Review Article

An Overview of Common Symptoms and their Management in Chronic Kidney Disease

Vinu B*, Durga K**, Balaji R*

*Assistant Professor,**Professor, Chettinad Hospital & Research Institute, Chettinad Academy of Research & Education, Chennai, India.

Dr Vinu did her undergraduation in Kilpauk Medical college and Postgraduation from PSG institute of medical science and Research. Her area of interest is Rheumatology.

Corresponding author - Dr. Vinu B - (vinuboopathy@gmail.com)

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Abstract

CKD is a global health issue associated with increased financial burden and affects the quality of life to a vast extent. The symptoms confronted by patients in various stages of chronic kidney disease are very debilitating. The most common symptoms of CKD are itching, sleep disturbance, anorexia, fatigue, muscle wasting, nausea, vomiting, chronic pain, shortness of breath, bleeding and sexual dysfunction. Most of the symptoms are due to increased proinflammatory mediators like IL-6 and TNF α. Recent research studies have discovered new biochemical substances like orexin, ghrelin, melatonin and adiponectin as mediators of some of the symptoms like fatigue and muscle wasting. This review focuses on the possible pathophysiological mechanisms and management of the above mentioned symptoms.

Key Words: CKD- Chronic Kidney Disease, IL – Interleukin, TNF- tumour necrosis factor, ESRD- End Stage Renal Disease, LBM- Lean Body Mass, ADP- Adenosine Diphosphate, ATP- Adenosine Triphosphate, CRP- C Reactive Protein.

Introduction

CKD is a global health issue associated with poor outcomes, increased financial burden and affects the quality of life. A meta analysis from 44 studies has reported the prevalence of CKD to be 13.4%.[1] CKD is associated with varied physiological and metabolic alterations. The symptoms confronted by patients in various stages of chronic kidney disease are very debilitating. The symptoms are mostly overlooked by the treating physicians as the current literatures do not relate the declining renal functions to the symptoms of the patient, hence the focus has shifted to achieving numerical targets rather than a holistic approach. This situation is further aggravated since there is a lack of systematic tool to evaluate the renal failure symptoms to the severity and outcome of CKD. This review provides an outlook on the most common symptoms, possible pathophysiological mechanisms and their management.

Symptoms of Chronic Kidney Disease

The most common symptoms experienced by patients with CKD are listed in Table 1.

Symptomatological manifestations of CKD
Dermatological manifestation - Pruritus
Nervous system manifestation - Sleep disturbance, Pain and parasthesia
Gatrointestinal manifestation -Anorexia , Nausea and vomiting
Musculoskeletal manifestation - Increased fatigue, Muscle wasting
Cardiovascular manifestation - Shortness of breath
Haematological manifestation – Anemia , Bleeding
Sexual dysfunction

Table 1: Common symptoms of CKD[2]

Pruritus In Chronic Kidney Disease

Pruritus is one of the most agonizing symptom of CKD. Though 'Uremia associated pruritus' is used more frequently, the term "CKD associated pruritus" is considered more precise. The prevalence of pruritus as documented by a largest epidemiological study is estimated to be about 42%.[3] Patients on hemodialysis are mostly affected (50-90%). Pruritus in CKD is postulated to be a result of a proinflammatory state mediated by derangement of immune system. Recent studies have established an association between imbalance in opioidergic system and pruritus. Mu and Kappa receptors not only mediates pain but also has its role in regulation of pruritus. Researches have proved that Mu receptor antagonist and Kappa receptor agonist can decrease prutitus[3] (Figure 1).

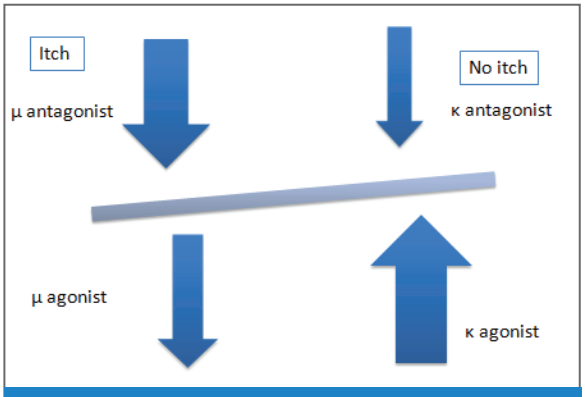

Fig 1: Interplay of Mu and kappa receptors in pruritus.

Increased amount of serum calcium and phosphates also contributes to pruritus in CKD. The formation of calcium phosphate crystals which gets precipitated under skin stimulates the itch receptors and leads to itch. One another postulated mechanism is disruption of the calcium ion gradient in the deepest layer of the epidermis. Based on indirect immunochemistry studies conducted it was found that patients experiencing pruritus in CKD had an abnormal pattern of cutaneous innervation mediated by neuron- specific enolase nerve fibres appearing all over the epidermis.[4]

Other factors involved in the pathophysiology could be hypervitaminosis A, xerosis, altered number of mast cells, inadequate removal of uremic toxic products, high serum magnesium, histamine, parathormone and substance P.

Treatment of Pruritus[5] :

- Topical emollients and analgesics.
- Oral antihistamines.
- Gabapentin – if resistant to antihistamines.
- Ultraviolet B (UVB) – for refractory pruritus.
- Correction of calcium, phosphate and parathormone levels.

Sleep Disturbance In CKD

Sleep disorders most commonly encountered among CKD are insomnia, excessive sleep , sleep apnoea and restless leg syndrome. The prevalence of sleep disturbance in a systemic review involving 17 studies in patients with CKD was 44%.[6] Of the above mentioned sleep disorders the most common symptom experienced is insomnia. The metabolic factors involved in pathogenesis of insomnia are anemia, bone pain, pruritus, psychological stress and uremia. Varied time shift of dialysis is also a factor for sleep disturbance. Insomnia is also a contributor of increased mortality in ESRD. This could possibly be due to heightened systemic inflammation which mediates worsening of CKD and also worsens the cardiovascular outcomes. Other contributors for insomnia in CKD are orexin and melatonin. Orexin (hypocretin) is a neuropeptide that promotes and regulates wakefulness. Plasma levels of orexin are elevated in ESRD patients which leads to poor sleep. The diurnal rhythm of melatonin is disturbed in end stage renal disorder and this is also a contributor for insomnia.

Excessive sleepiness in chronic kidney disease is due to subclinical uremic encephalopathy, sleep apnea leading to excessive day time sleepiness, increased melatonin even in daytime, altered sleep - wake cycles. Metabolism of dopamine is regulated by tyrosine, deficiency of tyrosine in CKD leads to altered sleep wake rhythm.

Sleep apnea in CKD is both obstructive and central sleep apnea.[8] Mechanism for obstructive sleep apnea is pharyngeal narrowing due to interstitial edema which leads to upper airway obstruction. Another cause for pharyngeal narrowing is upper airway muscular dysfunction due to myopathy associated with uremia. Central sleep apnea is due to loss of respiratory drive.

Sleep apnea leads to exaggerated oxidative stress and untreated sleep apnea may lead to daytime sleepiness and reduced cognitive function and also lower the quality of life. It is also a important risk factor for cardiovascular complications by accelerating atherosclerosis and myocardial infarction, which is a leading cause for mortality and morbidity in CKD.

Treatment of sleep disoders[7,8] :

- Nocturnal hemodialysis.
- Moderate regular exercise.
- Positive airway pressure therapy.
- Behaviour modification.

Anorexia , Muscle Wasting And Malnutrition In CKD

Loss of Lean Body Mass(LBM) and muscle wasting in CKD is linked to metabolic acidosis, uremia, inhibition of insulin anabolic signalling pathways and activation of proteolytic enzymes. There is also increased activation of proinflammatory cytokines such as TNF, IL-1β and IL-6 which activate a catabolic state.[9,10] Muscle mass shows a inverse relation to circulating inflammatory mediators (Figure 2). There is also a role of 'ATP-ubiquitin - proteasome' pathway in muscle wasting. This pathway leads to accelerated proteolysis

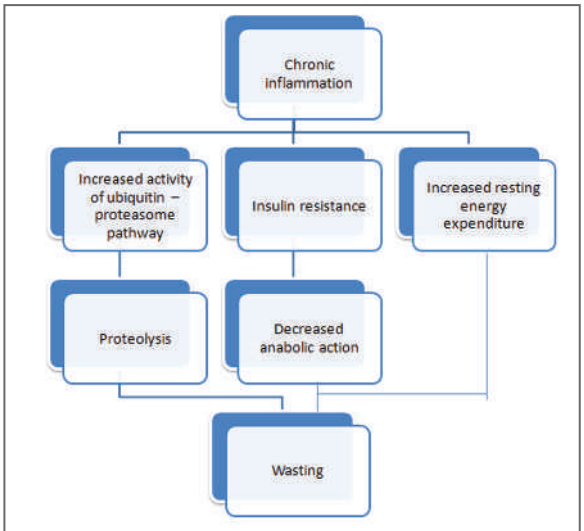

Fig 2: Pathways linking inflammation and wasting in CKD

mediated by activation of ATP and increased mRNA levels[11,12]

Recent research have identified many potential adipokines like leptin, ghrelin, adiponectin involved in muscle wasting. Raised leptin levels and leptin resistance leads to stimulation of energy expenditure and reduces the food intake. All the above factors exert oxidative stress and cellular dysfunction systemically and locally. Protein catabolism is hastened in the peripheral tissues to meet the demands of increased aminoacid requirements in liver for production of acute phase reactants and glucose. These factors lead to increased production of reactive oxygen species which further activates cytokine production and accelerated damage.

Fatigue In Chronic Kidney Disease

Fatigue is a common symptom experienced by most of the patients with chronic kidney disease. The estimated prevalence of fatigue in chronic kidney disease patients ranges between 42 to 89 percent[13]. " fatigue is a complex , multifactorial phenomenon defined as extreme persistent tiredness, weakness or exhaustion - mental, physical or both". Researches on fatigue in advanced kidney disease have found fatigue correlates with physical inactivity and anorexia. High levels of IL-6 and CRP which are suggestive of chronic inflammation have a significant role through their direct effect on central nervous system, hypothalamus and adrenal glands (Figure 3). Several biochemical and haematological factors like low haemoglobin , low serum albumin play an important role in fatigue in CKD.

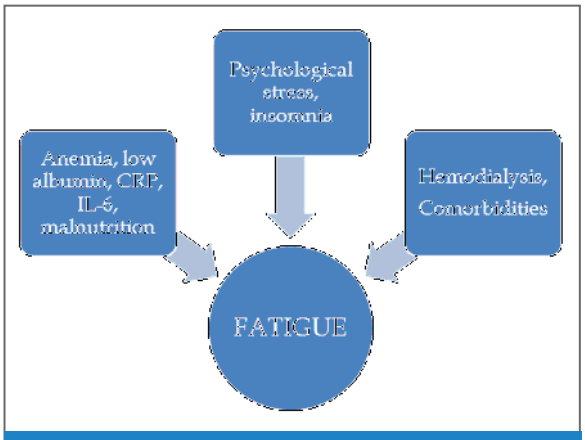

Fig 3: Factors associated with fatigue in renal disease

Treatment [14]

- Adequate calorie intake – 35Kcal/ kg.
- Intake of proteins of high biological value.
- Average protein intake of at least 1.5g / kg / day.
- Adequate supplementation of micronutrients.

Pain In Chronic Kidney Disease

Pain is a most common symptom amongst CKD patients than in general population. The prevalence of pain in various stages of CKD ranged from 64-75 percentage.[15] Pain in CKD might be attributed to primary kidney disease like polycystic kidney disease or a sequelae of CKD like calciphylaxis. Pain is also directly related to dialysis treatment like AV fistulas leading to painful ischemic neuropathies and infections. Muscle and bone pain in CKD is related to deranged metabolism of calcium, phosphate and parathormone.

Pain can generally be classified as nociceptive or neuropathic type. Nociceptive pain in CKD is due to renal osteodystrophy, dialysis induced amyloid arthropathy, osteoarthritis and autosomal dominant polycystic kidney disease(ADPKD). Neuropathic pain in CKD is due to abnormal neural activity secondary to diabetic neuropathy, phantom limb pain etc.

Ischemic pain due to peripheral vascular disease and calciphylaxis is usually mixed type of nociceptive and neuropathic pain.

The uremic polyneuropathy presents with symptom is involving the distal part of lower extremities. It can manifest with pricking or burning sensation which progresses proximally. Patients with advanced renal disease may manifest with motor symptoms like weakness of distal muscles and sometimes even before the onset of sensory symptoms.

Treatment [16]

- Nociceptive pain : treat with acetaminophen, tramadol.
- Neuropathic pain- treat with gabapentin, pregabalin, tricyclic antidepressants.
- Avoid NSAIDS
- If NSAIDS are indicated, start with a low dose with strict eGFR monitoring.

Bleeding In Chronic Kidney Disease

Important causes of uremic bleeding is platelet dysfunction and abnormal platelet endothelial interactions.[17] Impaired platelet adhesion and aggregation contributes to bleeding. Intrinsic dysfunction of glyoprotein IIb/IIIa leads to impaired platelet adhesion. Altered release of adenosine diphosphate, decreased prostaglandin metabolism, increased nitric oxide and abnormal platelet cytoskeletal assembly are also additional factors for risk of bleeding.

Anemia is also a contributor for platelet dysfunction, the possible explanation is that normally RBC's primarily occupy the center of the vessel, while the platelets along the endothelial surface. This allows the platelets to adhere to the endothelial surface to form a platelet plug at sites of endothelial injury. In anemia the platelets are more dispersed and impair their adherence to the endothelium. A uremic toxin guanidinosuccinic acid which is a precursor for Nitric Oxide increases the levels of cyclic GMP, which reduces the levels of thromboxane A2 and ADP levels which impairs platelet aggregation.

Treatment [18]

- Heparin free dialysis.
- Desmopressin (DDAVP) – for acute treatment of bleeding.
- Correction of anemia.
- Infusion of cryoprecipitate.

Shortness of Breath In CKD

In CKD the total body content of water is increased as also sodium levels. There is disruption of glomerulo-tubular feedback which leads to sodium retention and ECF volume expansion.[19] One another reason is metabolic acidosis due to deranged electrolyte clearance in CKD. Heart failure is also a important contributor to dyspnoea. This is secondary to cardiomyopathy, myocardial infarction or left ventricular hypertrophy. Heart failure may be due to systolic or diastolic dysfunction or both. Advanced CKD presents with pulmonary edema attributed to increased permeability

of alveolar capillaries due to uremia. Other contributing factors for dyspnea are anemia, hypertension and sleep apnea.

Treatment [19]

- Salt and fluid restriction.
- Diuretic therapy.
- Timely hemodialysis.
- Adequate control of hypertension.

Nausea And Vomiting In CKD

Nausea and vomiting in CKD are manifestations of uremic gastropathy leading to histopathological abnormalities in the upper GI tract.[20] Uremia may also lead to uremic fetor. Mechanism of nausea is attributed to hypergastrinemia, acid abnormalities and GI dysmotility. The levels of gastrin and cholecystokinin are increased. The mechanism for hypergastrinemia is reduced renal clearance and neutralization of gastric acid by ammonia results in a feedback excessive production of gastrin. Gastric mucosa becomes susceptible for colonization of H.pylori as the urea in gastric mucosa is high in uremic patients. Other metabolic factors like hyperkalemia and metabolic acidosis also contributes to nausea in CKD.

Treatment [20]

- Correction of uremia.
- H-2 blockers- Ranitidine is the preferred drug.
- Correction of electrolyte imbalance and metabolic acidosis.

Sexual Dysfunction In CKD

Chronic kidney disease is associated with impaired spermatogenesis and testicular damage[21]. It leads to decreased spermatogenic activity, damage to seminiferous tubules and atrophy of Sertoli cells. Uremia leads impaired gonadal steroidogenesis with reduced testosterone levels. This diminished testosterone feedback leads to elevated FSH and LH levels.

Treatment [22]

- Bromocriptine – if increased serum prolactin.
- Replacement of testosterone.
- Zinc supplementation - zinc deficiency causes gonadal failure.
- Phosphodiesterase inhibitors - effective for erectile dysfunction.

Conclusion

Most of the symptoms in CKD are due to ongoing inflammatory process and dysregulation of immune system. Extended research on pathophysiology of the disease process and targeted symptom management is needed. Achieving target blood pressure, correcting anemia, metabolic acidosis and renal replacement therapy are all mandatory in the treatment of CKD. A focus on symptom management will provide a good quality of life and reduce unforeseen complications.

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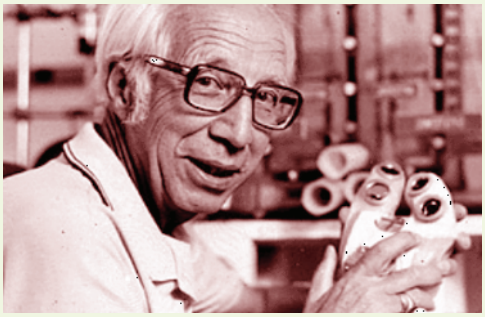
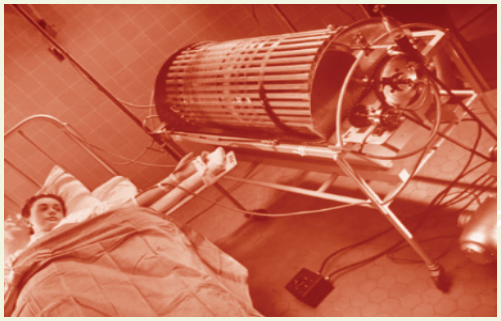


Dr Willem Kolff
Known as the Father of Haemodialysis



He succeeded in extracorporeal Hemodialysis by Rotating drum kidney (1945) in acute renal failure patients following trauma or poison.

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