Review Article

Kidney Diseases

Kidney Dis 2020;6:85–91
DOI: 10.1159/000504622

Received: February 12, 2019
Accepted after revision: October 30, 2019
Published online: December 18, 2019

Detailed Review of Chronic Kidney Disease

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Keywords
Chronic kidney disease · Glomerular filtration rate · Albumin creatinine rate · Acute kidney injury · Cystatin C

Abstract
Background: Nephropathy problems in the Udhanam region of Andhra Pradesh in India have motivated researchers to investigate the various factors related to chronic kidney disease (CKD). Initially, studies came across the markers of identification of CKD, i.e., glomerular filtration rate (GFR) and albumin creatinine rate, as global markers of identification. Cystatin C (Cys C) and its reciprocal (1/Cys C) are used to calculate GFR. This is a very easy method compared to the more accurate methods such as radiolabelled tracer clearances, which are invasive, may involve radiation, and require several hours to perform, e.g., 99-diethylene triamine pentaacetic acid (^{99m}Tc-DTPA) and ^{51}Cr-EDTA. This article provides the causes (or risk factors), symptoms, and complications of CKD in a clear manner such that even common people can easily understand. Once a patient is detected and proved to be affected by CKD then the patient as well as the caretakers, including doctors, must follow some constraints. Thereby it is possible to prevent CKD progression in the patient. Modern methods are needed to prevent the pathogens which are responsible for CKD. ***Summary:*** With the help of various engineering techniques one can easily design controllers to assess as well as to prevent CKD permanently. The easiest procedure for identifying CKD is to screen people. Current recommendations suggest screening of individuals with diabetes, hypertension, cardiovascular disease, and family history of kidney diseases in the course of routine health checkups. Much work has been done in medical sciences in the area of CKD, but there is still scope for further research. From the recent studies, advanced tools such as data mining, etc., are considered to be the current trend in the area of CKD. ***Key Message:*** From this article, the authors propose that patients who are already affected by urinary tract infection, acute kidney injury, and a family history of CKD should be examined via some basic tests for the presence of CKD.

Introduction

Udhanam is a greenish region with rich flora and fauna consisting of many villages in various mandals in the district of Srikakulam, Andhra Pradesh, India. Ganguli [1] reveals that large numbers of farmers in agronomy are

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affected by chronic kidney disease (CKD), which differs from the nephropathy diseases [2]. Gadde et al. [3] have provided the integer numbers regarding the affected people and the national prevalence of CKD. Literally, chronic means long-lasting, and CKD has been defined based on the presence of kidney damage and its structure or decreased kidney function or kidney damage and diminished function that lasts longer than 3 months [4, 5]. CKD is a serious public health issue with a universal prevalence of 13.4% and a mortality rate of 1.2 million (approx.) per year. To understand the aetiology of CKD, the physical and chemical causative factors such as soil, water, food, heat stress, pesticides, and environmental samples have been analysed by different research groups, but failed to provide the clues about the exact causative factors. It has been observed that the majority of people who are affected by this kidney disease in the Uddanam region are agricultural labourers. In 2013, this CKD of the Uddanam region was named as Uddanam nephropathy at the International Congress of Nephrology in China. Parvati Sai Arun et al. [6] came up with a past studies report which stated that there is a relationship between alteration of the gut microbiome (biological factor) and renal failure. The kidney is an important regulator of homeostasis by filtration, re-absorption, secretion, synthesis, and degradation of metabolites in various pathways.

Serum metabolites which are associated with all-cause mortality in CKD – as given by a modification of diet in renal disease (MDRD) study – are glutamine, α-ketoglutarate, ribonate, fumarate, allantoin, and γ-glutamyl glutamine. These metabolites are part of organic molecules in amino acids, carbohydrates, etc., and are related to events in outcome studies among diabetic patients. According to the literature, the mortality rate is higher in kidney transplantation compared with CKD due to cardiovascular disease (CVD) and also comparisons made between diabetic and non-diabetic recipients by which the impact of diabetes on survival of renal transplant recipients has lessened over decades [7].

Methods of Assessment and Literature

Kidney damage can be assessed by albumin creatinine rate (ACR); albuminuria is one of the identifiers of kidney function in a timed urine collection. Udhayarasu et al. [8] have stated that one of the reasons for CKD, i.e., excretion of proteinuria, is due to the intake of cooked meat or increased intake of protein or any kidney infection. Basically, the ACR in young adults is <10 mg/g. The urine ACR categories are as follows: ACR 10–29 mg/g indicates high/normal risk, 300 mg/g high risk, >300 mg/g very high risk, and when ACR is >200 mg/g symptoms of nephrotic syndrome (low serum albumin, oedema, high serum cholesterol) appear. The glomerular filtration rate (GFR) is helpful to estimate the performance of the kidney function. Glomeruli are microscopic refiners in the kidney that filter out waste from the blood. Insulin is used as an exogenous filtration marker but it is costly and inconvenient, so the alternative method used to assess kidney performance is by the endogenous markers, creatinine and cystatin, because these are highly available and give accurate results. The parameters for calculating GFR are mainly age, gender, ethnic origin, and body size. GFR can be classified into five stages with increasing risk from stage 1 to stage 5: (1) more than 90 mL/min/m^2, (2) 60–89 mL/min/1.73 m^2, (3) 30–59 mL/min/1.73 m^2, (4) 15–29 mL/min/1.73 m^2, and (5) 15 mL/min/1.73 m^2. When GFR is <15 mL/min/1.73 m^2, this is termed kidney failure, at which point there is an urgency for kidney treatment either by dialysis or transplantation. Treatment given to patients at this stage is called end-stage renal disease treatment [9]. Cystatin C (Cys C) is a cationic non-glycosylated low-molecular-weight (13,389 kDa) cystine proteinase. This compound is stably produced by all nucleated cells in constitutive fashion and meets the criteria for a GFR marker. Use of serum Cys C value or its reciprocal (1/Cys C) as a measure of GFR was proposed in 1985. Cys C has a greater correlation coefficient than serum creatinine. Cys C and its reciprocal (1/Cys C) are used to calculate GFR as it is a very easy method compared to the more accurate methods such as radiolabelled tracer clearances, which are invasive, may involve radiation, and require several hours to perform, e.g., 99-diethylene penta-acetic acid or (^{99m}Tc-DTPA) and ^{51}Cr-EDTA [10]. It was discovered via signal analysis that the activin receptor is stimulated in the skeleton, vasculature, heart, and kidney during CKD [11].

Risk Factors

Kaur and Sharma [12] informed us that in the 21st century there are many types of booming in an individual's life due to the wide variety of changes taking place due to hereditary issues and lifestyles. Our study provides additional evidence that low HDL cholesterol and high triglyceride levels are associated with an increased risk of CKD and microalbuminuria. Experimental studies on animals indicate that obesity is associated with a slowing

down of renal activity. Our analysis indicated that abdominal obesity is characterized on the basis of waist circumference, i.e.,102 cm or more in men and 88 cm or more in women was associated with 2-fold increase in odds of CKD. This evidence advises that abdominal obesity can be an important modifiable risk factor for CKD in addition to diabetes and hypertension, which have been cited in earlier research [13]. A classic western starvation and absorption of high sodium and potassium are undoubtedly associated with an increase in microalbuminuria and a rapid decline in kidney activity [14].

The natural risk factors in the body associated with the development of CKD are diabetes and hypertension, known as hypertensive nephrosclerosis (it is severe). The main symptom is a concentration of albuminuria increases and the second one is diabetic glomerulosclerosis (main cause of CKD in many countries); symptoms are slowly worsening albuminuria, decrease in GFR, breakout of hypertension, and nephrotic syndrome. According to Weaver et al. [15] the possible outside causes for the progression of CKD are aetiologic factors, i.e., poisoning of the kidney due to nephrotoxicants; such type of CKD is called CKD due to unknown aetiology (CKDu). The most familiar CKD associated with occupational or environmental exposure is chronic interstitial nephritis; it has been noted due to excessive exposure to lead, cadmium, aristolochic acid, melamine, and diethylene glycol. CKDu caused by lead is known as chronic glomerulonephritis. In this type of kidney disease the healthy kidneys turn into granular contracted kidneys; lead is mainly exposed through lead paints. Exposure to cadmium results in itai-itai (ouch-ouch). In this type of disease the main symptoms are secondary fractures and severe pain, mainly because of toxic rice due to cultivating the paddy fields with polluted water coming from the industries. Exposure to aristolochic acid results in urothelial carcinoma. It is mainly found in the category of Aristolochiaceae plants (Chinese herbal plants used for weight loss). Non-communicable and communicable diseases also cause CKD, such as schistosomiasis, infectious glomerulonephritis, HIV infection, and leishmaniasis [16].

People with acute kidney injury (AKI) (i.e., stones in kidney) usually suffer with great pain so they prefer nonsteroidal anti-inflammatory drugs (NSAIDs) as the first choice of medical treatment. Sometimes apparently quick-and-easy medical treatment creates a serious medical complication and results in CKD [17]. The authors reported about receptors, which are the exogenous binding sites for both synthetic and natural cannabinoids that are used for diversion purposes. They mainly pointed out that the endcannabinoid system (ECS) is present in the kidney and it has recently emerged as an important player in the prognosis of diabetic nephropathy, drug nephrotoxicity, and progressive CKD. The ECS has renoprotective characteristics (because of pharmacological modulations) as seen in experimental animals, raising an aspiration for its future possible utilization for humans. In addition, over the last years there has been a number of reported cases of AKI associated with the use of synthetic cannabinoids that appear to have a higher potency and rate of toxicity than natural cannabis, particularly in young people [18]. Herbs can cause AKI, hypertension, electrolyte disturbances, tubular dysfunction, renal capillary necrosis, urolithiasis, urothelial cancer, and CKD. Herbal causes are taken into account in cases of unexplained kidney disease, especially in a few regions where the consumption of herbal preparations is high. Balkan-endemic nephropathy is associated with people living along the tributaries of the river Danube, where more cases have been reported of chronic interstitial fibrosis; consumption of aristolochic acid due to flour obtained from wheat grown in the fields of contaminated *Aristolochia clematitis* results in aristolochic acid nephropathy. Various disorders directly or indirectly affected due to water can cause kidney disease, e.g., high temperatures frequently lead to water scarcity in many places in tropical regions, which results in dehydration of the human body and finally has a severe impact on the kidneys. Flowing water might be contaminated by heavy industrial toxic metals and organic compounds leached from soil, and grain (seeds) in waterlogged fields can become contaminated with harmful substances. Many water-borne diseases such as, for example, leptospirosis, schistosomiasis, malaria, hantavirus, and scrub typhus can affect the kidneys. Children are particularly affected by AKI because of diarrhoeal diseases. Several cases of CKD of unknown origin have been reported in some areas of Sri Lanka and India. Most of the affected are young male farmers. Clinical presentation resembles that of interstitial nephritis, but histology shows that it is of interstitial fibrosis, interstitial mononuclear cell infiltration, and tubular atrophy. A few years ago, the Sri Lankan Government took a decision to prevent CKD by preventing the contamination of water, food, or both by heavy metals, industrial chemicals, fertilizers, and pesticides. It is strange that in a study funded by the Research and Prevention Committee of the International Society of Nephrology carried out in the Udhanam region of the Srikakulam district (Andhra Pradesh, India), no excess of heavy metals was found in the water [19]. The total volume of the kidney and the rate

of kidney growth are associated with the progression of CKD in autosomal dominant polycystic kidney disease (ADPKD). ADPKD is a severe life-threatening disease occurring due to genes, primarily affecting adults. It is caused predominantly by mutations in 2 genes, PKD1 (which accounts for 80% of cases) and PKD2 (which accounts for 15% of cases). In ADPKD, kidney cysts likely begin from before birth and grow exponentially throughout life. During this time, cysts progressively compress and severely injure neighbouring structures including the vasculature and tubules, causing interstitial fibrosis and inciting inflammation [7]. Stage-wise risk factors for CKD are given below [17].

Various Stage-Wise Risk Factors for CKD

There are 4 main stage-wise risk factors for CKD: (1) susceptibility factors, including family history of CKD, low birth weight, reduction in kidney mass, older age, ethnic origin (black, white, and coloured), and low income or lack of awareness, (2) Initiation factors, including high blood pressure, diabetes, systemic infection, drug toxicity, autoimmune diseases, urinary tract infections, urinary stones, and lower urinary tract obstruction, (3) Progression factors, including smoking, higher level of proteinuria, high blood pressure, and poor glycaemic control in diabetes, and (4) end-stage factors, including late referral, lower dialysis dose, temporary vascular access, anaemia, and low serum albumin level.

Symptoms and Complications of CKD

Webster et al. [4] have mentioned some symptoms of CKD. In brief, they are the appearance of anaemia, cognitive changes, hypertension, gastrointestinal disturbances, shortness of breath, change in kidneys, change in output, itch and cramps, damage to glomerular capillary wall and tube, and also peripheral oedema due to sodium. The complications of CKD are mainly anaemia, bone diseases, CVD, and cancer diseases.

Detection and Management

Nishanth and Thiruvaran [20] stated that those who are affected by CKD are unaware of the medical tests; even if they go for primary health check-ups sometimes it may contain useful information related to CKD. This is not used effectively to tackle the identification of the disease, therefore different medical tests have been investigated to find useful information about CKD. Common spatial pattern and linear discriminant analysis are used first for identifying the key attributes that could contribute to the detection of CKD [20]. Some analyses suggest that haemoglobin, albumin, specific gravity, hypertension, diabetes mellitus, blood glucose, and blood pressure together with serum creatinine are the most important attributes in the early detection of CKD. Regarding the methods of assessment and dialysis types, GFR [7], ACR [21], and Cys C, modification of diet in renal disease (MDRD) [4], CKD-epidemiology collaboration (CKD-EPI), and skin texture [8] are mainly using in many places around the world. With regard to skin texture, this parameter is mainly used in South India because the people of this region belong neither to a white nor black race, i.e., coloured race. Actually, the remaining four methods are based on age, gender, body size, and race (American or African). We have already discussed the GFR and ACR. MDRD is independent of the patient's condition and varies according to the type of CKD. It is rare in India but Western countries are following this method, especially the UK. The MDRD and CKD-EPI equations were developed with ^{125}I-iothalamate clearance as the gold standard, and the CKD-EPI creatinine equations have correction factors for African Americans, the Japanese MDRD equation uses modified inulin clearance, and the Chinese MDRD equation uses mTc-DTPA clearance. In a total comparison study, ^{99m}Tc-DTPA clearance gave 10 mL/min/1.73 m^2 higher values than did insulin clearance [19]. Udhayarasu et al. [8] reported the analysis of CKD based on skin texture, and from that paper the following points are found to be important. First, they compared the skin texture of normal and CKD-affected persons, and in that assessment they considered skin wrinkles as a parameter. Because skin wrinkles are natural occurring due to various factors such as skin dryness, skin thickening, ageing, loss of skin elasticity, and also because of ulcers (past cases) and collagen (that binds muscles and bones with skin).The author used the skin wrinkles as a parameter using the following steps. They first established the correlation between CKD and skin texture; the classification tool using an artificial neural network was built to categorize CKD level based on demographic values and the four-parameter model obtained through skin texture, namely contrast, energy, correlation, and entropy. Later, the authors developed a novel equation which modifies the GFR equation for coloured race like Indians by considering the 4-parameter model. Based on individual skin texture the GFR equation can be evaluated; it requires real-time data. Hence,

demographic and biochemical indices were collected from volunteers of normal and CKD-affected persons [22].

Management

Hladunewich et al. [23] described that women who are pregnant as well as suffering with CKD are difficult for both obstetricians and nephrologists. In this complex patient community pre-pregnancy counselling with respect to risk stratification, optimization of maternal health prior to pregnancy, as well as management of the many potential pregnancy-associated complications are important; the condition remains challenging due to the paucity of large, well-designed clinical studies [23]. In people with an estimated GFR (eGFR) >60 mL/min/1.73 m^2, in whom the cause of CVD is typically atherosclerotic, the proportional effects of statin therapy on vascular events seem to be independent of renal function [5, 7]. However, when eGFR falls below about 30 mL/min/1.73 m^2, a different cardiovascular pathology emerges, with vascular stiffness and calcification, structural heart disease, and sympathetic overactivity contributing to an increasing risk of cardiac arrhythmia and heart failure. Atherosclerotic statin therapy is more effective in patients who are taking dialysis rather than non-dialysis patients [24]. Some cephalosporins might cause hypoprothrombinaemia in patients with renal failure and low vitamin K levels (malnutrition, parenteral feeding) by interfering with vitamin K metabolism if there is no dosage reduction [25]. Quality of care should be taken in 4 primary domains, including (1) monitoring the stage of CKD, (2) cardiovascular risk management, (3) metabolic bone disease and anaemia monitoring, and (4) drug safety. All measures were assessed to allow a minimum of 1 year following the initial diagnosis of CKD prior to assessing clinical performance [26].

Prevention by Using Modern Techniques

Foremost are control of blood pressure preferably with agents that block the renin-angiotensin pathway, lipid-lowering therapy (irrespective of the starting cholesterol concentration), and good glycaemic control (lowers the incidence of major atherosclerotic events in patients with CKD). Correction of acidosis is thought to slow the decline in GFR, but this requires confirmation. An easy approach is to take the optimum intake of salt and protein. Finally, self-management is necessary, and support groups can work to improve the lifestyle and dietary habits of CKD victims. In addition, patients should be aware of the disease, must adhere to treatment, and keep an eye on the indices of glycaemic and blood pressure control. The cost-effectiveness of a self-management intervention for people with stage 3 CKD is currently being investigated in a randomized clinical trial. A multidisciplinary approach is required to develop treatment strategies [19]. The four interventions that reduce CKD progression are blood pressure <140/90 mm Hg, diabetes control, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers for albuminuria and hypertension, and correction of metabolic acidosis. To reduce risks from medications, the level of eGFR must be taken into account during the prescription, and nephrotoxins should be avoided, such as NSAIDs. eGFR <30 mL/min/1.73 m^2 refers to severe albuminuria and AKI. The ultimate goal is to prevent CKD progression, minimize the complications, and promote quality of life [27]. Regarding the renin-angiotensin-aldosterone system (RAAS), ACE inhibitors were the first treatment discovered to be effective in slowing down diabetic nephropathy in 1993 by Lewis et al. [28]. The research followed on animal studies in many laboratories, the most notable one being the study by Zatz et al. [29] in the 1980s. ACE inhibitors and angiotensin II receptor blockers (ARBs) are the standard drugs for primary hypertension and are related to the GFR in CKD. Mostly people were studied with these agents during the state of diabetic nephropathy.

In both diabetes mellitus types 1 and 2, slowing the rate of progressive renal injury with RAAS inhibition has been intimately affiliated with the stabilization or reduction of proteinuria. These factual findings have been demonstrated in patients with micro- and macroalbuminuria. The benefit of RAAS inhibition in subjects with non-diabetic kidney disease without proteinuria is less clear. In certain disease states such as ADPKD, there may be less to no benefit from ACE inhibitors and ARBs despite measurable reductions in proteinuria. It may be aberrant to interpret reductions in albuminuria as a surrogate for developed renal function. Although few authors argue that experimental evidence suggests that proteinuria has direct toxic impacts, currently there is no clear evidence that establishes a cause and effect role for CKD. For this reason, the necessity of the antiproteinuric properties of ACE inhibitors and ARBs is unclear. Metabolic derangements of CKD are taken into account during the prescription and self-management, which include acid base, phosphate, dietary protein, vitamin D, parathyroid hormone, anaemia, and uric acid, [30–32]. Early prediction of CKD is a challenging task for researchers and one

which can be possible by implementing advanced technical tools such as machine learning, artificial intelligence techniques, data mining, etc., some of which have already been implemented in this area of CKD [33–35]. In the study by Murshid et al. [36], the authors proposed novel technical tools such as decision trees, logistic regression, naïve Bayes, artificial neural networks, and data mining tools which are used to build an automated diagnostic system which simplifies the lengthy process in health care. The operation behind the automated diagnostic system is to process the data from the system database and give early predictive automated results which is more precise compared to the traditional diagnostic system. From all these reviews, it is noted that these technical tools will play a vital role in the prevention of CKD.

Conclusion

A good approach for identifying CKD is to screen people, Current recommendations suggest screening of individuals with structural diseases of the renal tract, hypertension, CVD, diabetes, family history of kidney disease, and autoimmune diseases with potential for kidney involvement during routine primary health encounters. In the stream of health sciences not much work has been carried out concerning CKD. Still, there is always hope for better results and there are a number of ways to detect CKD. With the help of engineering techniques we can design predictive control systems for assessing as well as preventing CKD. Finally, data mining has become a current area of research and is considered to be the current trend in the latest technologies all over the world.

Acknowledgements

We thank Prof. Arun Kumar Singh in the Department of Electrical and Electronics Engineering, National Institute of Technology Jamshespur, India, for his invaluable support to us.

Disclosure Statement

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding Sources

The authors have no funding sources to report.

Author Contributions

Yesubabu Kakitapalli and Janakiram Ampolu collected the data and reviewed the literature. Satya Dinesh Madasu and M.L.S. Sai Kumar provided valuable input in the collection of data and drafting the article. All authors read and approved the manuscript and met the criteria for authorship.

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