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Hyperkalemia Treatment in Chronic Kidney Disease

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Abstract
Hyperkalemia defined as a condition with serum potassium level of >5.0 mEq/L and referred as severe if >6.0 mEq/L. Basic pathogenesis of hyperkalemic states is either shifts of intracellular potassium into extracellular or disturbtion in renal excretion. The kidneys play role in potassium excretion. Chronic kidney disease (CKD) refers to an irereversible deterioration in renal function which develops over a period of years, depletion of functioning nephrons leads to reduced potassium exctretion. CKD patients less tolerant to potassium challenge due to depletion of tubular mass, increasing their risk in developing hyperkalemia. Some drugs used in CKD, such as antihypertensive, are able to block renal excretion of potassium. Overall goals of hyperkalemia management are to reverse cardiac manifestation, reducing serum potassium level and remove excess potassium. Hyperkalemia in CKD is considered as a chronic hyperkalemia, in which can be lowered slowly. The chosen therapy is to remove excess potassium using diuretics and cation exchange resins, or dialysis if needed.
Keywords: *Hyperkalemia, Chronic Kidney Disease, Hyperkalemia treatment*

I. INTRODUCTION

Chronic kidney disease complicated with several disturbances, among others is electrolyte balance disorder. Hyperkalemia is one of great concerns for those who treat CKD because of the complication risk. Impaired glomerular filtration rate, metabolic disorders, other medication used in CKD patients can further causing hyperkalemic states by inhibit renal excretion of potassium. In this review, we elaborate kidneys role, hyperkalemia and their management.

II. ANATOMY AND PHYSIOLOGY OF KIDNEY

Each kidney contains approximately 900000 to 1 million similar subunits called nephrons. Each nephron consists of an initial filtering componen called the renal corpiscle, a tubule that extends out from the corpuscle. The component of nephrons and their function are shown in table below. Kidney play several roles, such as in excretion of many metabolic breakdown products, including ammonia, urea and creatinine from protein, uric acid from nucleic acids, drugs and toxins. Main roles of the kidney:

a. Glomerular filtration and tubular reabsorption

Urine formation begins with plasma filtration from glomerular capillary into the Bowman's space, this process is called glomerular filtration and the filtrate is called the glomerular filtrate. Filtrate are cell-free and contains all substances almost in the same concentration as in the plasma, called the ultrafiltrate. As it pass the tubules, the composition of filtrate will be changed by the substances' movement from tubular lumen to the peritubular capillary plasma, this process is called tubular reabsorption.

Table 1 Components of nephrons and their functions

Components	Function
Glomerulus Consists of loops of capilaries and surrounded by Bowman's capsule (Goddard & Turner, 2014).	Blood enters glomerulus will undergo ultrafiltration accross the glomerular basement membrane (GBM) which contain pores, through which molecules can pass. Glomerular epithelial cells (podocytes) have multiple long foot processes, maintaining selective barrier to filtration (Goddard & Turner, 2014).
Proximal tubule Consists of pars convulta and pars recta. A diverse family of tight junction proteins, claudins are expressed throughout the renal tubule system (Fenton & Praetorius, 2016).	Proximal tubule plays major role in reabsorption Na^+, HCO^{3-}, Cl^-, K^+, Ca^{2+}, $PO4^{3-}$, water and organic solutes such as vitamins, glucose, and amino acids. Claudins has various ion permeability properties, mediating the paracelllular permeability of the thight junction. Each pars convulta cell has a well-developed endocytic-lysosomal apparatus that is involved in reabsorption and degradation of macromolecules from ultrafiltrate (Fenton & Praetorius, 2016).
Loop of Henle Connect the proximal and distal tubules.	Type II epithelium has significant level of Na^{+}-K^{+}-ATPase activity. The permeability properties of the thin limb

Components	Function
Morphologically composed of 4 types of epithelia (Fenton & Praetorius, 2016).	epithelium are important for the maintenance of hypertonic insterstitium (Fenton & Praetorius, 2016).
Distal tubule Composed of pars recta (TAL), macula densa, pars convulta (DCT), and connecting tubules (CNT) (Fenton & Praetorius, 2016). Macula densa is not a distinct segment but a plaque of cells in the ascending loop of Henle (Widmaier, Raff, & Strang, 2014).	TAL involved in active transport of NaCl from the lumen. This epithelium is almost impermeable to water, the reabsorption of salt contributes to formation of a hypertonic medullary interstitium and the delivery of a dilute tubule fluid to DCT. Also involved in transport of divalent cations (Fenton & Praetorius, 2016). Macula densa mediating feedback tubuloglomerular, acting as a sensor of solute

Table 1 Components of nephrons and their functions (continued)

Components	Function
	delivery and tubular flow rate (George & Neilson, 2015). DCT has the highest Na^{+}-K^{+}-ATPase activity of all nephron segments, providing driving force for ion transport. Participate in K^{+} homeostasis by regulation of $Na^{-}Cl$ cotransporter (NCC). Express vasopressin receptors which positively regulates Na^{+} transport and NCC activity (Fenton & Praetorius, 2016). CNT capable of transporring large amounts of water. CNT is an important site of calcium reabsorption. Also play an important role in secretion of K^{+}, which is at least in part regulated by mineralocorticoids (Fenton & Praetorius, 2016).
Collecting duct Divided into 3 regions on the basis of their location, cortical (CCD), outer medullary (OMCD), inner medullary (IMCD) (Fenton & Praetorius, 2016).	CCD has major function in secretion of K^{+}, regulated by mineralocorticoid, which stimulate K^{+} sceretion and Na^{+} reabsorption. OMCD plays an important role in urine acidification with H^{+} secretion via Na^{+}. IMCD involve in reabsorption of Na^{+}, Cl^{-}, K^{+}, urea, and water and the acidification of urine (Fenton & Praetorius, 2016).

The opposite movement is called tubular secretion (Widmaier, Raff, & Strang, 2014). Approximately 100-120 ml/minutes filtrate formed in healthy adult with both kidney fully functioning. Around 30 ml/minutes isotonic filtrate flow into the loop of Henle after undergoes reabsorbption (most of the filtered Na^{+}, K^{+} and glucose) and secretions of substances such as organic cations, creatinine, histamine, and toxins. Not more than 5-10 ml/minutes of the glomerular filtrate is delivered into the collecting ducts. In collecting duct occurs water reabsorptions that controlled by vasopressin or antidiuretic hormone (ADH). The remaining 1-2 ml/minutes of the original glomerular filtrate exits into the ureters as urine (Perlman, Heung, & Ix, 2014).

b. Blood pressure and volume regulation

The kidneys play an important role in blood pressure regulation mainly because of its effect on Na+ and water balance. Sodium concentration in proximal tubules is sensed by the macula densa of the juxtaglomerular apparatus. The apparatus itself also assesses the perfusion pressure of the blood, which is normally an important indicator of intravascular volume status. Through the action of these two sensors, either low sodium or perfusion pressure will act as a stimulus of renin release. Renin is a protease produced juxtaglomerular cells, breaking the angiotensinogen and yielding angiotensin I, which will be further changed become angiotensin II by angiotensin-converting-enzymes (ACE). Angiotensin II raises blood pressure by directly triggering vasoconstriction and stimulating aldosteron productions and secretion in adrenal cortex, resulting in collecting ducts sodium and water retention. These will increase renal extracellular fluid and eventually perfusion pressure, completing homeostatic negative feed-back cycle, diminishing initial stimulant of renin release (Perlman, Heung, & Ix, 2014).

c. Acid-base balance regulation

Along with respiratory system, kidneys involve in acid-base regulation. In normal condition, arterial blood pH maintained between 7.35 to 7.45 via buffer system played by bicarbonate:

$$H^{+} + HCO_3^{-} \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

pH decrease (increase in hydrogen concentration) will increase carbondioxide, which exhaled from the lungs. This buffering effect result in bicarbonate depletion. The kidney then excreting more hydrogen, which will

replace bicarbonate stores. The lungs only excrete volatie acids, removal of nonvolatile acids relies on the kidneys. Normal daily diet generate an obligate acid load from protein metabolism, the kidneys maintain homeostasis by excreting this acid load mainly in distal collecting duct. In addition, the kidneys regulate acid-base through the reabsorption and regenaeration of bicarbonate primatily in the proximal tubules (Perlman, Heung, & Ix, 2014).

d. Potassium balance regulation

Potassium balance mainly controlled in distal collecting duct, where it is secreted into the lumen as a response to aldosterone-mediated Na^+ reabsorption. Therefore, aldoseterone is the main hormon in potassium regulation. Hyperkalemia is a sign to release aldosterone, meanwhile hypokalemia is the negative feedback. The kidneys play role in potassium excretion. Hypokalemia occurs as a result from intracellular potasium shifting (alkalosis, beta-agonist therapy), extrarenal losses (diarrhea), or renal losses. Meanwhile hyperkalemia resulted from extracellular shift of poatassium, increase of cellular potassium release, or decrease of potassium renal excretion (Perlman, Heung, & Ix, 2014).

e. Erythopoiesis regulation

The kidneys are the main site of hormone erythropoietin production, which stimulates red blood cells production and maturation in bone marrow. The kidneys are monitoring level of blood oxygenation, which thought to be the signal of erythropoietin production. Progressive renal disease altered kidneys' capacity to produce erythropoietin, resulting in anemia (Perlman, Heung, & Ix, 2014).

III. CHRONIC KIDNEY DISEASE

Renal disease can be classified based on the location of the injury (glomerulopathy, tubulointerstitial) or based on the underlying factor (immunologic, metabolic, infections). Chronic kidney disease (CKD) refers to an irreversible deterioration in renal function which develops over a period of years. In early stage, the patients only show biochemical abnormality, but eventually, develops loss of excretory, metabolic and endocrine functions, leads to clinical symptoms and signs of renal failure, collectively referred as uremia. Patient that cannot survive without RRT called patient with end-stage renal disease or failure (ESRD or (ESRF) (Goddard & Turner, 2014). At least 6% of adult in US has CKD stages 1 and 2, and 4,5% in stage 3 and 4. The most common cause in developing countries is diabetes mellitus followed by hypertension. In the US, CKD mostly caused by nephropathy diabetes with type 2 diabetes mellitus (Bargman & Skorecki, 2015).

The pathogenesis of CKD is not the same with acute renal disease. Acute injury leads to death and sloghing of tubular epithelial cells often followed by regeneration of normal architecture. Meanwhile chronic injury leads to irreversible loss of nephrons. Kidney disease alters water-sodium balance, results in sodium intake greater than the excretion, leads to sodium retention followed by increase in extracellular fluid volume. This increase will contribute in hypertension and further damaging the nephrons. Potassium excretion not always decline along with the decrease of GFR, which the secretion is mediated by aldosterone in distal nephrons. Potassium retention also occurs in GIT by increasing the excretion. Some drugs are blocking renal excretion of potassium, causing hyperkalemia. Some of the underlying conditions can cause further hyperkalemia, for example in diabetes, obstructive uropathy and sickle cell nephropathy. Hypokalemia often seen in CKD and usually found in extreme decrease of potassium intake or diuretic therapy or GIT loss. Metabolic acidosis condition usually happens in advance CKD. Most patients still capable for urine acidification, but producing less ammonium, so that fail to adequately excreting proton for urine buffering process. Calcium-phosphate disturbances are almost universal in advanced CKD. There is impaired conversion of 25-hydroyvitamin D to its metabolite (1,25- hydroyvitamin D) because of renal tubular cell damage and elevated FGF23 levels. Reduced metabolite alterscalcium absorption in instestine, thereby causing hypocalcemia, which in turns increase PTH production by parathyroid glands. Reduction in GFR will increase serum phosphate, in which increase hormone FGF32 production from osteocytes. This homeostatic response eventually fails, because renal failure progresses and hyperphosphatemia develops. Heart failure and lung oedema can occur in water and sodium overload. Hypertension are the most common disorder found in CKD. Cardiovascular disease causing most mortality and morbidity in every stage (Bargman & Skorecki, 2015; Perlman, Heung, & Ix, 2014).

Proper salt restriction and loop diuretics to maintain euvolemia. Water restriction for patient with hyponatremia. Mild metabolic acidosis can be treated with oral sodium bicarbonate. Alkali suplement if bicarbonate serum <20-23 mmol/L can decrease catabolic and slowing CKD progression. Phosphate binding agents should be used in phosphate disturbances with monitoring serum concentration. These agents taken

orally and form a complex with food. Calcitriol can directly supress PTH and indirectly increase ionized calcium. Goals of hypertension therapy in CKD is inhibiting extrarenal high blood pressure complication such as CVD and stroke. Salt restriction is the first line, and if needed, ACEI and ARB can be considered (Bargman & Skorecki, 2015; Perlman, Heung, & Ix, 2014).

Treatment of specific causes is mentioned above. Nonspecific therapy should aimed to slow the progression of CKD. First reducing intraglomerular hypertension and proteinuria. ACE inhibitors and ARBs inhibit the angiotensin-induced vasoconstriction of the afferent arterioles of the glomerular microcirculation. This inhibition leads to a reduction in both intraglomerular filtration pressure and proteinuria. They slow CKD progression by lowering proteinuria. The combination of both is associated with greater reduction of proteinuria, but also greater incidence of acute kidney injury and adverse cardiac events (Bargman & Skorecki, 2015).

IV. HYPERKALEMIA IN CHRONIC KIDNEY DISEASE

Hyperkalemia defined condition with serum potassium level of >5.0 mEq/L and referred as severe if >6.0 mEq/L. Basic pathogenesis of hyperkalemic states is either shifts of intracellular potassium into extracellular or disturbtion in renal excretion. Increased potassium dietary intake hardly cause serious and sustained hyperkalemia, unless there has been existing pathological conditions (Mushiyakh, et al., 2011). Chronic kidney disease and ESRD are very common cause of hyperkalemia, because depletion of functioning nephrons. In CKD, tubular mass also diminished, therefore less tolerant to potassium challenge leading to increased risk in developing hyperkalemia. Acidosis metabolic non anion-gap can also result in hyperkalemia because of the intra to extracellular shift, in which to maintain cellular pH by taking H+ and removing K+ (Mount D. B., 2015; Mushiyakh, et al., 2011).

Hyperkalemia is a medical emergency because of the effect on the heart. Cardiac arrhythmias associated with hyperkalemia include sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole. Increase in extracellular potassium effects on repolarisation phase of cardiac action potential, resulting in changes of T-wave. Further increase will depress intracardiac conduction, with progressive prolongation PR and QRS interval. Severe hyperkalemia results in loss of P wave and widening QRS complex, suggesting impending ventricullar fibrillation or asystole (Mount D. B., 2015).

V. MANAGEMENT OF HYPERKALEMIA

Management of hyperkalemia depends on its severity and the rate of development. If ECG changes are present, the first step is to infuse 10 ml 10% calcium gluconate. Ultimately, a means of removal potassium from the body is generally necessary. When renal function is reasonably preserved, loop diuretic may be effective. In renal failure, ion-exchange resins acting through GIT or dialysis maybe required (Goddard & Turner, 2014).

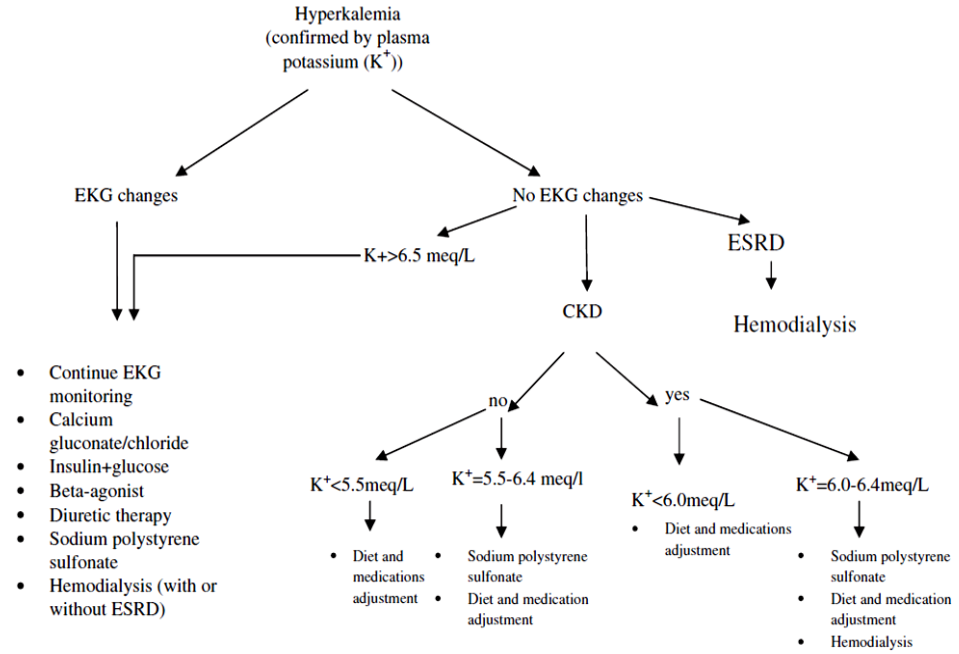

Figure 1 Algorithm for hyperkalemia (Mushiyakh, et al., 2011)

There are 3 risk stratification for hyperkalemia. Those with severe hyperkalemia (>6.5 mEq/L) or with moderate hyperkalemia but also have renal impairment, ongoing tissue breakdown, ongoing potassium absorption, or metabolic/respiratory acidosis, are grouped as emergency hyperkalemia. These conditions need rapid acting therapies because serious manifestation and complications risk. Second group is for those with hemodialysis, marginal renal function/urine output, or impending surgery. These conditions' potassium serum should be lowered promptly, within 6 until 12 hours. Last group is those who has chronic but mild or moderate hyperkalemia due to CKD or usage in RAAS inhibitors, can be lowered slowly (Mount D. , 2016).

Table 2 Management of hyperkalemia (Mount D. , 2016; Kasper, et al., 2016)

OBJECTIVE	THERAPY	MECHANISM
IMMEDIATE		
Antagonist cardiac effect	IV calcium gluconate (10 ml of 10%)	Raise action potential treshold & reduce excitability → reverse depolarization blockade
Reduce plasma K+ concentration	IV Insulin reguler (10 U) + D5 (50 ml of 50%)	Shifting K+ into cells
	Inhaled β2-agonists	Additive effect with insulin
	IV Sodium bicarbonate	Raise systemic pH → K+ moves into cell to buffer
URGENT		
Remove potassium	IV thiazide or loop diuretic	Increase K+ renal excretion
	Ion exchange resin*	Exchange Na+ for K+ in GIT → increase K+ fecal excretion
	Dialysis for patients with severe renal dysfunction	
CHRONIC		
Remove potassium	Ion exchange resin *	Exchange Na+ for K+ in GIT → increase K+ fecal excretion
	Diuretic	Increase K+ renal excretion
Prevent Hyperkalemia	Avoid NSAID Adjust Dose ACEI/ARB Correction of metabolic acidosis Dietary intervention (potassium restrictive diet)	

In CKD, patients may be less liable to cardiac toxicity due to their metabolic disorders, hence reducing sensitivity to cardiac event complications and more expected to develop chronic hyperkalemia with better tolerance. Studies showed those with CKD can present with serum potassium more than 6.0 mEq/L without cardiac manifestion or in electrocardiograph (Einhorn, et al., 2009). In this population, the chosen therapy is to remove excess potassium using diuretics and cation exchange resins, or dialysis if needed.

Table 3 Cation exchange resins for hyperkalemia (Chaitman, Dizit, & Bridgetman, 2016)

	Sodium Polysterene Sulfonate	Patiromer	Sodium Zirconium Cyclosillicilate
FDA approval	1958	2015	pending
Mechanism of action	Nonspecific sodium-cation exchange resin	Calcium-potassium cation exchange	Selective potassium cation trapping agent
Formulation	• Oral suspension • Powder for reconstituton • Rectal enema	• Oral suspension	• Oral suspension • Dissolvable tablet
Onset	1 to 2 hours	7 hours	1 hour
Dosing	• 15-60 g daily peroral (1-4 times daily) • 30-50 g daily perrectal (up to 4 times daily	• 8.4-25.2 g once daily	• 5-10 g once daily
Common adverse event	• GI disturbances • Electrolyte disorders • Systemic alkalosis	• GI disturbances • Hypokalemia • Possible calcium load • Hypomagnesia	• GI disturbances • Hypokalemia
Serious adverse	Colonic necrosis	none	none

event			

Diuretics are useful in the management of most patients with CKD. Using diuretics can produce better extracelullar fluid volume; lower blood pressure; potentiate the effects of antihypertensive such as ACE inhibitors, ARBs, and other agents; and also reduce the risk of CVD in CKD. Resins approved by FDA was limited. Sodium Polysterene Sulfonate was introduced in 1950, FDA had yet required to establish safety and effectivity of approved drug. The drug was later found to have serious adverse event risk. Patiromer calcium, approved in 2015, was claimed to have none serious adverse event risk, but slower onset, therefore indicated for chronic hyperkalemia that does not need to be lowered urgently or immediately. Sodium Zirconium Cyclosillicilate is newly proposed as potassium binding agent, claimed to have rapid onset and less, but still under clinical investigation.

VI. CONCLUSION

Hyperkalemia is a common but potentially life-threatening electrolyte disorder. In CKD, patients were more in risk but had better tolerance, resulted from underlying chronic metabolic imbalance. Therefore, their potassium level can be lowered slowly. The pharmacologic options were using diuretics or cation exchange resins.

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