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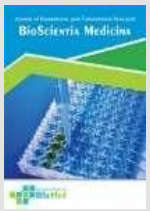

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The Role of Urinary Potassium Examination on the Progressivity of Chronic Kidney Disease: A Narrative Literature Review

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A B S T R A C T

Kidneys play an important role in potassium homeostasis. The important role of the kidneys in maintaining potassium balance is reflected in the high level of potassium disturbances in patients with decreased kidney function, especially patients with severely decreased renal function and patients who have comorbidities, such as diabetes, hypertension, or heart failure. Chronic kidney disease is characterized by abnormalities of kidney structure or function that persist for more than 3 months, have many complex causes, and have a major impact on global health status. There are several methods to measure the amount of potassium intake consumed, including a food frequency questionnaire, dietary recall, temporary urine potassium examination, and 24-hour urine potassium examination. The standard gold measurement for evaluating urinary potassium excretion is through 24-hour urine collection. This literature review aims to describe the role of urinary potassium excretion in assessing the progression of chronic kidney disease.

1. Introduction

Chronic kidney disease has many complex causes and has a major impact on global health status. In addition to causing direct morbidity and mortality, CKD also increases the risk associated with the other three major killers, namely cardiovascular disease, diabetes, and hypertension.[1,2] Based on the 2017 Global Burden of Disease study, there were 697.5 million cases and 1-2 million deaths due to CKD, with a global prevalence of 9.1%.[1] In Indonesia, the prevalence of CKD in the population aged ≥ 15 years, based on the results of the 2018 Basic Health Research, is 0.38%. This figure has almost doubled compared to 2013 (0.2%), and most patients are in the age group 65-74 years (0.82%).[3]

Lifestyle risk factors, such as dietary potassium intake, may influence the development of CKD.[4] Examination of urinary potassium excretion is the easiest method of assessing potassium intake. This urine potassium examination can be done through a 24-hour urine collection which is the gold standard of assessment, or by examining the spot urinary potassium concentration.[5] This literature review aims to describe the role of urinary potassium excretion in assessing the progression of chronic kidney disease.

Definition of chronic kidney disease (CKD)

Chronic kidney disease is defined by the presence of structural or functional abnormalities of the kidneys that persist for more than 3 months, characterized by one or more of the following conditions: glomerular filtration rate (GFR) less than 60 ml/minute/1,73 m^2; albuminuria (urinary albumin ≥ 30 mg per 24 hours or urine albumin-creatinine ratio (ACR) ≥ 30 mg/gr); abnormalities in urine sediment, histology, or imaging suggestive of kidney damage; renal tubular disorders; or a history of kidney transplantation. If the duration of kidney disease is unclear, a reassessment should be performed to differentiate CKD from acute kidney injury (changes in kidney function occurring within 2-7 days) and acute kidney disease (kidney damage or decreased kidney function lasting ≤ 3 months).[6-8]

Epidemiology of CKD

Based on the Global Burden of Study, there were 27.2 million cases and 35,446 thousand deaths in Indonesia due to CKD,[1] and according to the 2018 Basic Health Research, the prevalence of CKD in Indonesia was 0.38%. The highest prevalence was in North Kalimantan (0.64%), age group 65-74 years (0.82%), male gender (0.42%), education no/never attended school (0.57%), and not working (0.48%). The proportion of CKD patients who underwent dialysis was 19.33%.[3] In West Sumatra, the prevalence of CKD in the population aged more than 15 years is 0.40%, the highest is in the 45-54 year age group (0.79%), male sex (0.42%), education is not graduated from SD/MI (0.56%), farmer/farm laborer (0.61%), and lives in rural areas (0.42%). The proportion of hemodialysis in CKD patients in West Sumatra is 15%.[9]

Etiology and risk factors

Chronic kidney disease can occur as a result of the disease process in three locations, namely: pre-renal (decreased renal perfusion), renal (pathology of blood vessels, glomeruli, or tubule-interstitium), and post-renal (obstruction). Impaired fasting plasma glucose, high blood pressure, high body mass index, and high sodium diet are risk factors for CKD found in the global burden of disease study.

Diabetes mellitus is a major cause of CKD and ESRD in both developed and developing countries. Eight percent of patients newly diagnosed with type 2 diabetes mellitus have proteinuria at the time of diagnosis. After the onset of proteinuria, the risk of CKD in the next 10 years is 11%. In patients who do not have proteinuria, the risk of diabetic nephropathy in the next 20 years is approximately 41%. Hypertension has also long been recognized as a risk factor for CKD and end-stage renal disease (ESRD). Systemic hypertension is transmitted to the intraglomerular capillaries causing glomerulosclerosis and loss of kidney function. Decreased kidney function will occur if the patient's blood pressure is not controlled for at least 10 years. Another risk factor for ESRD is obesity. Obesity may contribute to the pathogenesis of kidney damage through inflammation, oxidative stress, endothelial dysfunction, prothrombotic state, hypervolemia, and adipokine disturbances.[10]

Table 1. Risk factors for chronic kidney disease.[6,11]

Diabetes mellitus	Family history of CKD
Hypertension	Obesity
Autoimmune disease	Low birth weight
Nephrolithiasis	Exposure to certain chemicals (lead, cadmium, arsenic, mercury, uranium)
Neoplasia	
Lower urinary tract obstruction	Exposure to certain drugs
Urinary tract infection	Smoking
Systemic infection	Ethnicity (Blacks, American Indians, Asians, Pacific Islanders)
Genetic	
Dyslipidemia	Old age
History of acute kidney injury	Low income or education

Based on the Genome-Wide Association study (GWA study) conducted in Europe to identify the loci involved in cases of CKD, It is known that mutations in uromodulin (which encodes the Tamm-Horsfall protein in urine) are associated with impaired renal function. APOL1 mutations, which are inherited in an autosomal recessive manner, are also associated with the risk of ERSD (having a 10-fold higher risk of ERSD due to focal glomerulosclerosis and a 7-fold higher risk of hypertension). In addition to mutations in certain genes, smoking and the use of certain drugs are also associated with increased progression of CKD. Smoking can increase the risk of CKD through the pro-inflammatory state, oxidative stress, prothrombotic shift, endothelial dysfunction, glomerulosclerosis, and tubular atrophy. Smoking more than 20 cigarettes per day increases the risk of CKD, and an additional five cigarettes per day is associated with an increase in serum creatinine >0.3 mg/dl (31% of cases).[11]

Table 2. Drugs causing nephrotoxicity[12,13]

Acyclovir (Zovirax)	Acute interstitial nephritis, crystal nephropathy
Aminoglycosides	Tubular cell toxicity
Amphotericin B	Tubular cell toxicity
Chinese herbal preparations containing aristolochic acid	Chronic interstitial nephritis
Contrast media	Renal ischemia
Lithium	Chronic interstitial nephritis
Nonsteroidal anti-inflammatory drugs	Acute and chronic interstitial nephritis, impaired glomerular hemodynamics
Phenytoin (Dilantin)	Acute interstitial nephritis
Sulfonamides	Acute interstitial nephritis, crystal nephropathy
Vancomycin	Acute interstitial nephritis
Zoledronic acid (Zometa)	Tubular cell toxicity

Pathogenesis of CKD

Kidneys have a limited capacity for regeneration. Repeated or persistent kidney damage can lead to maladaptive responses, such as excessive deposition of extracellular matrix ((especially collagen) in the glomerulus and renal tubulointerstitium. Pathological changes that occur in CKD include glomerulosclerosis and tubulointerstitial fibrosis, leading to loss of normal renal architecture, capillary thinning microvascular, hypoxia, and tubular atrophy. These changes lead to loss of renal filtration capacity and eventually to end-stage renal disease.[14]

Classification of CKD

In 2002, the NKF-KDOQI published guidelines on the definition and classification of CKD. This classification system was developed based on the level of kidney function, which is measured by the glomerular filtration rate. Kidney Disease Improving Global Outcomes in 2012 recommended that CKD be classified based on the CGA, namely cause, GFR, and Albuminuria. The cause of CKD is determined based on the presence or absence of systemic diseases and diseases it is localized within the kidney (based on anatomic pathological findings).[15,16]

Table 3. Classification of CKD according to KDIGO 2004.[16]

Stages	Description	Classification based on the severity	
		GFR (ml/min/1.73m^2)	Related terms
1	Kidney damage with normal or increased GFR	≥ 90	Albuminuria, Proteinuria, Hematuria
2	Kidney damage with decreased Mild GFR	60-89	Albuminuria, Proteinuria, Hematuria
3	Moderate decrease in GFR	30-59	Chronic renal insufficiency, early renal insufficiency
4	Severe decrease in GFR	15-29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD
5	Renal failure	< 15 (or dialysis)	Renal failure, uremia, end-stage renal disease

Table 4. GFR categories in CKD according to KDIGO 2012.[15]

GFR categories	GFR (ml/min/1.73m^2)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mild decrease
G3a	45 -59	Mild to moderate decrease
G3b	30-44	Moderate to severe decrease
G4	15-29	Severe decrease
G5	< 15	Renal failure

Albumin is a sensitive marker of CKD caused by diabetes, hypertension, and glomerular disease. Microalbuminuria is most commonly found in patients with stage 1 and 2 CKD. Two of the three abnormal albumin readings are required to confirm persistent albuminuria. Diabetic kidney disease can be diagnosed based on the urine albumin-creatinine ratio, duration of diabetes, and the presence of diabetic retinopathy. CKD patients with diabetes and microalbuminuria (which progresses to macroalbuminuria) are at increased risk for end-stage renal disease.[17]

Table 5. Categories of albuminuria in CKD according to KDIGO 2012.[13]

Categories	Albumin Excretion Rate (mg / 24 hours)	Albumin-to-Creatinine Ratio		Term
		(mg/mmol)	(mg/gr)	
A1	< 30	< 3	< 30	Normal – Mild increase
A2	30-300	3-30	30-300	Moderate increase
A3	> 300	> 30	> 300	Severe increase

Diagnosis of CKD

Chronic kidney disease can usually be identified by routine screening of serum and urine profiles or by incidental findings. Patients may present with symptoms such as gross hematuria, foamy urine (a sign of albuminuria), nocturia, pelvic pain, or decreased urine output. In advanced CKD, patients may present with complaints of fatigue, poor appetite, nausea, vomiting, metallic taste, weight loss, pruritus, altered mental status, dyspnea, or peripheral edema. To evaluate a patient with suspected CKD, the physician should ask for additional symptoms that may indicate a systemic cause (e.g., neuropathy) or an obstructive cause (urinary hesitancy, urgency, or frequency). The patient's risk factors for kidney disease should also be assessed, including previous

exposure to nephrotoxins, history of nephrolithiasis or recurrent urinary tract infections, comorbidities (hypertension, diabetes, autoimmune disease, or chronic infection), and family history of kidney disease.[14]

A detailed physical examination can provide additional clues about the underlying cause of CKD. Findings of arteriovenous retinopathy on retinal examination suggest long-term hypertension or diabetes. Patients with carotid or abdominal bruits may have the renovascular disease. Patients with flank pain or renal enlargement may present with obstructive uropathy, nephrolithiasis, pyelonephritis, or polycystic kidney disease. Patients with advanced CKD may also appear pale with skin excoriation, muscle wasting, asterixis, myoclonic jerks, altered mental status, or pericardial rub.[18,19]

Once the diagnosis of CKD is established, staging can be determined based on GFR, albuminuria, and the cause of CKD. GFR staging is classified as G1 (GFR 90 ml/min/1.73 m^2), G2 (GFR 60-89 ml/min/1.73 m^2), G3a (GFR 45-59 ml/min/1.73 m^2), G3b (GFR 30-44 ml/min/1.73 m^2), G4 (GFR 15- 29 ml/min/1.73 m^2), and G5 (GFR < 15 ml/min/1.73 m^2). In situations requiring greater accuracy and precision, cystatin C may be added. Adding cystatin C is particularly beneficial in individuals with altered creatinine production and/or metabolism (e.g., very high or very low body size or muscle mass, limb amputations, high protein diet, use of creatinine supplements, or use of drugs that affect tubular creatinine secretion).[20-23]

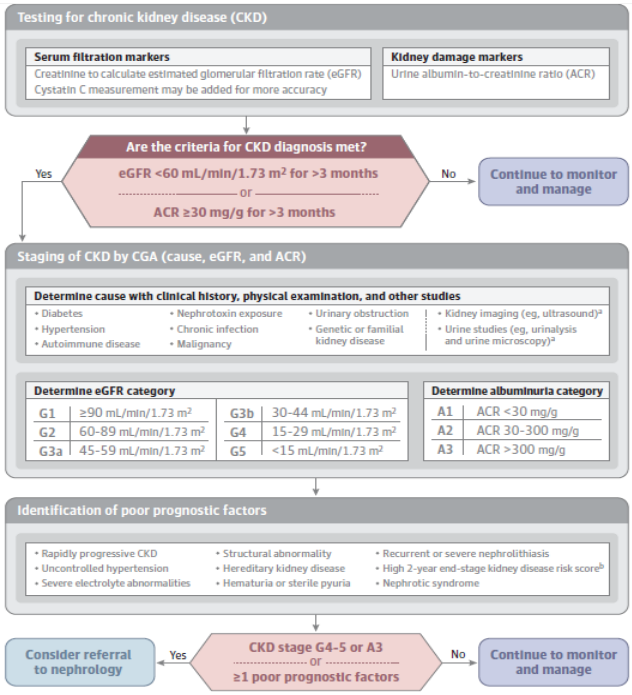

Figure 1. Diagnosis, staging, and referral of patients with CKD.[12]

The 2012 KDIGO guidelines recommend the use of urinary ACR to determine CKD staging compared to the use of urine protein to creatinine ratio. Staging albuminuria was classified as A1 (urinary ACR < 30 mg/gr), A2 (ACR 30-300 mg/gr), and A3 (ACR > 300 mg/gr). This ACR examination is considered to have been standardized and has better accuracy for low albuminuria values. In addition, urine ACR is also believed to be a more sensitive and specific marker for glomerular disorders because, in normal physiological conditions, there are also several other urinary proteins, such as uromodulin. The most accurate measurements are taken from the first-morning urine sample or 24-hour urine to rule out biological

variability in urinary albumin excretion throughout the day.[12,13]

Determining the cause of CKD has important implications for prognosis and therapy. The causes of CKD are generally classified in the presence or absence of systemic disease or anatomic abnormalities of the kidney. Systemic diseases can be caused by diabetes, autoimmune disorders, chronic infections, malignancies, or genetic disorders, where the kidneys are not the only organ affected. Renal anatomic abnormalities are divided into glomerular, tubulointerstitial, vascular, and cystic/congenital diseases. Polycystic kidney disease can progress to ESRD more quickly than other causes and often requires evaluation of extrarenal manifestations and specific therapy.[12]

Homeostasis of potassium

Source and amount of potassium intake

Fruits, vegetables, meat, poultry, and fish are the main sources of potassium. Consumption of these potassium-rich foods can affect an individual's potassium intake, and the effect varies widely around the world. For example, the daily potassium intake in China is about 52 mmol (2.1 g), and in the United States about 68 mmol (2.6 g).[20] This potassium intake appears to be safe for generally healthy individuals because it is still below the upper limit of the tolerable intake level for individuals without kidney disease, diabetes, heart failure, adrenal insufficiency, or individuals not taking ACE inhibitors, ARBs, or other drugs. Which can increase blood potassium levels. Very high potassium intake can cause side effects and, in extreme cases, can lead to death.[21]

Table 6. Recommended adult potassium intake.[20.21]

	Dietary Potassium	
	g/day	**mmol/day**
DRI – AI (2019) > 19 years		
Males	3.4	88
Females	2.6	68
WHO (2012)	3.5	90
K/DOQI (2004)		
CKD G1-G2	> 4.0	> 104
CKD G3a-G4	2.0–4.0	52-104
AND/NKF		
CKD/HD	2.0–4.0	52-104
Expert opinion		
HD	2.7– 3.0	70–78
PD	3.0-4.0	78–104
Hyperkalemia	< 3.0	< 78

There are several methods to determine the amount of potassium intake consumed, including a food frequency questionnaire, dietary recall, temporary urine potassium examination, and 24-hour urine potassium examination. There are advantages and disadvantages to each method. Of all the existing methods, the easiest method to do is to measure the level of potassium in the urine. The gold standard for measuring urine potassium levels is through 24-hour urine collection. However, 24-hour urine collection is sometimes considered impractical and can be burdensome for patients, especially outpatients. This 24-hour urine collection is also often unreliable because of the difficulty in obtaining 24-hour urine accurately (which can lead to over or under-collection). Meanwhile, no method is available to accurately identify the number of incomplete samples.[23]

In contrast to the 24-hour urine test, a single urine sample (temporarily) is easy to collect and store without the potential for over- or under-collection. Urine samples are currently widely used to detect proteinuria and have been evaluated for their potential for assessing sodium levels in urine in order to estimate sodium intake. In a study conducted by Jedrusik et al. in Europe to assess the relationship between spot urine potassium and 24-hour urinary

potassium excretion, it was found that there is a strong correlation between the urinary potassium/creatinine ratio at times and the 24-hour urinary potassium/creatinine ratio. The urinary potassium/creatinine ratio can be used as a screen when 24-hour urine collection is not possible.[24]

Regulation of potassium excretion

Regulation of daily potassium excretion occurs through three mechanisms. (1) Circadian rhythm. Circadian rhythms lead to increased potassium excretion during the day when more potassium is consumed and digested. That way, the increase in serum potassium levels can be minimized. (2) Negative feedback system. This negative feedback system relies on potassium homeostasis, both after potassium load and after potassium depletion, to maintain a stable serum potassium level. Changes in serum potassium levels will encourage mechanisms that involve internal or external potassium balance systems. (3) Feedforward system. The mechanism of this feedforward system is still not widely understood. However, the existence of this system is based on observations in experimental animals that the calliuretic response to potassium load is greater on enteral intake than with intravenous infusion. This system is mediated by receptors in the gut, portal vein, and/or liver, leading to decreased tubular sodium reabsorption. Thus, there is an increase in sodium delivery to the ASDN. This sodium is then reabsorbed, with the secretion of potassium instead.[25,26]

Internal potassium balance

Potassium (K^+) is the main intracellular cation, with a total body content of about 3000-4000 mmol in an adult weighing 70 kg (50 mmol/kgBW). Of the total potassium in the body, about 98% is stored in the intracellular fluid at a level of 140-150 mmol/l, and only 2% is stored in the extracellular fluid with a normal plasma potassium level of 3.5 to 5.0 mmol/l. The ICF potassium level is much greater than the ECF potassium level, creating a steep gradient across the cell membrane. This gradient is maintained by the Na^+-K^+-ATPase pump, which actively transports sodium out of the cell and potassium into the cell in a ratio of 3:2.[27]

Insulin and catecholamines are major factors in the regulation of internal potassium balance. After eating, insulin release the postprandial function not only to regulate serum glucose levels but also to move potassium into cells until the kidneys respond to excrete K^+ load to maintain potassium homeostasis. This process of potassium transfer into cells is mediated by insulin binding to cell surface receptors, which causes phosphorylation of insulin receptor substrate protein (IRS-1), which then binds to phosphatidylinositide 3-kinase (PI3-K). The interaction of IRS-1 and PI3-K causes activation of 3-phosphoinositide-dependent protein kinase-1 (PDPK1). The stimulatory effects of insulin on glucose uptake and potassium uptake are branched at this point. Glucose uptake involves protein kinase B (Akt), which mediates the insertion of the glucose transporter GLUT4 on the membrane surface, whereas activation of atypical protein kinase C (aPKC) causes the insertion of the Na^+-K^+-ATPase pump on the membrane surface.[28,29]

Catecholamines also work to regulate the internal distribution of potassium, with -adrenergic receptors acting to inhibit the movement of potassium into cells and -adrenergic receptors that promote the movement of potassium into cells receptors$_2$cause potassium uptake by increasing the activity of the Na^+-K^+-ATPase pump via the cAMP and protein kinase A (PKA) pathways.[27] During exercise, potassium moves from intracellular to interstitial muscles that contract receptors β_2.[27]

Changes in plasma osmolality and acid-base disturbances affect the internal potassium balance. Hyperosmolality, if caused by effective osmoles (based on their ability to cause osmotic displacement of water molecules), can induce potassium movement out of cells, causing hyperkalemia. An increase in plasma osmolality induces the movement of water out of the cell, which decreases cell volume and increases intracellular potassium levels. This is then thought to

induce feedback inhibition of Na^+-K^+-ATPase, which causes the transfer of potassium from intracellular to extracellular, and normalizes intracellular potassium levels. It should be noted that this only occurs in effective osmoles, such as hyperglycemia in patients with diabetes. Hyperglycemia in non-diabetic patients, when stimulated by endogenous insulin secretion or when exogenous insulin is administered, can lead to cellular potassium uptake and result in hypokalemia.[25,27]

Metabolic acidosis caused by inorganic anions (mineral acidosis), such as NH_4Cl and HCl, can cause hyperkalemia. A decrease in extracellular pH will decrease the exchange of Na^+-H^+ (NHE1) and inhibit the inward rate of Na^+-$3HCO_3$ cotransport (NBCe1, NBCe2). A decrease in Intracellular Na^+-K^+-ATPase will reduce activity, which causes loss of cellular potassium. In addition, decreased extracellular HCO_3 increases the inward movement of Cl^- through Cl-HCO^-, which further promotes K^+ release by K^+-Cl^-. Organic acids (such as lactic acid) in organic acidosis generally do not cause transcellular potassium shifts.[25,27]

External potassium balance

Gastrointestinal potassium excretion

The adult human body must maintain a zero potassium balance. Of all potassium consumed, 80% to 90% will be excreted through the kidneys (renal potassium handling), and 10% to 20% will be excreted through the feces. Potassium can be found in the secretions of the gastrointestinal tract in varying amounts. Saliva contains about 20 mmol/l potassium, esophageal and gastric secretions about 11-35 mmol/l potassium, and pancreatic secretions about 3.5-5.0 mmol/l potassium. Colonic cells can also actively secrete potassium via the basolateral pumps Na^+-K^+-ATPase and Na^+-K^+-$2Cl^-$-cotransporter as well as through the apical potassium “big” conductance (BK) channel. Most of this potassium will be reabsorbed along the intestinal tract.[26]

The gastrointestinal tract also plays an important role in the excretion of potassium. The excretion of potassium through the gastrointestinal tract is influenced by several conditions. (1) ESRD patients have increased BK channel expression in the colon so that potassium excretion through feces increases up to 30-80% of the amount of potassium consumed. (2) Pathological conditions, such as secretory diarrhea and ulcerative colitis, are associated with increased BK channel expression, which in turn increases intestinal potassium loss. (3) Emesis causes potassium loss because it contains five times more potassium than serum. (4) Hormones (aldosterone, epinephrine, and prostaglandins) and certain drugs can increase gastrointestinal potassium excretion.[26]

Renal potassium handling

Potassium is freely filtered by the glomerulus. A large amount of filtered potassium is reabsorbed in the proximal tubule and loop of Henle so that less than 10% will reach the distal nephron. In the proximal tubule, potassium reabsorption occurs passively via paracellular pathways in proportion to Na^+ and water. In the ascending limb of Henle, potassium reabsorption in the thick layer occurs via a transcellular pathway, which is mediated by Na^+-K^+-$2Cl^-$-cotransporters in the apical membrane. Urinary potassium excretion is the result of potassium secretion along the aldosterone-sensitive distal nephron (ASDN), which consists of the last part of the distal convoluted tubule (DCT2), the connecting tubule, and the collecting duct.secretion$^+$ is mediated by 2 types of apical K^+ channels, namely renal outer medullary K^+ (ROMK) channel and BK channel, and is driven by transepithelial tension oriented in the lumen-negative direction. The tension is largely generated by Na^+ through the epithelial Na^+ channels (ENaC), which are located in the apical membrane.[27]

There are two main determinants of renal potassium secretion: mineralocorticoid activity and Na^+ water to the distal part. Aldosterone is the main mineralocorticoid in humans that can affect potassium secretion. First, aldosterone increases intracellular potassium levels by stimulating Na^+-K^+-ATPase activity in the basolateral membrane. Second,

aldosterone stimulates ENaC activity which increases luminal electronegativity, thereby increasing the electrical gradient that promotes potassium secretion. Finally, aldosterone has a direct effect on the luminal membrane so that its permeability to potassium increases.[26]

The increase in the flow of Na+ towards the distal stimulates the absorption of Na+ in the distal. This distal absorption of Na+ causes the luminal potential to become more negative, and thus increases the secretion of K+. An increase in the luminal flow rate can also increase K^+. Normally, when K^+ is secreted in the collecting duct, luminal K^+ increases so that the luminal membrane diffusion gradient is decreased and ultimately slows K^+. However, at high luminal flow rates, the same amount of K^+ has diluted with a larger volume so that the luminal membrane diffusion gradient increases, and ultimately K^+ also increases.[28-30]

The increase in renal potassium excretion following a high potassium intake can be traced to an increase in Na^+ to ASDN. This effect begins in the early part of DCT (DCT1), where Na^+ is driven exclusively by the thiazide-sensitive Na^+/Cl^--cotransporter (NCC). The increase in plasma K^+ due to high potassium intake is felt by the Kir4.1/5.1 channel (located on the basolateral surface of DCT1), which causes changes in WNK kinase activity and its regulatory proteins, namely SPAK and OxSR1 so that NCC activity decreases. As a result, there is greater delivery and flow of Na^+ to the ASDN, leading to more potassium secretion. In contrast to high potassium intake, low potassium intake and decreased plasma potassium levels led to increased NCC activity in DCT1.secretion$^+$ by reducing Na^+ to the ASDN.[30]

Urinary potassium excretion and progression of chronic kidney disease

Potassium balance in chronic kidney disease

In patients with chronic kidney disease, the loss of nephron mass is usually offset by an adaptive increase in the rate of K^+ in the remaining nephrons so that K^+ is generally well maintained up to a normal rate. Glomerular filtration falls below 15-20 ml/min.[31,32] The adaptive increase in the rate of potassium secretion in the nephrons of CKD patients is thought to be similar to the adaptive process that occurs in a normal human high-potassium diet. Chronic potassium load increases the secretory capacity of the distal nephron, so renal potassium excretion increases significantly at various levels of plasma potassium levels. Increased potassium secretion in this condition occurs due to structural changes characterized by cellular hypertrophy, increased mitochondrial density, and basolateral membrane proliferation in cells in the distal nephron and principal cells in the collecting duct.[33-35]

Severe renal dysfunction can always lead to K^+, and hyperkalemia can occur because the number of nephrons is sharply decreased, and their maximal capacity to secrete potassium is limited.[36] Patients with advanced chronic kidney disease eventually have more difficulty managing acute potassium loads, even when serum potassium levels are within normal limits.[37] Despite this adaptive response, the ability of the kidneys to increase potassium secretion in response to exogenous load, is very limited, so hyperkalemia can occur even at the lowest increase in potassium intake. CKD patients usually also receive routine therapy with drugs that can affect renal potassium handling, such as ACE inhibitors, angiotensin receptor blockers (ARBs), and -adrenergic receptor blockers. These drugs can decrease the sensitivity of the kidneys to potassium, leading to high serum potassium levels.[38]

Urinary potassium excretion and progression of chronic kidney disease

Initially, potassium excretion was thought to be dependent on glomerular filtration, and hyperkalemia will develop only when potassium intake exceeds the glomerular filterable potassium capacity. However, in further studies, it was found that the urinary potassium output sometimes exceeds the filtered potassium load. This indicates that urinary potassium is also secreted by tubular cells. In fact, most urinary

potassium comes from tubular secretion and not from glomerular filtration. Adaptations to prevent elevated serum potassium levels in renal failure depend more on increasing tubular potassium secretion than on decreased tubular potassium reabsorption. Most of the knowledge regarding urinary potassium excretion in renal failure was obtained through experimental animals that underwent subtotal nephrectomy. In the animals with the remaining half of the kidney, it was found that the excretion of potassium per nephron increased fourfold in 24 hours. At 7 days, 24-hour urinary potassium excretion accounted for 87% of urinary potassium excretion by both kidneys calculated during the control period (before subtotal nephrectomy).[39]

There are few studies that specifically evaluate the relationship between urinary potassium excretion and renal outcomes. Based on previous studies, it was found that the mean age of the study subjects was 66 years, with an average eGFR of 68.4 ml/min / 1.73 m^2 and an average urinary potassium excretion of 2.18 g/day. Patients with higher urinary potassium excretion had higher eGFR and urine albumin-creatinine ratio (UACR). A nearly linear, strong, and statistically significant relationship was found between 24-hour urinary potassium excretion with primary outcomes and the occurrence of proteinuria in the study subjects.[39.40]

Table 7. Renal outcome by urinary potassium excretion rate.[39]

Outcomes	**Number of Outcomes**	**Odds Ratio**	
		Moderate Potassium Excretions	**High Potassium Excretions**
eGFR decline of 30% or chronic dialysis	2052 (7.6%)	0.88 (0.84–0.92)	0.74 (0.67–0.82)
eGFR decline of ≥ 40% or chronic dialysis	941 (3.3%)	0.91 (0.85–0.97)	0.81 (0.69–0.94)
Rapid progression of renal disease	3717 (13.7%)	0.89 (0.86–0.92)	0.77 (0.71–0.84)
Doubling of creatinine or chronic dialysis	302 (1.1%)	0.88 (0.79–0.99)	0.75 (0.58–0.98)
Progression of proteinuria	2471 (9.5%)	0.89 (0.85–0.93)	0.76 (0.69–0.84)
Hyperkalemia	768 (2.7%)	1.07 (1.00–1.14)	1.16 (0.99–1.36)

Primary renal outcomes were defined as a decrease in eGFR ≥ 30% or chronic dialysis. Subjects with higher urinary potassium excretion had significantly worse primary outcomes. Higher urinary potassium excretion is also associated with a lower risk of a decrease in eGFR ≥ 40%, rapid progression of renal disease, a two-fold increase in creatinine, and the development of proteinuria. The relationship between urinary potassium excretion and the incidence of hyperkalemia is not significant, but there is a tendency for hyperkalemia to occur at higher potassium excretion.[39]

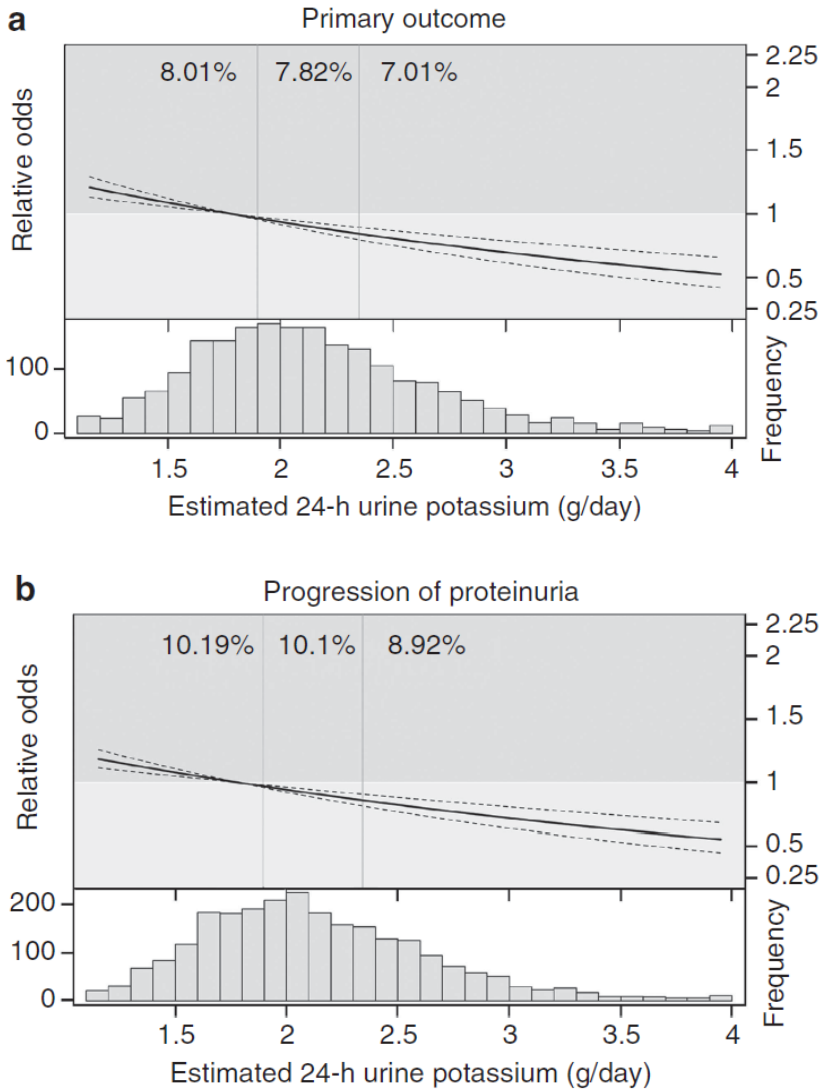

Figure 2. Relationship of urinary potassium excretion with renal outcomes.[37]

A previous study of 623 types 2 diabetes mellitus patients with eGFR 60 ml/min/1.73 m^2 also found that higher urinary potassium excretion was associated with a lower risk of renal dysfunction. This beneficial effect of higher urinary potassium excretion on the kidneys is attributed to the blood pressure lowering effect of potassium. The subgroup of subjects with the greater urinary potassium quartile showed lower systolic blood pressure than the subgroup with the lower quartile. However, this positive effect of higher urinary potassium excretion on the kidneys may also be related to other factors or have a direct effect on the kidneys without involving the effect of lowering blood pressure. Here are Kaplan-Meier curves which represent the cumulative incidence of renal end-points per quartile of urinary potassium excretion. The short dotted line represents Q1 (<1.72 g/day); the short dotted line represents Q2 (1.72–2.32 g/day); the long dotted line represents Q3 (2.33–2.90 g/day); and the solid line represents Q4 (>0.2.90 g/day).[41,42]

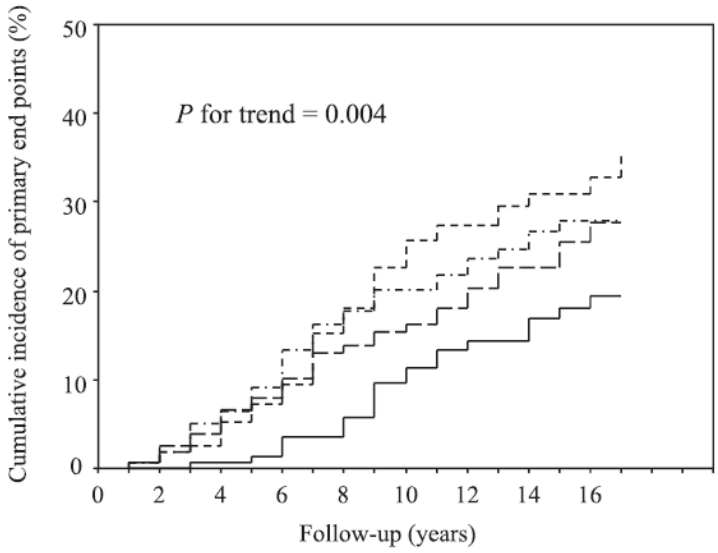

Figure 3. Incidence of renal end-points per quartile of urinary potassium excretion.[36]

2. Conclusion

Potassium intake in patients with CKD needs serious attention because of the high incidence of hyperkalemia, especially in patients with advanced CKD. There are several methods to measure the amount of potassium intake consumed, including a food frequency questionnaire, dietary recall, temporary urine potassium examination, and 24-hour urine potassium examination. The standard gold measurement for evaluating urinary potassium excretion is through 24-hour urine collection.

3. References

1. Bikbow B, Purcell C, Levey AS, Smith M, Abdoli A, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the global burden of disease study 2017. Lancet. 2020; 395:709–33.
2. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. Bull World Health Organ. 2018; 96:414–22.
3. Balitbangkes. National Riskesdas Report 2018. Jakarta: Kementerian Kesehatan RI; 2019: 169-74.
4. Kim HW, Park JT, Yoo TH, Lee J, Chung W, et al. Urinary potassium excretion and progression of CKD. Clin J Am Soc Nephrol. 2019; 14:330-40.
5. Mente A, Donnell MJ, Rangarajan S, McQueen MJ, Poirier P, et al. Association of urinary sodium and potassium excretion with blood pressure. N Engl J Med. 2014; 371:601-11.
6. Dhondup T, Qian Q. Electrolyte and acid–base disorders in chronic kidney disease and end-stage kidney failure. Blood Purif. 2017; 43:179-88.
7. Nakhoul GN, Huang H, Arrigain S, Jolly SE, Schold JD, et al. Serum potassium, end-stage renal disease and mortality in chronic kidney disease. Am J Nephrol. 2015; 41(6):456-63.
8. Ueda Y, Ookawara S, Ito K, Miyazawa H, Kaku Y, et al. Changes in urinary potassium excretion in patients with chronic kidney disease. Kidney Res Clin Pract. 2016; 35:78-83.
9. Balitbangkes. West Sumatra Province Riskesdas 2018 Report. Jakarta, Kementerian Kesehatan RI; 2019: 131-2.
10. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: A Review. JAMA. 2019; 322(13):1294-304.
11. Kazancioglu R. Risk factors for chronic kidney

disease: An update. Kidney Int Suppl. 2013; 3:368-71.

12. International Society of Nephrology. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). Kidney Int Suppl. 2017; 7(1):8.
13. Argawal R. The challenge of discovering patient-level cardiovascular risk factors in chronic kidney disease. Kidney International. 2008; 73:1340-2.
14. Baumgarten M, Gehr T. Chronic kidney disease: Detection and evaluation. Am Fam Physicians. 2011; 84(10):1138-48.
15. International Society of Nephrology. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013; 3(1):5-10.
16. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, et al. Definition and classification of chronic kidney disease: A position statement from kidney disease: Improving global outcomes (KDIGO). Kidney International. 2005; 67:2089-100.
17. Adissoda CM, Houehanou C, Chianea T, Dalmay F, Bigot A, et al. Estimation of daily sodium and potassium excretion using spot urine and 24-hour urine samples in a Black Population (Benin). J Clin Hypertens. 2016; 18(7):634-40.
18. Collister D, Ferguson T, Komenda P, Tangri N. The patterns, risk factors, and prediction of progression in chronic kidney disease: A narrative review. Semin Nephro. 2016; 136:273-82.
19. Mullins LJ, Conway BR, Menzies RI, Denby L, Mullins JJ. Renal disease pathophysiology and treatment: Contributions from the rat. Dis Model Mech. 2016; 9:1419-33.
20. Mirmiran P, Nazeri P, Bahadoran Z, Moghadam SK, Azizi F. Dietary sodium to potassium ratio and the incidence of chronic kidney disease in adults: A longitudinal follow-up study. Prev Nutr Food Sci. 2018; 23(2):87-93.
21. Matovinovic MS. Pathophysiology and classification of kidney diseases. JIFCC. 2009; 20(1):2-11.
22. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: A systematic review. JAMA. 2015; 313(8):837-46.
23. Traeger KA, Wen SF. Pathophysiology of potassium metabolism. Elsevier. 2009; 61:49-59.
24. Weiner ID, Linas SL, Wingo CS. Disorders of potassium metabolism. Comprehensive Clin Nephrol. 2010: 118-29.
25. Besouw MT, Bockenhauer D. Potassium metabolism. Elsevier. 2019; 3:31-46.
26. Palmer BF. Regulation of potassium homeostasis. Clin J Am Soc Nephrol. 2015; 10:1050-60.
27. Bhave G, Neilson EG. Body fluid dynamics: Back to the future. J Am Soc Nephrol. 2011; 22(12):2166-81.
28. Clase CM, Carrero JJ, Ellison DH, Grams ME, Hemmelgarn BR, et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a kidney disease: Improving global outcomes (KDIGO) Controversies Conference. Kidney International. 2020; 97:42-61.
29. Leonberg-Yoo AK, Tighiouart H, Levey AS, Beck GJ, Sarnak MJ. Urine potassium excretion, kidney failure, and mortality in CKD. Am J Kidney Dis. 2017; 69(3):341-49.
30. Kieneker LM, Bakker SJ, Boer RA, Navis GJ, Gansevoort RT, et al. Low potassium excretion but not high sodium excretion is associated with increased risk of developing chronic kidney disease. Kidney International. 2016; 90:888-96.

31. Smyth A, Griffin M, Yusuf S, Mann JF, Reddan D, et al. Diet and major renal outcomes: A prospective cohort study. The NIH-AARP Diet and Health Study, J Ren Nutr. 2016; 26(5):288-98.
32. He J, Mills KT, Appel LJ, Yang W, Chen J, et al. Urinary sodium and potassium excretion and CKD progression. J Am Soc Nephrol. 2015; 27(4):1202-12.
33. Eisenga MF, Kieneker LM, Soedamah-Muthu SS, Berg EV, Deetman PE, et al. Urinary potassium excretion, renal ammoniagenesis, and risk of graft failure and mortality in renal transplant recipients. Am J Clin Nutr. 2016; 104(6):1703-11.
34. Araki S, Haneda M, Koya D, Kondo K, Tanaka S, et al. Urinary potassium excretion and renal and cardiovascular complications in patients with type 2 diabetes and normal renal function. Clin J Am Soc Nephrol. 2015; 10(12):2152-8.
35. Smyth A, Dunkler D, Gao P, Teo KK, Yusuf S, et al. The Relationship between estimated sodium and potassium excretion and subsequent renal outcomes. Kidney International. 2014; 86:1205-12.
36. Noori N, Zadeh KK, Kovesdy CP, Murali SB, Bross R, et al. Dietary potassium intake and mortality in long-term hemodialysis patients. Am J Kidney Dis. 2010; 56:338-47.
37. Udensi UK, Tchounwou. Potassium homeostasis, oxidative stress, and human disease. Int J Clin Exp Physiol. 2017; 4(3):111-22.
38. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis: Core curriculum 2019. Am J Kidney Dis. 2019; 74(5):682-95.
39. Stallings VA, Harrison M, Oria M, et al. Dietary reference intakes for sodium and potassium. Washington DC: The National Academies Press; 2019: 136.
40. Jedrusik P, Symonides B, Wojciechowska E, Gryglas A, Gaciong Z. Diagnostic value of potassium level in a spot urine sample as an index of 24-hour urinary potassium excretion in unselected patients hospitalized in a hypertension unit. PLoS One. 2017; 12(6):1-16.
41. Gennari JF, US Segal. Hyperkalemia: An adaptive response in chronic renal insufficiency. Kidney Intl. 2002; 62:1-9.
42. Strihou CV. Potassium homeostasis in renal failure. Kidney Intl. 1977; 11:491-504.