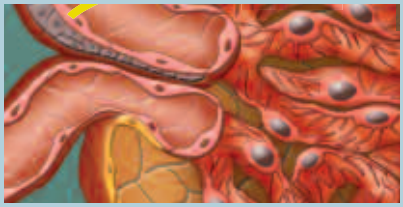
abstract



Alterations in potassium balance occur frequently in all patient populations, but in particular, among older adults. Physicians commonly encounter such disorders when taking care of patients in the clinic or in the hospital. Most often the etiology of such disturbances is due to prescribed medications, but a number of clinical conditions exist which predispose people to both hyperkalemia and hypokalemia. These conditions can have grave consequences if not addressed quickly. Furthermore, the approach to definitive treatment depends on the underlying physiology that often occurs at the tubular level within the kidney.

Key words: *potassium balance, hyperkalemia, hypokalemia, older adults*

Disorders of Potassium Homeostasis

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Introduction

Derangements in serum potassium levels are very common. Studies have shown that hyperkalemia (when defined as greater than 6 mEq/litre) occurs in 1.3–10% (when defined as greater than 5.3 mEq/litre) of all patients.[1] The prevalence of hypokalemia (defined as less than 3.6 mEq/litre) among hospitalized patients is greater than 20%.[2] The greatest factor attributed to these abnormalities is due to medications, but other etiologies must be excluded as well. The risks of potassium derangements are many, and depending on comorbid conditions and patient factors, the consequences can be fatal. A known risk factor for such disorders is older age.

Medications

As mentioned, medications account for a large percentage of disordered potassium balance. Specifically, drugs that inhibit the renin-angiotensin-aldosterone system (RAAS) are common causes of hyperkalemia (Figure 1). The reason for this relationship is due to alterations in sodium delivery to the cortical collecting duct in the distal nephron. The cortical collecting duct is largely influenced by aldosterone, which is inhibited by angiotensin-converting enzyme inhibitors (ACEIs) and aldosterone receptor blockers (ARBs). The effect of aldosterone at this portion of the nephron is to reabsorb sodium from the tubular fluid and excrete potassium ions to maintain electroneutrality. When these medications are used, this series of events is also inhibited. By preventing the secretion of potassium ions which are to be lost in urine into the lumen, the risk of hyperkalemia increases. This risk increases even further when such medications are used in combination for common disease states such as congestive heart failure and chronic kidney disease.

In addition to inhibitors of the RAAS system, other commonly used medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and beta-blockers may also cause hyperkalemia. NSAIDs decrease the production of prostaglandins and cause constriction of the arterioles that supply the filtration units of the kidney called the glomeruli. Furthermore, renin secretion is dependent on prostaglandins as well. When afferent arteriolar constriction occurs, the amount of sodium delivery to the distal nephron is once again reduced and may cause hyperkalemia. Older adults are particularly vulnerable as they have age-related decline in kidney function and are increasingly dependent on the effect of prostaglandins to maintain normal kidney function and kidney perfusion. Beta-blockers can cause hyperkalemia in two manners: by blunting the sympathetic drive to release renin and by blocking the sodium-potassium exchanger and inhibiting cellular uptake of potassium.

On the other hand, medication-induced hypokalemia is most often due to the use of thiazide and loop diuretics. Both of these classes of medications inhibit sodium reabsorption along the proximal portions of the nephron. This leads to increased sodium delivery distally allowing for sodium uptake and potassium excretion. Loop diuretics also block potas-

sium absorption in the loop of Henle at the sodium-potassium-2chloride transporter. Often times, combinations of diuretics are utilized in the settings of volume overloaded states and the magnitude of hypokalemia can be greater. It is not uncommon to see contraction alkalosis accompany decreased serum potassium when due to diuretic use.

Other medications that may lead to hypokalemia include beta-agonists, insulin and certain calcium-channel blockers. Beta-agonists cause increased activity of the sodium-potassium pump and it is often seen in treatment of an acute asthma attack where nebulized beta-agonists are commonly used. Insulin and verapamil, when ingested in large amounts, causes increased cellular uptake of potassium and decrease plasma concentration.

Comorbid Conditions

In addition to older age, common medical problems heighten the risk of disordered potassium balance. The situation most frequently encountered by nephrologists is one in which a patient with chronic kidney disease (CKD) starts to develop hyperkalemia. In this clinical scenario, the renal handling of potassium is impaired because damage at the tubular level leads to resistance of the effect of aldosterone. In CKD, treatment with ACEIs or ARBs is standard of care but as kidney function deteriorates the risk of hyperkalemia in setting of inhibitors of the RAAS system increases. An estimated glomerular filtration rate of less than 30 ml/min should serve as a demarcation for when hyperkalemia risk is very high.[3] Also highlighted is the fact that a serum creatinine of 1.0 milligrams/decilitre can often correspond to levels of glomerular filtration rate less than 30 ml/min because of declining muscle mass with age.

Often the causes of CKD exponentially increase rates of potassium imbalance. Frequently, the etiology of CKD is diabetes mellitus. Diabetes on its own increases the rates of hyperkalemia as it causes a hyporeninemic hypoalderstone state as seen in renal tubular acidosis type IV. In diabetes and in aging, the changes at the level of the arteriole and the juxtaglomerular apparatus leads to decreased production of renin and, as a result, decreased aldosterone. There is also further data that diabetic patients have less conversion of prorenin to renin.[4] In addition to this mechanism, insulin resistance also leads to hyperkalemia because of decreased cellular uptake of potassium. The combined effects of CKD and diabetes place patients at increased risk of hyperkalemia.

Given the focus on the RAAS system up to this point, it is not surprising that primary adrenal insufficiency can also lead to hyperkalemia. The differences between the aforementioned clinical states and this one are that adrenal insufficiency will be accompanied by hyponatremia and/or hypotension. Often times the etiology of this disease is autoimmune destruction of cells in the adrenal cortex that are responsible for producing hormones needed to produce aldosterone. In a similar manner, heparin can be toxic and lead to the destruction of these same cells. Hyperkalemia due to heparin is rare but risks are higher when other factors related to potassium handling are also present such as medications like ACEIs.

A common cause of hyperkalemia in the critically ill is tissue death in setting of sepsis or crush injuries. Most of the body's potassium is stored intracellularly and, in such instances, large potassium loads are released due to cell lysis. Furthermore the acidemic state encountered in such situations promotes hyperkalemia as hydrogen ions are taken up by cells in exchange for potassium ions. Such a combination can rapidly increase the serum potassium concentration. There are situations where an acidemic state seen in diabetic ketoacidosis will lead to hypokalemia.

A variety of clinical syndromes can lead to hypokalemia. Hyperthyroidism leads to a hyperadrenergic state. In this setting, the sodium-potassium exchanger is stimulated in skeletal muscle cells leading to increased uptake of potassium. Furthermore, elevated levels of thyroid hormone stimulate not only stimulate the receptor but increase the sensitivity of beta receptors leading to further potassium uptake.[5] Rarely this can lead to the syndrome of thyrotoxic periodic paralysis.

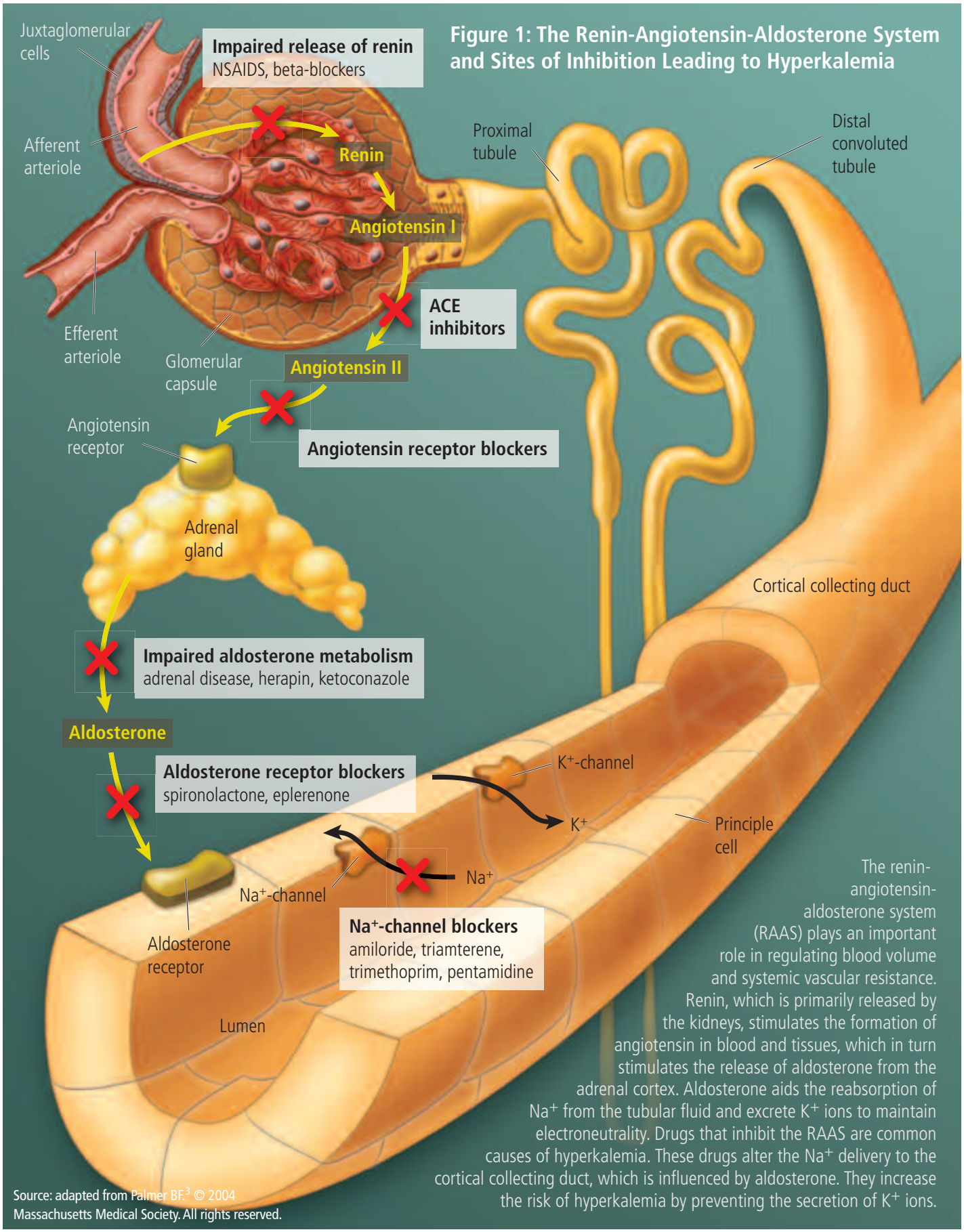
Decreased potassium intake rarely leads to hypokalemia. In states of extreme starvation, the kidney at a variety of levels within the tubules will act to conserve potassium losses in the urine. If lack of food consumption is prolonged, the tissue breakdown that occurs leads to release of potassium and prevents hypokalemia. When decreased potassium consumption is accompanied by decreased stores of magnesium, hypokalemia can occur. The lack of magnesium stores is thought to affect the sodium-potassium exchanger. The exact mechanism is unknown. This combination of hypokalemia and hypomagnesemia is often encountered in cases of prolonged alcoholism due to diet lacking in these elements.

Diabetic ketoacidosis can also lead to hypokalemia. The osmotic effect of elevated glucose levels leads to increased urine output and loss of potassium. The magnitude of effect is usually not severe due to the insulin deficient state. However, when treating these individuals with insulin supplementation, the potassium deficiency can be unmasked quickly.

Inherited disorders

Inherited disorders of potassium balance are rare but must be considered when other diagnoses have been excluded. A thorough family history can lead the physician to an appropriate diagnosis. Bartter and Gitelman's syndromes are characterized by hypokalemia, increased urinary excretion of potassium, and hypochloremic metabolic alkalosis. As with some of the other conditions discussed earlier, hyporeninemic hypoaldosteronism can be seen. Bartter syndrome is differentiated into a neonatal variant and the classical form. In the neonatal form, polyhydramnios occurs with polyuria occurring after childbirth. This can lead to dehydration and renal stones. Nephrolithiasis is due to increased urinary loss of calcium. The classical form starts

Figure 1: The Renin-Angiotensin-Aldosterone System and Sites of Inhibition Leading to Hyperkalemia



The renin-angiotensin-aldosterone system (RAAS) plays an important role in regulating blood volume and systemic vascular resistance. Renin, which is primarily released by the kidneys, stimulates the formation of angiotensin in blood and tissues, which in turn stimulates the release of aldosterone from the adrenal cortex. Aldosterone aids the reabsorption of Na^+ from the tubular fluid and excrete K^+ ions to maintain electroneutrality. Drugs that inhibit the RAAS are common causes of hyperkalemia. These drugs alter the Na^+ delivery to the cortical collecting duct, which is influenced by aldosterone. They increase the risk of hyperkalemia by preventing the secretion of K^+ ions.

Source: adapted from Palmer BF.[3]

after the age of two. Renal stones are less frequent because of less calcium excretion. Although rare, both of these states can lead to end-stage renal disease.

Gitelman's syndrome is a milder variant of the forms of Bartter syndrome. Affected individuals are often diagnosed in adulthood, and the symptoms include polyuria, polydipsia, muscle weakness and cramping, joint pains, and salt craving. Gitelman's syndrome is distinguishable from Bartter because hypomagnesemia and hypocalciuria is seen the in former. Low magnesium levels can be seen with Bartter's syndrome but hypocalciuria is never seen.[6]

Inherited forms of renal tubular acidosis type I may lead to hyperkalemia. This disorder occurs more frequently in areas of the world where consanguinity is more common.[7] The primary problem is with the hydrogen channel in the apical surface of alpha-intercalated cells. As a result, hydrogen ions are not secreted appropriately into the urine and leads to hyperkalemia.

Treatment

The treatment paradigm when dealing with disorders of potassium is focused on the ramifications on cardiac rhythms. Therapeutic maneuvers for hyperkalemia aim to stabilize cardiac potentials, increase uptake of potassium by cells, and remove potassium from the body. Intravenous calcium supplementation helps to decrease the membrane excitability of the myocytes. This is best done by administering 10% calcium gluconate ampoules. Alkalization with sodium bicarbonate therapy helps to ameliorate hyperkalemia due to acidosis. Once again, intravenous administration should be utilized. Insulin administration causes increased cellular uptake of potassium. Glucose should be given concomitantly to avoid hypoglycemia. A standard dose would be to give 10 units of regular insulin with hourly infusions of glucose. Polysulfone resin (Kayexalate) removes potassium by an enteric method. It exchanges sodium for potassium. Oral administration is appropriate unless the patient is not able to tolerate substances by mouth or has issues with intestinal motility. In these circumstances an enema can be utilized. If after all of the measures, hyperkalemia persists, extracorporeal methods such as hemodialysis should be utilized by potassium removal. On average it can remove 25–50 mEq of potassium hour.[8] Furthermore, hemodialysis will help to correct acidosis that can be the underlying cause of the elevated potassium.

Treatment of hypokalemia can be difficult and may often lead to hyperkalemia. Intravenous replacement should be utilized sparingly. No more than 20 mEq/hour should be given intravenously. The advantage to oral supplementation is that it enters the circulation slowly. A variety of oral preparations are available. The most appropriate form depends upon if other derangements are present such as acidosis. In this case, use of potassium bicarbonate would be ideal as it would treat both hypokalemia and acidosis. Mostly, potassium chloride is used because it has both a tablet and liquid form and is easily tolerated. It has been associated with gastric ulceration. Finally, ensuring a diet with adequate potassium intake should be ensured as well.

Key Points

- Alterations in potassium balance occur frequently in all patient populations, but in particular among older adults
- The etiologies are numerous and include drug-induced, hereditary, and as part of disease states. Most often the etiology of such disturbances is due to prescribed medications, but a number of clinical conditions exist which predispose people to both hyperkalemia and hypokalemia.
- As more patients develop such maladies, the rates and risks of both hyperkalemia and hypokalemia will continue to rise.
- The approach to definitive treatment depends on the underlying physiology that often occurs at the tubular level within the kidney.
- It is the physician's obligation to not only detect such disorders and treat appropriately but also to isolate modifiable risk factors to minimize the rates of occurrence.

Conclusion

Disorders of potassium balance are exceedingly common. They are a frequent cause of hospital admission and often seen during the course of an admission. The etiologies are numerous including drug-induced, hereditary, and as part of disease states. Comorbid conditions such as chronic kidney disease, older age, and other chronic medical conditions greatly increase the risk of abnormal serum potassium values. As more patients develop such maladies, the rates and risks of both hyperkalemia and hypokalemia will continue to rise. It is the physician's obligation to not only detect such disorders and treat appropriately but also to isolate modifiable risk factors to minimize the rates of occurrence.

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