


Review Article

Complications of Chronic Kidney Disease: Narrative Review

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Abstract

Chronic kidney disease (CKD) is associated with several adverse clinical outcomes, such as cardiovascular events, kidney failure requiring renal replacement therapy, mortality, and poor quality of life for survivors in general. CKD is a slow and progressive loss of kidney function over several years and may ultimately lead to the development of kidney failure. CKD has become a serious public health issue. Although cardiovascular disease, family history of CKD, and certain ethnic and racial backgrounds are important predictors of CKD risk, they do not contribute significantly beyond the scope of diabetes, hypertension, and older age. The number of CKD patients will continue to rise, reflecting the growing elderly population and increasing numbers of patients with diabetes and hypertension. As the number of CKD patients increases, primary care practitioners will be confronted with the management of the complex medical problems unique to patients with chronic renal impairment. As well documented in the literature, the nephrologist rarely manages the medical needs of CKD patients until renal replacement therapy is required. Whereas the symptoms of CKD in diabetes are few, many risk factors and biomarkers can be used to identify individuals at high risk for developing this condition. This article highlights the effect of risk factors and complications associated with chronic kidney disease at its various stages.

Keywords: Chronic kidney disease, Complications, Risk factors.

مضاعفات مرض الكلى المزمن: مراجعة سردية

الخلاصة

يرتبط مرض الكلى المزمن (CKD) بالعديد من النتائج السريرية الضارة، مثل الأزمات القلبية الوعائية، والفشل الكلوي الذي يتطلب العلاج ببدائل الكلى، والوفيات، وسوء نوعية الحياة للناجين بشكل عام. مرض الكلى المزمن هو فقدان بطيء وتدرجي لوظائف الكلى على مدى عدة سنوات وقد يؤدي في نهاية المطاف إلى تطور الفشل الكلوي. أصبح مرض الكلى المزمن قضية خطيرة تتعلق بالصحة العامة. على الرغم من أن أمراض القلب والأوعية الدموية، والتاريخ العائلي لـ CKD، وبعض الخلفيات العرقية هي مؤشرات مهمة لخطر مرض الكلى المزمن، إلا أنها لا تساهم بشكل كبير خارج نطاق مرض السكري وارتفاع ضغط الدم والشبوحية. مع زيادة عدد مرضى الكلى المزمن، سيواجه ممارسو الرعاية الأولية إدارة المشاكل الطبية المعقدة الفريدة للمرضى الذين يعانون من اختلال كلوي مزمن. بالإضافة إلى التوثيق الجيد في الأدبيات، نادراً ما يدير أخصائي أمراض الكلى الاحتياجات الطبية لمرضى الكلى المزمن حتى يصبح العلاج ببدائل الكلى مطلوباً. في حين أن أعراض مرض الكلى المزمن لدى مرض السكري قليلة، يمكن استخدام العديد من عوامل الخطر والمؤشرات الحيوية لتحديد الأفراد المعرضين لخطر كبير لتطور هذه الحالة. تسلط هذه المقالة الضوء على تأثير عوامل الخطر والمضاعفات المرتبطة بأمراض الكلى المزمنة في مراحلها المختلفة.

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INTRODUCTION

Chronic kidney disease (CKD) is a global general medical issue. It is one of the leading causes of morbidity and mortality worldwide and is increasingly recognized as a global public healthcare challenge, especially in developing countries [1]. In addition, the prevalence of renal replacement therapy (RRT) for end-stage kidney disease (ESKD) has increased tremendously since its introduction in the 1960s [2]. International comparison of CKD prevalence is challenging due to the different methods employed for the assessment of kidney dysfunction, such as decreased estimated glomerular filtration rate (GFR), proteinuria, hematuria, uncontrolled hypertension, pain, e.g., loin pain, burning on micturition, dyspnea on exertion, peripheral edema (pitting edema to extremities) and the use of different definitions of CKD [3]. Chronic kidney disease has not been included in the major chronic disease control strategies at international, regional, and/or national levels. The progressive nature of CKD, the associated cardiovascular morbidity and mortality, and the ensuing end-stage kidney disease place a considerable burden on global healthcare resources. A better understanding of CKD-related complications may help optimize the diagnosis, prevention, and management [1]. Prior to the introduction of the Kidney Disease Outcomes Quality Index (KDOQI) guidelines in 2002, there were numerous definitions of CKD in use. Many of these definitions were not well understood by patients and the lay public due to the use of the word renal and its Latin and Greek roots. Hsu and Chertow enumerated the different names used for CKD from abstracts submitted to the American Society of Nephrology (ASN) meetings in 1998 and 1999 and from articles indexed in Medline. They noted 23 different terms used to describe reduced GFR states and many different and overlapping definitions of kidney failure using serum creatinine, creatinine clearance, or GFR [4]. The term CKD is used worldwide to mean any form of kidney disease that continues for more than a few months [5]. In addition, CKD is defined based on the presence of kidney damage or reduced GFR, which is considered the best overall index of kidney function. The World Health Organization (WHO) (2015), and Kidney Disease: Improving Global Outcomes (KDIGO) (2018) defined CKD as abnormalities of kidney structure or function, present for more than three months, with health implications. The key elements of this definition include chronicity (>3 months), presence of kidney damage, decreased GFR, and implications for health [6,7]. National Kidney Foundation, (2020) guidelines define CKD as irreversible kidney damage or decreased kidney function for at least three months, ultimately affecting all kidney functions. Kidney damage is determined by any one of the following findings: persistent proteinuria, pathologic kidney abnormalities, other urine abnormalities, e.g., imaging abnormalities,

renal hematuria, and GFR <60 mL/min/1.73 m² on two occasions separated by ≥ 90 days, and that is not associated with a transient, reversible condition such as volume depletion [6]. Hemodialysis (HD) is the major treatment option for end-stage kidney disease (ESKD) patients. With the increase in the number of maintenance hemodialysis patients, debilitating conditions of muscle wasting and atrophy have become one of the biggest concerns for patients with CKD. Hemodialysis and transplantation cost about 2–3% of the annual healthcare budget in high-income countries. Most people with renal failure in low and middle-income countries do not have adequate access to life-saving dialysis and kidney transplantation [7].

Epidemiology

Around the world, many people lack access to renal replacement therapy, and millions of people die each year from kidney failure, often without supportive care. However, the global chronic kidney disease patient population is increasing rapidly, especially in low and middle-income countries. Hemodialysis is also expensive, and the current recommendations suggest that low- and middle-income countries should give hemodialysis the lowest priority if they want to set up a kidney care program [8]. The rising incidence of chronic diseases is one of the noticeable occasions in this century that societies and health staff have confronted, and people's health behaviors and habits significantly affect its pervasiveness. Unresolved CKD could ultimately lead to end-stage renal failure, which is a chronic disorder that arises when 95% of the kidney's function is destroyed [9]. Worldwide, there is a large variation in the epidemiology of both CKD and RRT [10]. The burden of CKD is also prominent and shows the fastest growth in low-income and middle-income countries. Disparities in access to RRT also exist [2]. Acute kidney injury (AKI), which may eventually develop into CKD or kidney failure, affects approximately 13.3 million people each year worldwide. Between 5.3 and 10.5 million people need dialysis or transplantation, yet many do not receive treatment due to financial barriers or lack of resources [11]. In 2015, an estimated 2.3-7.1 million people with CKD died without being able to afford renal replacement therapy (RRT). Hemodialysis access is highly inequitable within low- and middle-income countries. The global incidence of CKD increased from 19 million in 1990 to 33 million in 2015 [12]. An estimated 80% of this burden occurs in low- or middle-income countries and 25% in people younger than 60 years. Chronic kidney disease occurs with a lower incidence in high-income countries [13]. The important fall in this incidence in these countries matches the rise in the treatment of this disease as well as the fall in the prevalence of contributory risk factors. In contrast, the occurrence of CKD in low income countries increases by about 20% per year; for example, according to the report published by the Iraqi ministry of health in 2018, increase in kidney

diseases in Iraq by 20% in that year. The prevalence of hemodialysis varies widely across South Asia, with relatively high prevalence and rapid growth in India and lower prevalence in Afghanistan and Bangladesh [14]. The important rise in CKD incidence in developing countries matches more population exposure to physical inactivity, high blood pressure, smoking, diabetes, and a high salt fatty diet with less fruit and vegetable intake [15].

Risk factors

The natural risk factors associated with CKD development are diabetes and hypertension, known as hypertensive nephrosclerosis (severe type). The main symptom is an increase in the concentration of albuminuria, and the second is diabetic glomerulosclerosis (the leading cause of CKD in many countries). Other symptoms include a decrease in GFR, the emergence of hypertension, and nephrotic syndrome; the possible external causes for CKD progression are etiologic factors, i.e., kidney poisoning due to nephrotoxics; this type of CKD is known as CKD due to unknown etiology (CKDu). The most familiar CKD associated with occupational or environmental exposure is chronic interstitial nephritis due to excessive exposure to lead, cadmium, aristolochic acid, melamine, and diethylene glycol. CKDu caused by lead is known as chronic glomerulonephritis [16]. Several chronic diseases result from a shortlist of risky behaviors such as smoking and tobacco use, poor nutrition that includes diets low in vegetables and fruits, high sodium, excessive alcohol take, and lack of physical activity [17]. There are five important risk factors for CKD, including diabetes, hypertension, physical inactivity, high salt intake, and smoking. Other risk factors include a family history of kidney disease, age (over 60 years), cardiovascular disease, obesity, race or ethnicity, autoimmune diseases, and polycystic kidney disease. Several studies have shown an association between eating red meat, poor physical activity, CKD development, and increased mortality in people with CKD [18]. Having too little sleep and a disrupted sleep pattern is associated with a higher risk of progression in patients with CKD [19]. Unfortunately, only a few studies have investigated the impact of these and other lifestyle measures on kidney outcomes. A systematic review by Elihimas *et al.* described the effects of salt reduction on both hypertension and proteinuria in people with CKD [20], whereas another review has reported on the association between smoking cessation and kidney function. There is a need for these kinds of studies using hard renal outcomes, such as the start of renal replacement therapy [21]. The prevention of important risk factors may stop or delay the development of CKD and its complications, keeping in mind that lowering one risk factor for CKD may also affect the other risk factors for CKD [22]. It is worth mentioning that the effect of the public health policies targeting non-communicable diseases (NCDs) may likely differ among countries caused by

substantial international differences in the prevalence of CKD, the prevalence of the risk factors of CKD.

Pathophysiology of CKD

The pathophysiology of CKD is not yet clearly understood, but it involves the gradual loss of nephrons, and the renal mass progressively gets smaller. The kidneys have a remarkable ability to adapt to the loss of nephron mass. Symptomatic changes resulting from increased creatinine, urea, potassium levels, and salt and water balance alterations usually do not become apparent until renal function declines to less than 25% of normal when adaptive renal reserves have been exhausted [23]. In the early stages of CKD, there can be significant damage to the kidneys, and the unaffected nephrons compensate until they become damaged. The patient may remain asymptomatic during the initial phase [24]. During the last stages of CKD, the glomerular filtration rate is greatly reduced, and most of the nephrons are damaged. During which the patient may present with symptoms of CKD [25]. The damage to the kidneys is thought to be caused by prolonged acute inflammation that is not organ-specific and thus has subtle systemic manifestations [26]. The major contributors to chronic renal failure are thought to be: diabetes mellitus 30%, hypertension 24%, glomerulonephritis 17%, polycystic kidney disease 4%, chronic pyelonephritis 5%, and unknown 20% [27]. The glomerular filtration rate is the best measure of kidney function. A mathematical formula that uses a person's age, race, gender, and serum creatinine calculates a GFR [28]. The GFR is the volume of fluid filtered through the glomeruli per unit of time. Creatinine clearance is a measure of the amount of creatinine the kidneys are able to clear in 24 hours (Figure 1) [29,30,15]. A blood test to measure creatinine levels can calculate the estimated GFR, known as estGFR. This formula takes body size into account. The average adult body size is 1.73m². A normal GFR is around 100ml/min/1.73m² [15].

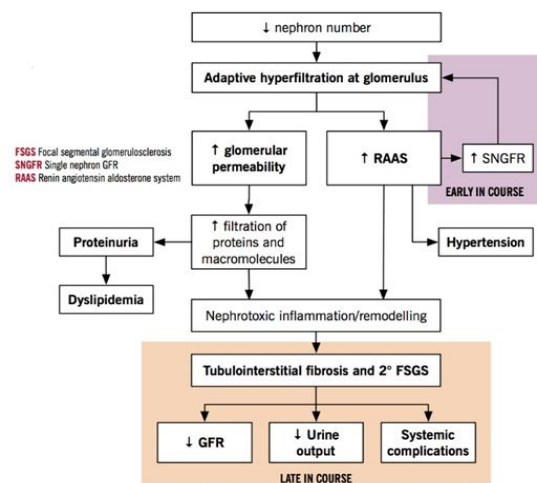


Figure 1: Pathogenesis of chronic kidney disease [15].

CKD-RELATED COMPLICATIONS

Progressive CKD is linked to several complications with higher prevalence and intensity at lower levels of kidney function, which interact with each other (Figure 2). These complications contribute to increased morbidity and mortality and poor quality of life. Some of these complications can be readily defined and quantified (cardiovascular disease, hypertension, anemia, mineral bone disorder, volume overload, electrolytes, and acid-base abnormalities) and may require a specific management approach such as the prescription of erythropoiesis-stimulating agents to correct anemia.

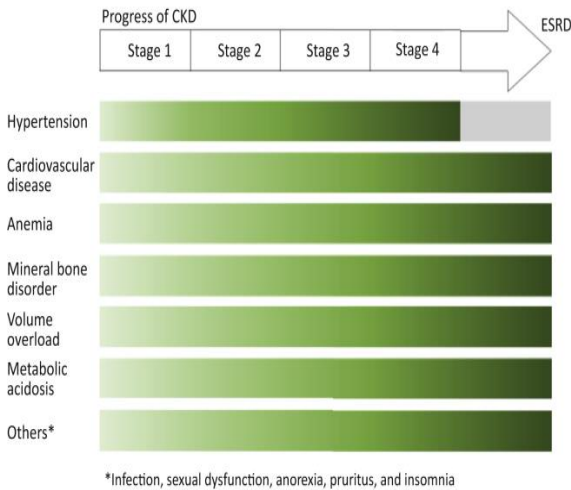


Figure 2: Progressive CKD and related complications by disease stage
CKD, chronic kidney disease; ESRD, end-stage renal disease.

Other less well-defined complications with less distinct pathogenesis, such as anorexia, fatigue, cachexia, pruritus, nausea, and sexual dysfunction, may manifest as complex symptoms often associated with advanced CKD. It has been recognized that the complications of CKD are being relevant to the global burden of poor health caused by CKD [1]. According to the International Society of Nephrology (ISN) 2018, the effects of kidney failure vary from person to person based on the stage of chronic kidney disease. When a kidney is damaged, the loss of normal function of part of the body may occur [30]. The kidney plays a critical role in the body's homeostasis, and many vital body functions depend on the proper functioning of the kidneys. Moreover, it controls the amount of sodium, potassium, phosphorous, calcium, and other chemicals in the body [31]. Kidney has a series of endocrine functions like the production of renin, erythropoietin, and activation of vitamin D [32]. Renal failure can affect almost all parts of the body, causing serious clinical complications.

Cardiovascular problems

Chronic kidney disease carries a five- to ten-fold higher risk of developing cardiovascular disease compared to age-matched controls [33]. Cardiovascular complications are the main reasons

for death in a patient with CKD, with mortality rates ranging from 30.4% in healthy patients to 56% in people with diabetes over 60 years of age. Cardiac hypertrophy includes a larger size of the right ventricle and left atrium, higher left ventricular mass, and coronary artery disease are reported in 30 to 70% of hemodialysis patients. For example, the risk of mortality from CVD is 8.1-fold greater in a patient with CKD stage G5 A3 (eGFR < 15 ml/min per 1.73 m² and urinary albumin-creatinine ratio > 300 mg/g) than in a reference population without kidney disease. While the risk of conventional atherosclerotic cardiovascular events increases with CKD, the most increased risk is attributable to non-atherosclerotic pathologies, such as left ventricular hypertrophy with diastolic and systolic dysfunction, and valvular disease, and arterial calcification. These pathologies can manifest as atrial and ventricular dysrhythmias, heart failure, and sudden death [34]. While it is generally accepted that the treatment of traditional cardiovascular risk factors, such as elevated cholesterol and hypertension, is efficacious in the CKD population, particularly in patients with CKD stages 1 to 3, there are additional risk factors to consider in CKD patients, most of which are considered to be CKD complications. For example, mineral and endocrine disturbances that reflect CKD-mineral bone disorder, such as phosphate retention, elevated levels of fibroblast growth factor 23, and disturbances in Klotho metabolism (Klotho is an anti-aging single-pass membrane protein predominantly produced in the kidney), may contribute to cardiomyopathy and vasculopathy. Improvements in our understanding of the factors that contribute to cardiovascular disease (CVD) associated with CKD and identification of additional therapeutic targets, along with efforts to control blood pressure and increased use of lipid-lowering therapies, could ultimately lead to a global reduction in the burden of CVD attributable to CKD [1].

Hypertension

Hypertension remains one of the most damaging complications of CKD. It is thought to accelerate the progressive decline in kidney function, cardiovascular diseases (CVD), and related mortality. Both detection and control of high blood pressure are frequently suboptimal, and improvements could directly help patients. The Systolic Blood Pressure Intervention Trial provided important information about the effects of a more stringent lowering of systolic blood pressure to a target of <120 mm Hg that may be relevant to CKD patients; although, this trial excluded high-risk subjects with CKD, proteinuria, or diabetes. Lifestyle modifications, such as weight loss and dietary salt restriction may also improve blood pressure control. Such interventions can be lower in cost than pharmacological therapies and have the potential to affect outcomes, such as heart failure and stroke, in both developed health care systems and low- and middle-income countries (LMICs). Since many anti-hypertensive agents are available and

affordable in LMICs, one feasible goal would be to improve the control of high blood pressure complications in CKD patients, aiming to achieve target ranges in many patients. Such a goal can be attained globally, and its impact is easily measurable [35]. Hypertension is reported by 63-86% of HD patients presenting higher values on systolic (16%) and diastolic (10%) pressure. The American Heart Association (AHA) gives a blood pressure target of < 130/80 mmHg for patients with high coronary artery disease risk, including patients with CKD. Guidelines from the WHO and the International Society of Hypertension (ISH) suggest the same goal blood pressure < 130/80 mmHg for patients with renal insufficiency, diabetes, and established heart disease [36].

Neurologic complications

Neurologic problems arise in hemodialysis patients as a complication of treatment, from metabolic derangements or disordered homeostasis [37]. Uremic encephalopathy may appear when GFR decreases to 10% of the normal value and typically leads to mental fatigue, confusion, impaired consciousness, lethargy, difficulty concentrating, and myoclonic twitching of distal muscle groups, pre-terminally, coma [38,39]. The severity of uremic encephalopathy correlates with the extent and kinetics of the accumulation of uremic toxins, and studies have shown that many of the abnormalities found in uremic encephalopathy and calcium-induced brain abnormalities are due to kidney failure [40]. Other common abnormalities are the syndrome of neurologic dysfunction, which appears in the last part of hemodialysis or shortly afterward when uremia is corrected rapidly. Chronic dementia in people on dialysis is caused by aluminum poisoning or progressive cerebrovascular illness due to widespread atheromatous plaques that predispose individuals to develop multi-infarct dementia; it is an additional neurological complication of CKD. It is believed that brain swelling causes headaches, agitation, vomiting, nausea, and confusion [38]. The occurrence of subdural hematoma in patients under hemodialysis increases by more than 20-fold when compared with the general population. These changes are connected with an increased risk of intracranial hemorrhage and polyneuropathy. It is an important risk for patients on long-term hemodialysis [41].

Metabolic complications

Many metabolic disturbances are associated with CKD. First, carbohydrate metabolism is altered in renal failure due to glucose intolerance produced by resistance to insulin-mediated glucose uptake in skeletal muscle [42]. Uremic skeletal muscle presents with reduced glycolysis and increased glucose content, with glycogen deposition being more prominent in Type II fibers. Second, there are complex effects on lipid metabolism, including a reduction in the catabolism of lipoproteins, which results in an increased concentration of very-low-

density lipoproteins (LDL) and triglycerides, and a decrease in high-density lipoproteins (HDL) [43]. Although carnitine seems to affect skeletal muscle growth and its deficiency negatively correlates with exercise performance, Rogerson *et al.* could not demonstrate that L-carnitine supplementation improves muscle function or plasma lipid profile. Chronically uremic patients who are receiving any form of uremia therapy present lean tissue depletion and reduction of total body amount of albumin and other proteins. Factors contributing to net proteolysis in CKD are metabolic acidosis, impaired protein synthesis, malnutrition, and decreased energy intake [44].

Mineral bone disorder (Osteodystrophy effects)

Renal bone disease, characterized by abnormal calcium/phosphate metabolism, results from the combination of secondary hyperparathyroidism, decreased metabolites of vitamin D, and hyperphosphatemia. Calcitriol deficiency caused by the decreased endocrine function of the kidney results in hypocalcemia. Other factors contributing to hypocalcemia are reduced calcium resorption in the intestine by insufficient active vitamin D and partial resistance of the skeleton to release bone minerals and calcium [45].

All these alterations are responsible for the appearance of *osteitis fibrosa* (increased bone turnover that results in the rarefaction of trabeculae in the bone), osteomalacia (decreased mineralization of the bone matrix), adynamic bone disease (decreased bone turnover that predisposes to hypercalcemia), osteopenia or osteoporosis. This complex group of disorders is poorly understood, and despite a considerable body of preclinical data, very few developments have been translated to clinical applications. High blood phosphate levels, vitamin D deficiency, and secondary hyperparathyroidism can be monitored and treated; although, the true benefits of interventions to correct these abnormalities are unproven. The role of low-cost calcium-based phosphate binders is controversial because of the potential of these agents to exacerbate tissue calcium deposition. A pragmatic approach based on our current level of knowledge would be to increase the availability of phosphate binders, nutritional vitamin D, and analogs of 1,25-dihydroxy vitamin D to alleviate the recognized symptoms of tertiary hyperparathyroidism [46].

Gastrointestinal complications

A variety of gastrointestinal system disorders are commonly found in patients with CKD. Anorexia and nausea, associated with inadequate dialysis or hypotension, are commonly found in uremic patients, both leading to decreased caloric intake and malnutrition [47]. Hepatitis C is common in renal care units because of exposure to blood transfusions [48]. Constipation is one of the common gastrointestinal disorders in patients with CKD partly because of their sedentary lifestyle, fluid intake and low fiber,

concomitant medications, and multiple comorbidities (e.g., diabetes) [49].

Uremic symptoms

The uremia syndrome encompasses a variety of symptoms: anorexia, fatigue, cachexia, pruritus, nausea, restless leg syndrome, sleep disturbances, and sexual dysfunction. Pruritus is common and may have a negative impact on quality of life. The cause is not well understood but probably due to the presence of certain urinary toxins in the skin. It is important to distinguish between urinary bleeding and bleeding caused by other diseases because management can vary. Topical therapy and antihistamines are accessible to LMIC. Other agents, such as gabapentin and opioid receptor modulators, are likely to be of more limited availability. The treatment of hyperparathyroidism and hyperphosphatemia may effectively relieve pruritus in at least some patients. Restless leg syndrome is a related clinical diagnosis that can be debilitating. Although this problem is recognized in individuals with normal kidney function, it is much more prevalent in CKD and dialysis patients. Both pruritus and restless leg syndrome are associated with sleep disturbance, depression, poor quality of life, higher cardiovascular morbidity, and higher mortality. Pathophysiology is not known, but it may reflect the general state of poor health. The symptoms of restless leg syndrome can be relieved by exercise and several pharmacologic agents, including gabapentin, dopaminergic modulators, serotonin antidepressants, and lithium. Although data on the efficacy of these interventions are limited, they are accessible in many LMICs [50].

Other alterations: Lungs, Skin, and Joints

The kidney and lung perform a closely interrelated function. Pulmonary manifestations appear in CKD patients because they are prone to develop pulmonary edema with relatively small increases in the extracellular fluid due to increased capillary permeability in uremic syndrome. Relatively few studies have investigated pulmonary function alterations in CKD patients undergoing hemodialysis treatment, and conflicting results have been reported [51]. Concerning the skin, various specific and nonspecific skin abnormalities are observed in patients with CKD. Patients with chronic kidney disease present a yellow-brown pigmentation in sun-exposed areas of their skin, attributed to the retention of melanocyte-stimulating hormone, vegetable-derived lipochrome and carotenoids, and iron. Pruritus, an exasperating symptom associated with xerosis (dry skin) and warm skin, has a multifactorial origin that includes raised phosphate product sensitivity to histamines, hyperparathyroidism, peripheral polyneuropathy, and uremia itself [52]. The potential complications or health problems that occur after chronic renal failure (CRF), reported that “up to 95% of all patients ESKD experience one or more medical or nephrological complications” [53]. The progression of CKD is associated with several

serious complications [54]. Most of the medical complications after chronic kidney disease develop within a few weeks of kidney damage (Figure 3).

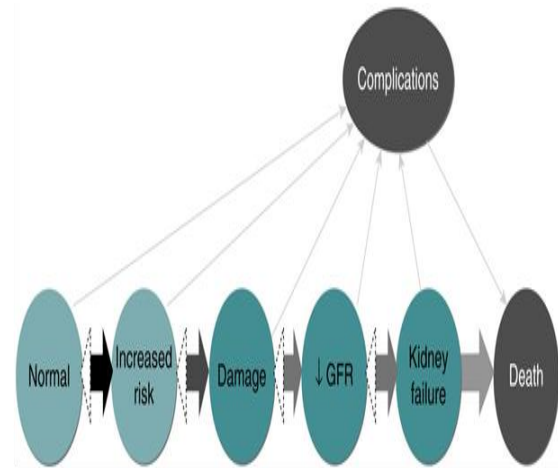


Figure 3: Conceptual model of renal decline [15].

Conclusion

Chronic kidney diseases are an important health problem in many societies. Understanding the risk factors and implementing screening of at-risk populations will increase early detection and initiate treatment of modifiable risk factors. Furthermore, early detection of CKD risk factors may reduce the economic burden of kidney replacement therapy costs (55). Patients with CKD present several complex management issues to health care providers. Interventions reduce the morbidity and mortality of these patients. With early identification and treatment of anemia, renal osteodystrophy, uremic malnutrition, hyperlipidemia, and cardiovascular disease, primary care physicians and nephrologists can significantly extend and improve patients' lives with chronic renal disease.

Recommendation

A good approach for identifying chronic kidney disease is to screen people. Current recommendations suggest screening individuals with structural renal tract diseases, hypertension, CVD, diabetes, family history of kidney disease, and autoimmune diseases with the potential for kidney involvement during routine primary health encounters. With the help of engineering techniques, we can design predictive control systems for assessing and preventing CKD.

Conflict of interests

The author declares no conflict of interests.

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