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Review Article

PHYSIOLOGICAL COMPLICATIONS IN CHRONIC KIDNEY DISEASE

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ABSTRACT

Kidney disease is a worldwide public health problem, with becoming increasingly incidence and prevalence, high cost, and poor outcome. Chronic kidney disease (CKD) involves an irreversible loss of renal function. CKD is becoming one of the major leading global health concerns that is projected to grow worldwide at a rate of 8% annually, and incidentally is doubled in last fifteen years; but it is under diagnosed and under treated. Patient with hypertension, diabetes, obesity, nephritic syndrome and stone diseases are at high risk for CKD. As number of CKD patient increases, primary care practitioners will be confronted with management of complex medical problems unique to patients with chronic renal impairment. The aim of the present study is to provide an overview and detailing the current knowledge of physiological complications associated with CKD.

INTRODUCTION

Chronic kidney disease (CKD) is an increasingly urgent public health concern that is projected to grow worldwide at a rate of 8% annually, with the fastest growth expected in developing countries (Ayodele and Alebiosu, 2010). The renal diseases pose a major cause of morbidity and mortality worldwide because kidneys are vital organs for maintaining a stable internal environment i.e., homeostasis (Picken, 2000). India is now becoming a major reservoir of chronic diseases like diabetes and hypertension. CKD is the 12th leading cause of death and 17th cause of disability. CKD is becoming increasingly common due to rising incidence of diabetes, hypertension, and obesity and ageing population in India (Hase, 2012).

Overview of CKD

Chronic Kidney Disease is defined as structural or functional abnormalities of the kidney, with or without decreased Glomerular Filtration Rate (GFR), manifested by markers of kidney damage or pathological abnormalities such as abnormalities in the composition of the blood or urine or abnormalities in imaging tests (Johnson *et al*., 2004).

Renal diseases are classified into acute and chronic stages depending on mode of onset. Loss of kidney function causes clinical syndrome known as uremia. The signs of renal failure and uremia is significant to the medical practitioner (Table 1) (Davidson, 1999).

Table 1 Signs and symptoms of renal failure and uremia (Kuravatti *et al*., 2016)

Signs	Symptoms
Peripheral edema	'Restless' legs
Hhypertension	Cramps in leg
Pericardial effusion	Ankle edema
Confusion, coma, lethargy	Loss of libido
Renal osteodystrophy	Feeling cold
Pallor due to anemia	Pruritus
Bruising due to platelet dysfunction	Insomnia

Stages of CKD

The level of GFR define the stages of CKD, and the relationship is inversely proportional that means, lower GFR levels represents higher stages of CKD and vise-versa (Table 2) (Kuravatti *et al*., 2016).

Table 2 Classification of CKD based on GFR (Kuravatti *et al*., 2016).

CKD Stage	Definition
1	Normal or Increased GFR, microalbuminuria, proteinuria, hematuria, radiologic and histologic changes.
2	Mild decrease in GFR (89-60ml/min per 1.73m^2), microalbuminuria, proteinuria, hematuria, radiologic and histologic changes.

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3	GFR 59-30 ml/min per 1.73m^2
3A	GFR 59 to 45 ml/min per 1.73m^2
3B	GFR 44 to 30 ml/min per 1.73m^2
4	GFR 29- 15 ml/min per 1.73m^2
5	GFR < 15 ml/min per 1.73m^2. Renal replacement therapy such as dialysis or renal transplantation has to be considered to sustain life.

Medical Management of Patient with Renal Failure

The treatment of renal failure requires long time due to its chronic nature. Mainly the treatment comprises of dietary changes, correction of systemic complications and dialysis or renal graft receipt. Few medical managements are: (1) moderate amounts of proteins and carbohydrates are included in the diet to minimize the nitrogenous waste products but fats are restricted (2) to improve the anemia repeated blood transfusions are required (3) the development of hypercalcemia and its metastatic complications can be prevented by assessing the level of serum calcium and serum alkaline phosphatase at regular intervals (4) to treat osteomalacia massive doses of Vitamin D are recommended (5) Hyperphosphatemia can be prevented by limiting phosphate containing foods (e.g. milk, cheese, eggs) and use of phosphate binding drugs e.g. aluminum hydroxide gel after meals (6) If any intercurrent infection develops, it should be treated with antibiotic (e.g. nandrolone) (7) low doses of digoxin is used in case of renal associated cardiac failure (8) chlorpromazine is used to control nausea and vomiting (9) uremic diarrhea is treated by high bowel wash with plain water. Bland anti-diarrheal drugs (e.g. pectin or kaolin) may be used. Renal failure is a debilitating disease carrying high mortality and morbidity. It needs long term treatment like continuation of lifelong renal replacement therapy in the form dialysis or renal transplantation and thus keeping a huge economic burden as well social stress on patients and their families (Sunil *et al*., 2012; Hase, 2012).

CKD Associated Anaemia

Anemia is defined as reduction of red blood cell (RBC) measurements in forms of hemoglobin concentration, hematocrit, or red blood cell count. The World Health Organization defines anemia as a haemoglobin level less than 13 g/dL in men and postmenopausal women, and less than 12 g/dL in premenopausal women (WHO, 1968). Usually CKD is accompanied by normochromic, normocytic anemia. Anemia may be diagnosed at any stage of CKD patients. there is a strong correlation between the prevalence of anemia and the severity of CKD. Primary care providers play an important role in diagnosing and managing anemia in CKD patients. (Besarab and Levin, 2000)

Anemia in CKD can result from iron, folate, or vitamin B_{12} deficiency; gastrointestinal bleeding; severe hyperparathyroidism; systemic inflammation; shortened red blood cell survival; and decreased erythropoietin synthesis. Erythropoietin, a glycoprotein, secreted by the kidney interstitial fibroblasts is essential for the growth and differentiation of RBCs in bone marrow. In CKD, tubular atrophy produces tubulointerstitial fibrosis, which compromises renal erythropoietin synthetic capacity and results in anemia (Ratcliffe, 1993). The anemia in CKD increases morbidity and mortality from cardiovascular complications (e.g. angina, left ventricular hypertrophy and worsening heart failure), which may lead to further deterioration of renal function and establish a vicious cycle known as "cardiorenal anemia syndrome" (Besarab and Levin, 2000).

CKD Associated Mineral and Bone Disorder

CKD associated mineral bone disorders significantly increase mortality in CKD patients. Renal osteodystrophy is the spectrum of histologic changes that occur in bone architecture of CKD patients (Gal-Moscovici and Sprague, 2007).

Changes in bone architecture can be caused by either a high bone turnover state or a low bone turnover state. Four types of bone phenotypes can be diagnosed in CKD patients: osteitis fibrosa cystic, osteomalacia, adynamic bone disorder, and mixed osteodystrophy. The predominant type of renal osteodystrophy and CKD associated mineral and bone disorder differs between predialysis and endstage renal disease patients. In predialysis patients, high bone turnover bone disease is most prevalent, where as low bone turnover predominates in dialysis patients. Patients with low turnover disease represent most cases of renal osteodystrophy (Joy *et al*., 2007). The cause of this prevalent bone phenotype results from oversuppression of parathyroid hormone and high calcium dialysate concentrations (Hruska and Teitelbaum, 1995).

CKD Associated Cardiovascular Risk

Progression of CKD is a major risk factor for cardiovascular morbidity and mortality. The increased cardiovascular risk is associated with end-stage renal disease with a cardiovascular mortality rates are 10 to 100-fold higher among dialysis patients. Mild to moderate degrees of renal impairment are associated with increased cardiovascular risk. Many traditional cardiovascular risk factors contribute to cardiovascular risk in CKD patients (Fig. 1) (Foley *et al*., 1998).

Hypertension, a traditional cardiovascular risk factor, contributes to the cardiovascular risk associated with stage 2-3 CKD (Muntner *et al*., 2005). Systolic blood pressure is more strongly associated with cardiovascular death in dialysis patients than either pulse or diastolic pressure (Port *et al*., 1999). Diabetes is associated with adverse outcomes in all stages of CKD (Tonelli *et al*., 2005). Lower fasting plasma glucose levels are associated with lower risk of cardiovascular death in patients with moderate to severe renal impairment. The presence of Left Ventricular Hypertrophy (LVH), a complication that increases in relation to lower levels of eGFR, is also a cardiovascular risk determinant in CKD patients. Anemia and hypertension are two CKD associated complications which play a role in the development of LVH. Tobacco use is also associated with increased mortality and incidence of heart failure among patients with stage 5 CKD (Combe *et al*., 2004).

Anemia is a risk factor for adverse cardiovascular outcomes in CKD patients. Higher calcium-phosphate products and the cumulative dose of oral calcium based phosphate binders correlate the extent and progression of arterial calcification in dialysis at stage 3 or 4 CKD patients (Goodman *et al*., 2004). Serum phosphate levels are associated with increased rates of death and myocardial infarction in stage 3 or 4 CKD patients (Kramer *et al*., 2005).

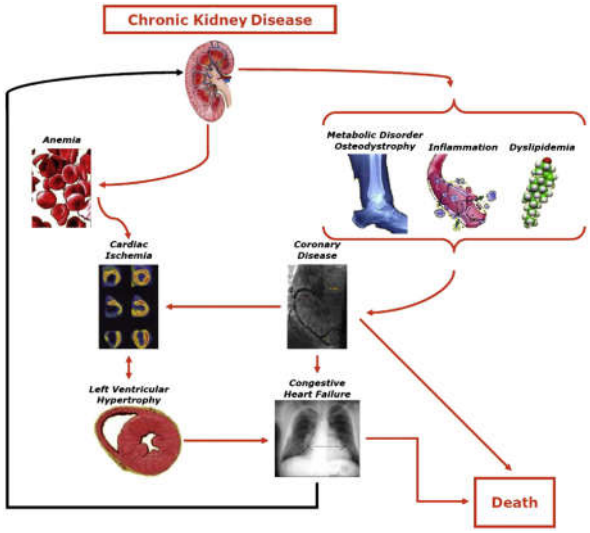

Figure 1: Interplay of processes secondary to chronic kidney disease leading to cardiovascular disease and death. Red arrows: Pathogenetic pathways; black arrow: feedback loop; kidney disease worsened by heart failure (Foley et al., 1998).

Inflammation, a nontraditional risk factor, believed to play a role in mediating cardiovascular risk in CKD patients. Inflammatory markers are often elevated in CKD patients. Recent studies reported, serum C-reactive protein (CRP) levels predict cardiovascular outcomes in CKD patients at stage 3, 4 or 5 (Menon and Sarnak, 2005). Proteinuria, a hallmark of renal impairment, is associated with an increased risk for cardiovascular disease and early cardiovascular mortality in patients with and without diabetes and hypertension (Hoehner *et al*., 2002).

CKD and Dyslipidemia

Dyslipidemia, a major risk factor for cardiovascular morbidity and mortality, is common among CKD patients. The level of kidney function and the degree of proteinuria in CKD patients are reflected by variation of lipid profiles. Generally, the prevalence of hyperlipidemia increases as renal function declines with the degree of hypertriglyceridemia and elevation of LDL cholesterol being proportional to the severity of renal impairment. CKD patients have reduced activity of lipoprotein lipase and hepatic triglyceride lipase. This interferes yielding increased circulation of atherogenic lipoproteins. Hypercholesterolemia in nephrotic syndrome is thought to be a result of increased production and decreased catabolism of lipoproteins. The degree of lipoprotein abnormality is roughly proportional to the amount of proteinuria and inversely proportional to serum albumin levels (Kasiske, 1998).

CKD and Nutritional Issues

As patients progress through the stages of CKD, nutritional requirements are altered and metabolism of protein, water, salt, potassium and phosphorus are affected (Appel *et al*., 1985). These changes lead to ineffective energy generation inspite of taking adequate protein and carbohydrate substrates, and develop a syndrome known as "uremic malnutrition". Both inadequate nutrient intake and ineffective nutrient use can contribute to nutritional disorders in CKD patients. A poor predialysis nutritional status increases patient morbidity and mortality after initiation of renal replacement therapy (Khan *et al*., 1995). Maintenance of neutral nitrogen balance is important for preservation of nutritional health in patients with chronic renal impairment. Several nutritional markers can be used to assess nutritional status. Serum albumin is the most extensively studied nutritional marker due to its easy availability and strong association with hospitalization and risk of death (Herrmann *et al*., 1992). Low levels of serum albumin are highly predictive of poor clinical outcomes in all stages of CKD, and therefore, serum albumin is considered a reliable marker of general clinical status. Low serum creatinine concentrations are associated with poor clinical outcome in maintenance of stage 5 CKD patients. Serum cholesterol concentration is an independent predictor of mortality in chronic dialysis patients (Owen *et al*., 1993).

CKD and Metabolic Disorders

Acid base balance

Acid–base disorder is observed in the course of Chronic Kidney Failure (CKF). Metabolic acidosis is noted when GFR decreases to less than 20 to 25 % of normal. The degree of acidosis correlates with the severity of CKF and usually it is more severe at lower GFR. In mild chronic renal insufficiency, metabolic acidosis is the result of a reduced ability to reabsorb bicarbonate, to excrete ammonia, and to eliminate titratable acid excretion, where as in more severe renal insufficiency, organic and other conjugate anions of acids cannot be sufficiently excreted, and elevated anion gap acidosis appears. Acidosis resulting from advanced renal insufficiency is called uremic acidosis. Several adverse consequences have been associated with uremic acidosis, including muscle wasting, bone disease, abnormalities in growth hormone and thyroid hormone secretion, impaired insulin sensitivity, and exacerbation of beta-2 microglobulin accumulation (Kraut and Kurtz, 2005).

Protein Metabolism

A strict low-protein diet (minimum 0.6 g of protein/kg/day) can have a negative effect on nitrogen balance in the predialysis period. In the dialysis period, the protein metabolism disorder are usually caused by protein and energy malnutrition that can be termed as uremic malnutrition, characterized by insidious loss of somatic protein stores (reflected in lean body mass and serum creatinine) and visceral protein concentrations (reflected in serum albumin and prealbumin concentrations). Urinary losses of protein and losses of amino acids during a dialysis session may also play a role (Ikizler, 2004). Metabolic acidosis markedly contributes to negative nitrogen and total body protein balance in CKF (Mehrotra *et al*., 2003). The presence of uremic malnutrition increases mortality and morbidity in chronic dialysis patients (Kopple 1994).

Carbohydrate Metabolism

Carbohydrate metabolism disorder is very frequent in CKD. Diabetics represent about 35% of all patients on dialysis therapy. Non-diabetic CKD patients often have glucose intolerance due to peripheral insulin resistance (Alvestrand, 1997). Insulin resistance is primarily detectable when the GFR is below 50 ml/min. Insulin resistance is related to arterial hypertension and may contribute to high cardiovascular morbidity and mortality in patients with CKF (Shinohara *et al*., 2002). It was reported that appropriately functioning endothelial NO *synthase* (eNOS) is important for the control of

not only arterial pressure but also glucose and lipid homeostasis (Duplain *et al*., 2001).

Lipid Metabolism

Serum triglycerides (TG) level is elevated in CKF because of enhanced production of TG-rich lipoproteins such as very low density lipoproteins (VLDL) in liver and also because of dysfunction of TG degradation resulting from insufficient mitochondrial beta-oxidation of fatty acids (Attman *et al*., 1993). It occurs due to deficit of L-carnitine, which is frequently present, especially in hemodialysis patients (Cibulka *et al*., 2005). Hyperinsulinemia is the main factor increasing synthesis of TG and also directly decreasing the activity of lipoprotein lipase. The most prominent changes in lipid metabolism found in many CKF patients are increased serum TG levels and low levels of high density lipoprotein (HDL). HDL cholesterol levels are inversely correlated with the risk of atherosclerosis (Dirican *et al*., 2004). HDL particles are structurally altered during the states of inflammation. Hypercholesterolemia, obesity, and increased blood levels of creatinine and homocysteine appear to be protective and paradoxically associated with a better outcome in CKF patients (Kalantar-Zadeh *et al*., 2005).

CKD and Mental Stress

CKD patients are susceptible to a variety of conditions affecting the Central Nervous System (CNS). From a functional standpoint, CNS disorders typically manifest as altered mental status and can be clinically subdivided into chronic (such as stroke, cognitive impairment, dementia, dialysis dementia, etc.) or acute (Encephalopathy altered brain function, encephalopathy syndrome, dialysis disequilibrium syndrome, cerebral oedema before and after dialysis, etc) stages (Fig. 2) (Arnold *et al*., 2016).

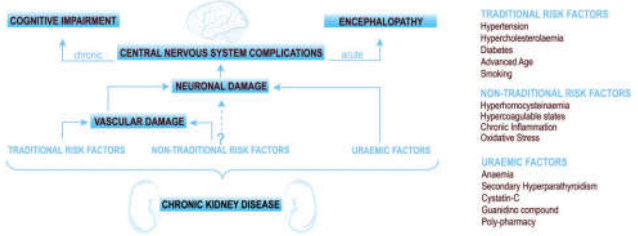

Figure 2: Flow chart of the exposures in CKD associated with central nervous system damage (Arnold et al., 2016).

CKD and Physical Disability

Physical disability is a common problem in CKD patients with a significant impact on activities of daily living and independence. Physical impairment may be a manifestation of various Parasympathetic Nervous System (PNS) disorders. The most common PNS disorders in CKD patients are peripheral neuropathy, autonomic neuropathy and myopathy (Arnold *et al*., 2016).

CKD and Sleep Disorders

In advanced stages of CKD sleep disorders are common and under recognized. Subjective sleep complaints are reported by more than 50% of patients on haemodialysis. Common organic sleep disorders in CKD patients include Sleep Apnea Syndrome (SAS), Periodic Limb Movement Disorder (PLMD) and Restless Leg Syndrome (RLS). These disorders are more common in the dialysis population than in the general population (Pressman and Benz, 1995). Sleep disorders in CKD patients after the quality of life and increased incidences of cardiovascular disease including coronary artery disease, LVH and hypertension. Heart disease is the major cause of death in CKD patients (Jung *et al*., 2005).

Hyperparathyroidism in Patients with CKD

High level of parathyroid hormone is an important factor in the genesis of myocardial fibrosis. Hyperparathyroidism is associated with LVH. The size and function of left ventricle has been improved after parathyroidectomy (Amann *et al*., 1994).

Summary

CKD incidence is increasing worldwide with increasing the cost of treatment, morbidity and mortality. The aim of a medical personal should be to detect, evaluate and diagnose CKD in patients early and refer them to nephrologists. Classifications of CKD into stages 1to5 facilities patient care through the applications of disease specific clinical action plans. During early stages, aggressive blood pressure control and decreasing proteinuria have been found effective to combat against CKD. CKD patients can be managed by: (i) treatment of reversible causes of renal dysfunction such as hypovolemia, infection, obstruction, primary active disease, malignant hypertension (ii) slowing progression (iii) reducing cardiovascular events managing risk factors (iv) treatment of complications and (v) preparation for renal replacement (dialysis and transplant) therapy.

These interventions may reduce morbidity and mortality in patients. With early identification and treatment of anemia, renal osteodystrophy, uremic malnutrition, hyperlipidemia and cardiovascular disease; primary care physicians and nephrologists together can make significant strides toward extending and improving the lives of CKD patients.

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Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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