To reduce cardiovascular disorders (CVD) related morbidity and mortality.

Ideal treatment for CKD-ESRD

Ideal treatment for CKD-ESRD is renal transplantation and maintenance dialysis. Since these modalities are costly, not suitable for many patients, required lifelong, associated with many complications and out of reach of 95-99% of patients, they are managed on conservative therapy. Conservative management is very important to prevent CKD and to prevent progression of CKD to ESRD.

A. Renal transplantation

It is the most appropriate treatment of ESRD. Kidney is removed from a deceased-donor or living-donor and transplanted inside patient after ABO and HLA (Human Leukocyte Antigen) matching. To suppress the kidney graft rejection, immunosuppressive drugs are used. Contraindications to kidney transplantation are mentioned in table 2.

Table 2: Contraindications to Kidney Transplantation

Absolute	Relative
- Reversible renal involvement	- Young age
- Effective conservative measures	- Presence of vesical or urethral abnormalities
- Active infection	- Iliofemoral occlusive disease
- Active glomerulonephritis	- Psychiatric problems
- Previous sensitization to donor tissue	- Oxalosis
- Advance forms of major extrarenal complications	

Complications of renal transplantation can be categorised into: urologic complications (urinomas, calculi and urinary obstruction), fluid collections (abscesses, hematomas and lymphoceles), graft dysfunction (acute tubular necrosis, acute and chronic rejection, drug toxicity), vascular complications (transplanted artery stenosis, infarction, arteriovenous fistulas and renal vein thrombosis), neoplasms (renal cell carcinomas and lymphomas, including post transplantation lymphoproliferative disorders).[4]

B. Maintenance dialysis

This is carried out using either hemodialysis or peritoneal dialysis.

1. Hemodialysis

Blood is removed from the body either through arteriovenous (AV) fistula, AV graft or central venous catheter and filtered through a dialyzer. The filtered blood is then returned to the body. This is done three times per week. Common side effects are low blood pressure, fatigue, chest pains, leg-cramps, nausea and headaches.

2. Peritoneal dialysis[5]

a. Continuous Ambulatory Peritoneal Dialysis (CAPD)

In CAPD, the dialysate is infused into the peritoneum via an indwelling catheter with tip positioned in the pelvis,

and the peritoneal membrane, a natural semi- permeable membrane, serves as the dialyzer.

b. Continuous Cycling Peritoneal Dialysis

Dialysis takes place at night, during sleep. The peritoneal cavity is filled with solution automatically. The waste solution is drained automatically. The last 'fill' of fluid is kept in the abdomen during the day.

Commonly associated complications of peritoneal dialysis are peritonitis, catheter tunnel infection, catheter dysfunction, dialysate leakage, hernias and sclerosing encapsulating peritonitis.

C. Conservative management

I. Dietary control

a. Protein restriction

Low protein diet (0.6 g/kg BW/day) as well as very low protein diet (0.3 g/kg BW/day) decreases accumulation of nitrogenous waste products, hydrogen ions, phosphates and inorganic ions while maintaining apt nutritional status to avoid secondary problems such as metabolic acidosis, bone disease as well as proteinuria and deterioration of renal function.[6,7]

b. Sodium and water

Salt and water intake varies from patient to patient. The typical initial recommendation is less than 6 g/day of sodium chloride (<2 g/day of sodium). Free water intake should be approximately equal to urine output plus an additional 500 ml/day to account for insensible losses. Generally, potassium containing food such as citrus fruits, coconut water, should be avoided.[8]

c. Phosphate restriction

Phosphate restriction appears to play key role in prevention of bone lesion in patients with chronic renal disease. Dietary restriction less than 800 mg/day results in significant increase in renal synthesis of 1,25-dihydroxyvitaminD_3 and may reverse the secondary hyperparathyroidism. It is also important to administer phosphate binder like aluminium hydroxide and calcium carbonate.[9]

Factors which cause rapid progression of CKD are enumerated in table 3.

Table 3: Factors which cause rapid progression of CKD

1. Poor hypertension/glycaemic control	6. Infections
2. Poor dietary control	7. Nephrotoxic drugs
3. Poor fluid and electrolytes control	8. Urinary tract obstruction
4. Anaemia	9. Co-morbid conditions such as HIV/ HBsAg/Anti-HCV positive
5. Proteinuria	10. Hyperuricemia

II. Methods to retard progression of CKD

a. Hypertension

Treatment of hypertension in patients of CKD is sodium and water restriction. If it is not controlled, ACE inhibitor or angiotensin II receptor blocker is administered. After initial dosing with an ACEi, ARB or other drug, diuretic is added to the regimen.[10]

b. Intra-glomerular Hypertension and Proteinuria

ACE inhibitors and ARBs inhibit angiotensin-induced vasoconstriction of efferent arterioles of glomerular microcirculation. This inhibition results in reduction of both intraglomerular filtration pressure and proteinuria. The combination is leads to a greater reduction in proteinuria compared to either agent alone.

c. Blood glucose

Proper diabetes mellitus control reduces the risk of kidney disease and its progression. As GFR decreases with progression of nephropathy, use and dose of oral hypoglycemics has to be re-evaluated. As renal function declines, renal degradation of administered insulin will also decline, so lesser insulin may be required for glycemic control.[3]

d. Infection

Infection worsens the severity of renal insufficiency and is common cause of death in patients with ESRD. Hence infections should be treated aggressively by appropriate antimicrobials in adequate amounts. Safe and effective drugs are fluoroquinolones and cephalosporins. Drugs which should be avoided in CKD include aminoglycosides, tetracyclines, nitrofurantoin.[11]

e. Metabolic acidosis

The first-line agent for treatment of metabolic acidosis is sodium bicarbonate in a dose of 650 mg three times daily. Sodium citrate is better tolerated than bicarbonate but is restricted to patients who are not taking aluminium-containing phosphate binders as it enhances aluminum absorption in the intestine.[12]

f. Anaemia

Anaemia in CKD is mainly treated by raising the erythropoietin in blood. This is achieved by recombinant human erythropoietin and modified erythropoietin products, such as epoetin-alfa and darbepoetin-alfa. Other treatments are iron and folic acid supplementation as well as blood transfusion.[13]

g. Hypocalcemia and renal osteodystrophy

The deficiencies of calcitriol and calcium are corrected mostly by oral administration. Calcitriol is now available in the form of oral capsules (0.25 and 0.50 μg), oral solution (1 μg/mL), and injectable (1 μg/mL). It may be dosed once a day or every other day depending on serum calcium. Oral calcium supplements such as calcium carbonate and calcium acetate are used mostly as phosphate binders.[9]

h. Dyslipidemia

It is managed by dietary measures. If it is not controlled, lipid-lowering agents, such as statins, should be used.

Traditional therapeutic modalities for CKD

Chronic kidney disease is an increasingly common condition with limited treatment options that is placing major financial and emotional burden on our community. Newer drugs are to be searched which can halt the progression of CKD in our setup and hence decrease morbidity and mortality. Botanical medicine (table 4) can be used to delay the need for dialysis by treating the causes and effects of renal failure.

Table 4: Medicinal plants used in chronic kidney disease

Plant name	Common name
Salvia miltiorrhiza[14]	Red sage, Chinese sage, tan shen, or danshen
Ginkgo biloba[15]	Ginkgo or the maidenhair tree
Rheum officinale[16]	Rhubarb, rheum, rhaptonic
Perila frutescens[17]	Bhanjira, ban tulsi, bhanjira, bhangra, jhutela
Cordyceps sinensis[18]	Caterpillar Fungus
Curcuma longa[19]	Tumeric
Beta vulgaris L. var. cicla[20]	Chard
Crataegus spp.[21]	Hawthorn, thornapple, May-tree
Astragalus membranaceus root[22]	Milkvetch, locoweed, goat's-thorn
Tripterygium wilfordii[23]	Tao et al 2006
Ligusticum wallichii[24]	Tang X 2003
Glycyrrhiza [licorice] root[18]	Yokozawa T et al 2005
Urticadioica(stinging nettle) seed[25]	Jonathan T et al 2003
Orthosiphon stamineus (Java tea)[26]	Kannappan N et al 2010
Centella asiatica[27]	Pang LL et al 2010
Capsicum spp.[28]	ShimedaY et al 2005

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