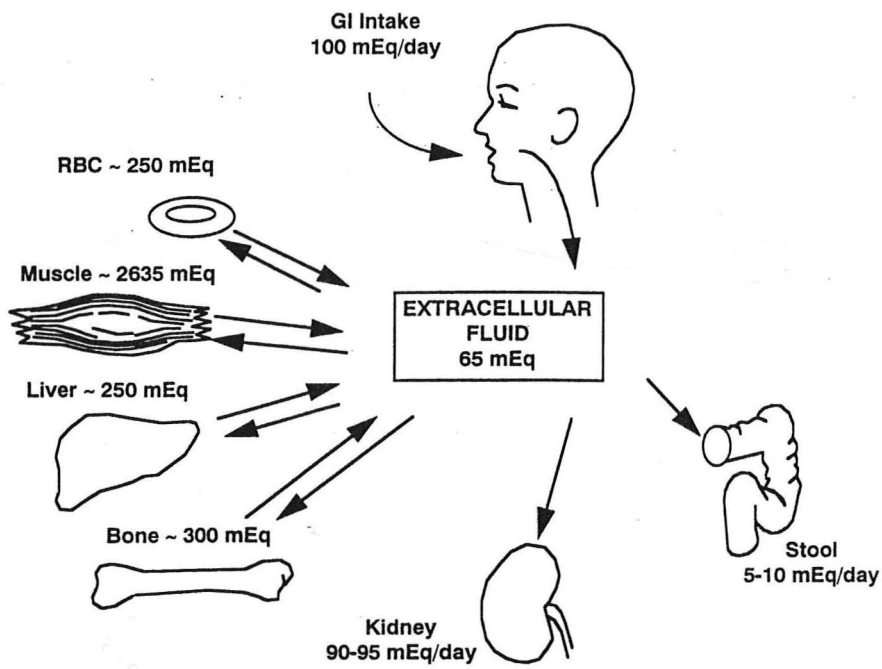
Clinical Disorders of Potassium Metabolism: Hypokalemia



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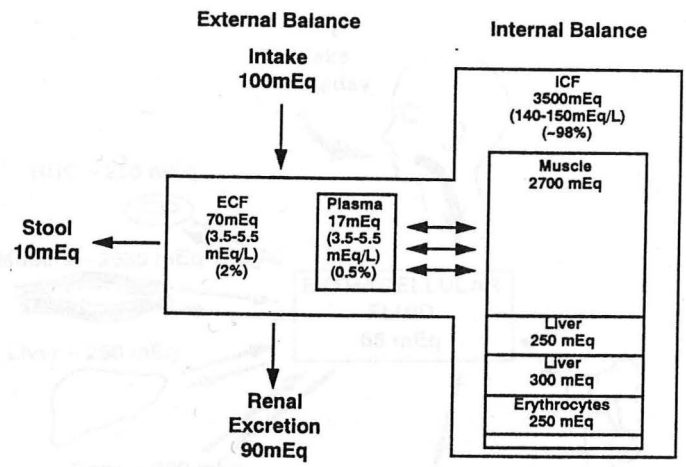
INTRODUCTION

Potassium deficiency resulting in hypokalemia is one of the most common electrolyte disorder in clinical medicine. The diagnosis and management of potassium deficiency can be clinically quite challenging for several reasons. Since 98% of total body potassium is intracellular, plasma potassium levels provide only an approximate index of total body potassium stores. Also, frequent occurrence of intercompartmental shifts further complicates the clinical assessment of potassium deficiency.

DISTRIBUTION AND PHYSIOLOGIC EFFECTS OF POTASSIUM

In an adult human the total body potassium content is approximately 50 mEq/kg body weight or about 3500 meq for an average 70-kg person. The majority of this potassium, roughly 98% is located inside the cells, primarily in muscle. Less than 2% of total body potassium is located in the extracellular fluid. The localization of sodium and potassium to the different fluid compartments is maintained by the Na, K-ATPase pump in the cell membrane, which transports Na^+ out of and K^+ into the cells in a 3:2 ratio. The net effect is that the K^+ concentration is about 140-150 meq/L in the cells, and 3.5-5.0 meq/L in the extracellular fluid (including the plasma).

Internal Potassium Homeostasis in a 70-kg Person



The maintenance of the large difference in plasma potassium concentration across the cell membrane is the primary determinant of the resting cell membrane potential, which is approximately -90 mV. The resting membrane potential (Em) across the cell membrane is expressed by the following formula.

$$Em = -61 \log \frac{r[K^+]_i + 0.01\,[Na^+]_i}{r[K^+]_e + 0.01\,[Na^+]_e}$$

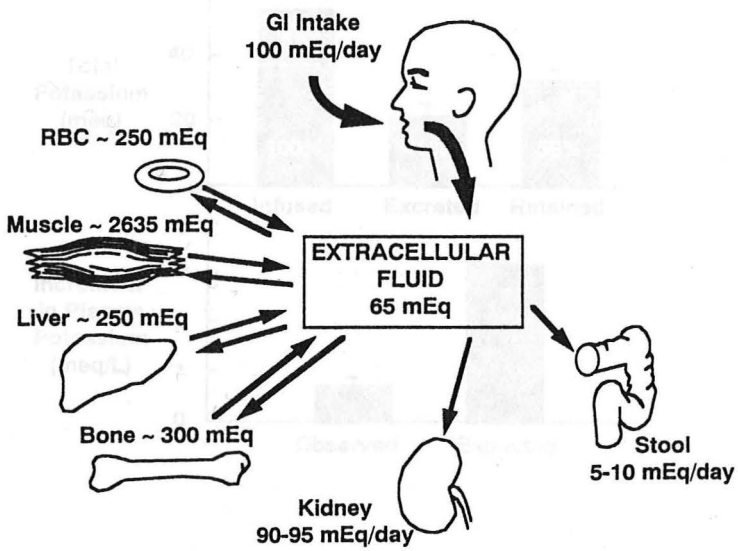
Where r is the 3:2 active transport ratio of the Na, K-ATPase pump, 0.01 is the relative membrane permeability of Na/K, and the subscripts i and e refer to the intracellular and extracellular K^+ and Na^+ concentrations, respectively. When one substitutes the average normal concentration for K^+ and Na^+,

$$Em = -61 \log \frac{3/2\,(140) + 0.01\,(12)}{3/2\quad(4) + 0.01\,(145)}$$

Em = -88 mV (Cell interior negative)

It is the resting membrane potential that sets the stage for the generation of the action potential that is essential for normal neural and muscular function. Even small changes in the intracellular/extracellular potassium ratio can markedly after this membrane potential and cause severe disturbances in neuromuscular function, particularly of the heart. It is therefore quite critical that both the total amount of K^+ within the body, as well as the distribution of K^+ between the intracellular and extracellular fluid compartments, must be closely regulated within a narrow range.

REGULATION OF POTASSIUM BALANCE

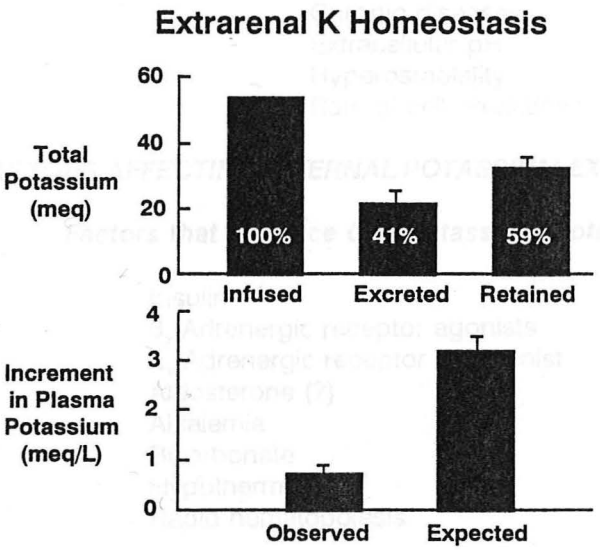


The average person consumes approximately 100 meq of K per day and the

majority of this is absorbed from the stomach and upper gastrointestinal tract. Approximately 10 meq/day of K is excreted in the stool. The colonic epithelial cells can secrete potassium; however, their capacity for K secretion is limited and the kidney is the primary organ responsible for the maintenance of **chronic** K balance. In contrast, **acute** K homeostasis is, in large part, regulated by extrarenal tissues.

The maintenance of K balance therefore involves the coordinated functions of **1)** the normal distribution of K between the extracellular fluid and the cells, and **2)** the renal excretion of the K added to the extracellular fluid from dietary intake.

This is the best illustrated by the following example. 4 large glasses of orange juice contain approximately 51 meq of K^+. The normal extracellular fluid volume is approximately 17 liters in a 70-kg man. Therefore, there would be a potentially dangerous 3.0 meq/L (51 meq/17L) increase in the plasma K^+ concentration if the ingested K^+ remained in the extracellular fluid. This is prevented by the rapid entry of most of the K^+ load into the cells. Within 6 to 8h, K^+ balance is then restored by the urinary excretion of the excess K^+.



DISTRIBUTION OF POTASSIUM BETWEEN EXTRACELLULAR FLUID AND CELLS

In the example given above, although the initial elevation in the plasma K^+ concentration directly promotes the intracellular movement of K^+, both catecholamines and insulin also play an important role in this process. In fact, in the daily minute to minute regulation of extrarenal potassium metabolism, insulin and catecholamines play an important role in maintaining the normal distribution of K^+ between the intracellular and extracellular compartments. Under pathophysiological conditions, however, changes in acid-base status and plasma osmolality can have profound effects on the plasma K^+ as well.

FACTORS INFLUENCING THE DISTRIBUTION OF K^+ BETWEEN THE CELLS AND THE EXTRACELLULAR FLUID

Physiologic

- Na^+-K^+-ATPase
- Catecholamines
- Insulin
- Plasma K^+ concentration
- Exercise

Pathologic

- Chronic diseases
- Extracellular pH
- Hyperosmolality
- Rate of cell breakdown

FACTORS AFFECTING INTERNAL POTASSIUM EXCHANGES

Factors that Enhance Cell Potassium Uptake

- Insulin
- β_2-Adrenergic receptor agonists
- α_1-Adrenergic receptor antagonist
- Aldosterone (?)
- Alkalemia
- Bicarbonate
- Hypothermia
- Rapid hematopoiesis

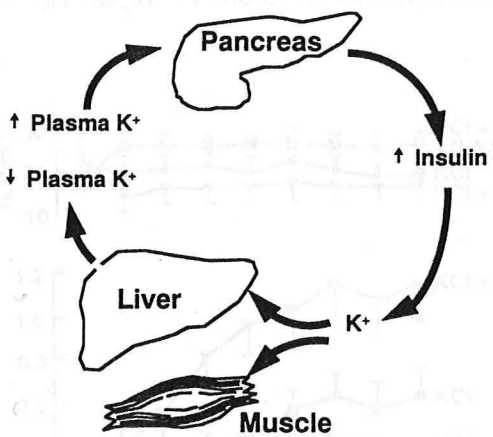
Factors that Reduce Cell Potassium Uptake or Increase Potassium Efflux

Glucagon
ß-Adrenergic receptor blockers (nonselective)
α-Adrenergic receptor agonists
Vigorous exercise
Aldosterone deficiency (?)
Acidemia (mineral acidosis, respiratory acidosis)
Hyperosmolality
Somatostatin

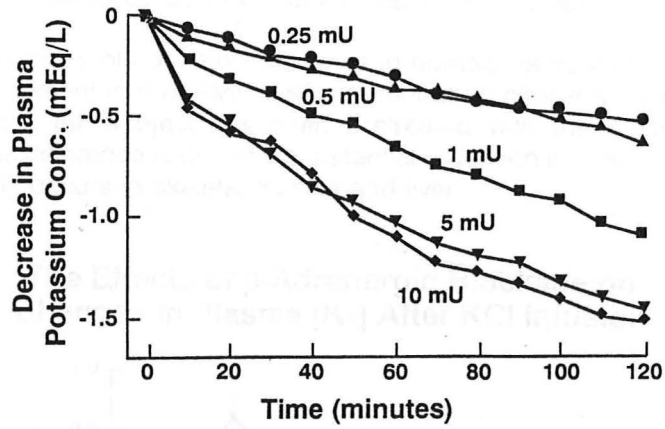
Insulin

Insulin promotes the entry of K^+ into the skeletal muscle and the liver, by increasing Na, K-ATPase activity. This property is independent of any effect on glucose transport, and plays a physiologic role in the regulation of the plasma K^+ concentration.

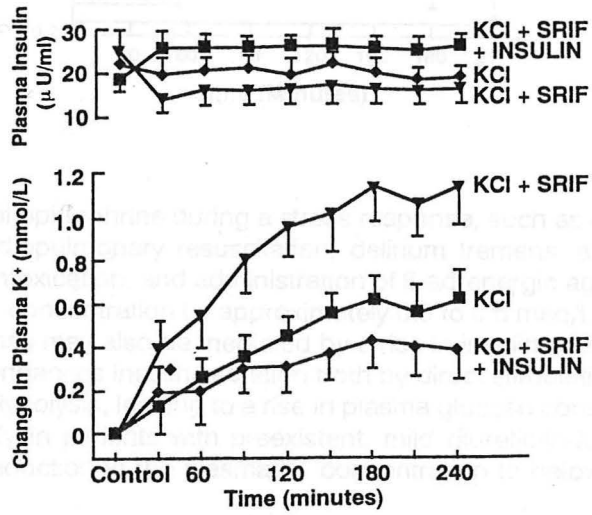
Feedback Loop Relating Changes in Plasma Potassium Concentrations to Changes in Insulin Secretion by the Beta Cell



Dose Related Effect of Euglycemic Hyperinsulinemia on Plasma Potassium Concentration



The importance of insulin is illustrated by studies in subjects in whom very low basal insulin levels were induced by an infusion of somatostatin, which impairs pancreatic insulin release. If KCL is infused to raise the plasma K^+ concentration by only 0.5-0.6 meq/L, while basal insulin secretion is inhibited by somatostatin, the increase in plasma K^+ is 2 to 3 fold greater than if the basal insulin concentration is maintained.

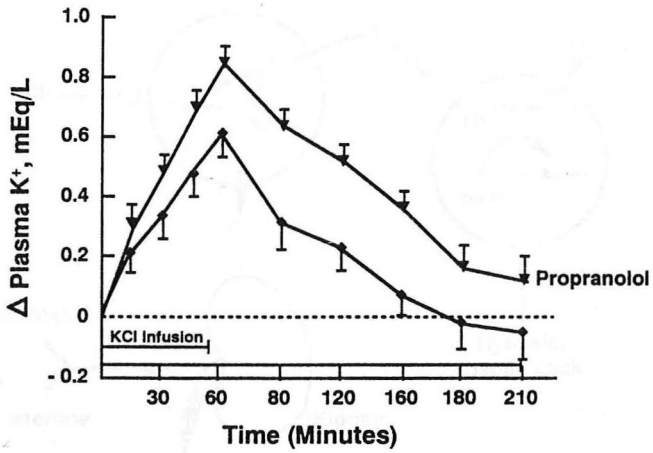


Catecholamines

Catecholamines also regulate internal K^+ distribution, with α-receptors impairing and β_2-receptors promoting the cellular entry of K^+. The β_2-receptor-induced stimulation of K^+ uptake is mediated by activation of the Na, K-ATPase pump.

The physiologic role of catecholamines in humans is illustrated by the next two studies. The increment in the plasma K^+ concentration after a K^+ load is greater and more prolonged if the subject has been pretreated with the ß-adrenergic blocker propranolol. This difference is due to a substantial reduction in cellular K^+ uptake, most of which normally occurs in skeletal muscle and liver.

The Effects of β-Adrenergic Blockade on Changes in Plasma [K+] After KCl Infusion

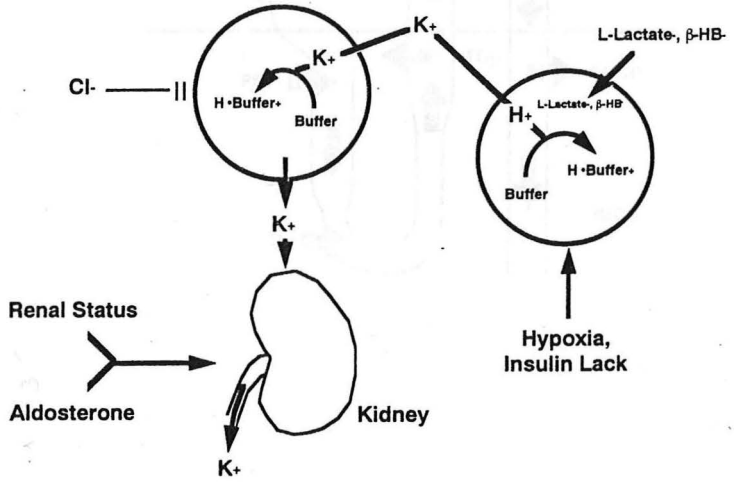


The release of epinephrine during a stress response, such as coronary ischemia, as well as post-cardiopulmonary resuscitation, delirium tremens, acute head trauma, acute theophylline intoxication, and administration of ß-adrenergic agonists, can acutely lower the plasma K^+ concentration by approximately 0.5 to 0.6 meq/L. In this setting the hypokalemic response may also be mediated by a rise in insulin release. Increased β_2-adrenergic activity enhances insulin secretion both by direct stimulation of the pancreas and by enhancing glycolysis, leading to a rise in plasma glucose concentration. The net effect can, especially in patients with preexistent, mild diuretic-induced hypokalemia, result in an acute reduction in the plasma K^+ concentration to below 2.8 meq/L.

Extracellular pH

Changes in acid-base balance may have important effects on the plasma K^+ concentration, particularly in those forms of metabolic acidosis that are not due to the accumulation of organic acids. In this setting more than 60 percent of the excess H^+ ions is buffered in the cells. Since the major extracellular anion Cl^- enters the cells only to a limited degree, electroneutrality is maintained by the movement of cellular K^+ and Na^+ into the ECF. The result is a variable increase in the plasma K^+ concentration of 0.2 to 1.7 meq/L for every 0.1 unit fall in the extracellular pH.

Buffering of H+ and the Consequent K+ Shift

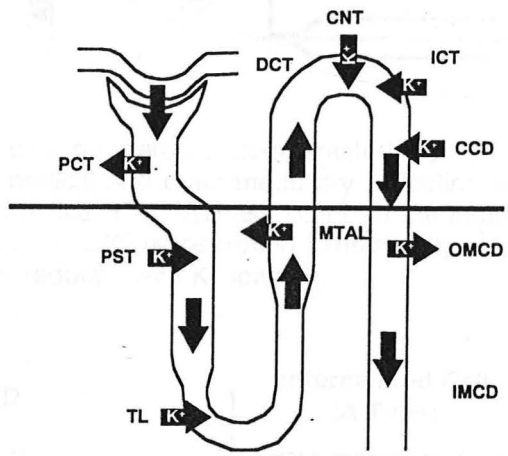


The change in the plasma K^+ concentration is less prominent in metabolic alkalosis. Although H^+ moves out of and K^+ moves into the cells in metabolic alkalosis, there is generally only a small reduction in the plasma K^+ concentration, unless there are concomitant urinary or gastrointestinal K^+ losses. Large changes in the plasma K^+ concentration is also not seen in respiratory alkalosis.

RENAL POTASSIUM EXCRETION

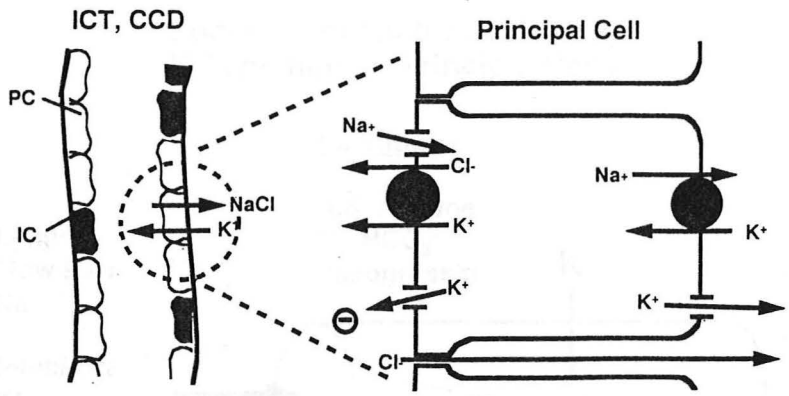
The kidney plays the major role in the maintenance of K^+ balance, appropriately varying K^+ secretion with changes in dietary K intake.

Schematic Diagram of Nephron in Mammalian Kidney

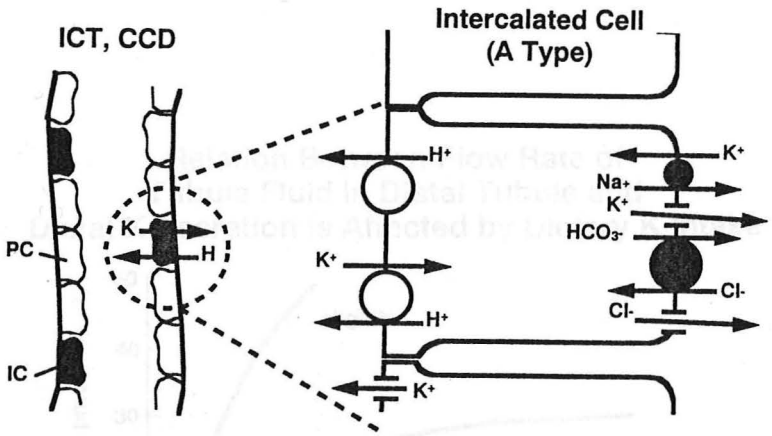


More than 90% of the filtered K^+ is reabsorbed in the proximal tubule and the loop of Henle, so that less than 10% of the filtered load is delivered to the early distal tubule. Proximal K^+ transport appears to passively follow that of Na^+ and water, whereas reabsorption in the thick ascending limb of the loop of Henle is mediated by the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane.

In comparison to these reabsorptive processes, K^+ is secreted by the connecting segment, the principal cells in the cortical and outer medullary collecting tubule, and perhaps the inner medullary collecting duct.

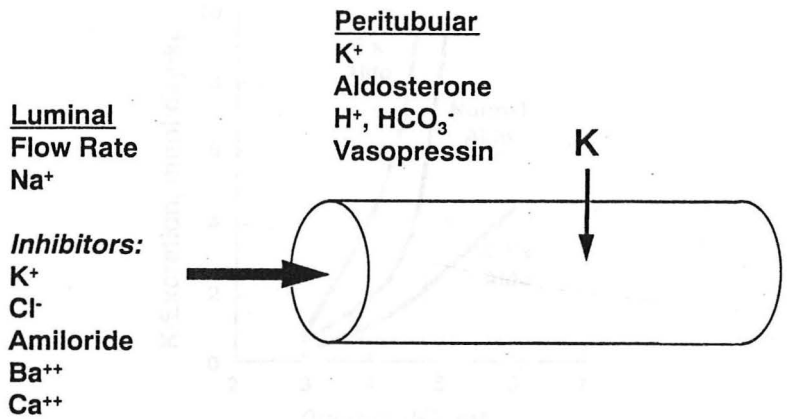


Distal secretion can be partially counteracted by K^+ reabsorption by the intercalated cells in the cortical and outer medullary collecting tubules. This process may be mediated by an active H^+-K^+-ATPase pump in the luminal membrane, which results in both H^+ secretion and K^+ reabsorption. The activity of this pump is increased with K^+ depletion, and is reduced with K^+ loading.

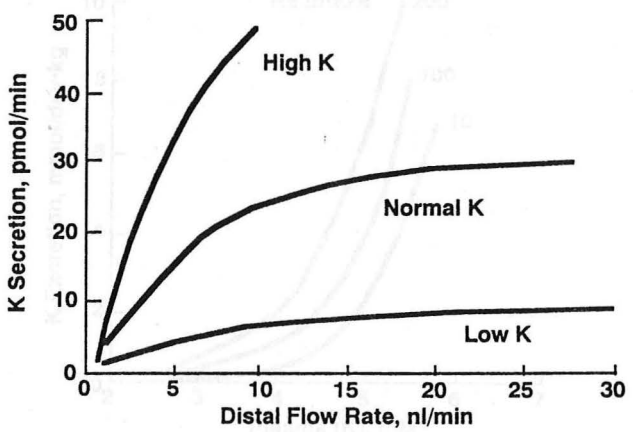


Aldosterone and plasma K^+ concentration, acting in concert, are the major physiologic regulators of K^+ secretion. Distal tubular flow rate, and transepithelial potential difference which is governed by Na^+ reabsorption, also play an important role in the regulation of K^+ secretion.

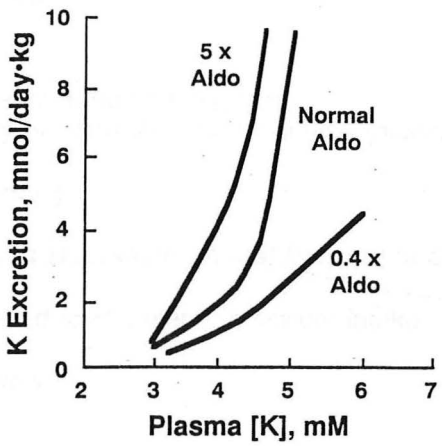
Summary of Factors Affecting K Secretion by Principal Cells



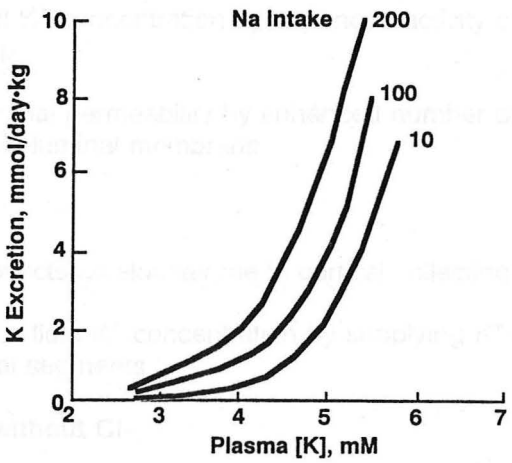
Relation Between Flow Rate of Tubule Fluid in Distal Tubule and Distal K Secretion is Affected by Dietary K Intake



Relation Between Plasma [K] and Renal K Excretion is Affected by Circulating Aldosterone



Relation Between Flow Rate of Tubule Fluid in Distal Tubule and Distal K Secretion is Affected by Dietary Na Intake



FACTORS AFFECTING RENAL POTASSIUM EXCRETION

Factors Increasing Distal Potassium Secretion

Increased plasma potassium or dietary potassium intake
Increased urine flow rate
Increased distal Na delivery
Increased aldosterone
Increased vasopressin
Increased potential difference (lumen negative)
Increased distal delivery of nonreabsorbable anions (bicarbonate)
Alkalosis
Metabolic acidosis (chronic)

Factors Decreasing Distal Potassium Secretion

Potassium depletion or reduced dietary potassium intake
Reduced urine flow rate
Reduced distal Na delivery
Reduced aldosterone
Vasopressin deficiency
Decreased PD (lumen positive)
Decreased distal sodium delivery
Metabolic acidosis (acute)
Enhanced chloride reabsorption

MECHANISMS REGULATING K^+ SECRETION IN THE DISTAL NEPHRON

Aldosterone

- Enhances luminal negativity by increased Na^+ reabsorption
- Increases cell K^+ concentration by enhanced activity of Na^+-K^+ ATPase pump
- Increases luminal permeability by enhanced number of open K^+ channels in luminal membrane

Plasma K^+

- Same renal effects as aldosterone in cortical collecting tubule
- Lowers tubular fluid K^+ concentration by supplying K^+-free fluid from more proximal segments

Na^+ reabsorption without Cl-

- Enhances luminal negativity

HYPOKALEMIA

Under normal circumstances K^+ enters the body by dietary intake, is primarily stored in the cells, and is then excreted in the urine, and to a lesser extent, in the stool and in the sweat. An abnormality in any one or more of these processes can result in hypokalemia.

APPROACH TO THE HYPOKALEMIC PATIENT

The search for the etiology of hypokalemia should include **a)** a careful history, including use of drugs, medications, presence of vomiting or diarrhea, **b)** physical examination, including blood pressure and orthostatic changes in blood pressure and heart rate, **c)** urine and plasma electrolytes and osmolality, **d)** when indicated arterial blood gas.

The most useful tests that are used to monitor the urinary K^+ excretion include:

a) 24 hour K^+ excretion rate: it should be less than 15 mmole/day in the presence of hypokalemia of extrarenal etiology. The disadvantage of this test is that it takes a long time before the clinician has access to the results.

b) Spot urine for K^+/creatinine ratio: it should be less than 1 mmol K^+/mmol creatinine in the presence of hypokalemia of extrarenal etiology. The advantage of this test is that it can be performed on a random urine sample, and the results are available within 1-2 hours.

c) TTKG or Transtubular $[K^+]$ Gradient which is also performed on a spot urine:

$$\textbf{TTKG} = \frac{\textbf{Urine/Plasma } [K^+]}{\textbf{Urine/Plasma OSM}}$$

TTKG is a test designed to reflect the driving force for K^+ secretion in the cortical collecting tubule. TTKG should be less than 2 in the presence of hypokalemia of extrarenal origin. If hypokalemia is a result of renal losses, for example secondary to hyperaldosteronism, then typical TTKG values are greater than 6.

DIFFERENTIAL DIAGNOSIS OF HYPOKALEMIA

A) ARTIFACTUAL OR PSEUDOHYPOKALEMIA

Metabolically active cells can take up K^+ after blood has been drawn. In cases of acute myeloid leukemia with a very high white blood cell count, the patient may have a relatively normal plasma K^+ but the measured value may be very low, in the absence

of symptoms, if the blood stands for a long period at room temperature. This problem can be avoided if the blood is stored at 4°C or if the plasma or serum is immediately separated from the cells.

B) TRANSCELLULAR DISTRIBUTION OF POTASSIUM

HYPOKALEMIA PRODUCED BY TRANSCELLULAR SHIFTS

Alkalemia
Respiratory alkalosis
Metabolic alkalosis
Insulin excess
Endogenous (glucose administration)
Exogenous
ß-Adrenergic catecholamine excess
Endogenous (acute stressful conditions)
Exogenous ($ß_2$-agonists)
Intoxications
Theophylline
Barium
Toluene
Hypokalemic periodic paralysis
Hereditary
Acquired (thyrotoxicosis)

Translocation of K^+ from the ECF into the cells can occur in a variety of conditions, leading to a transient reduction in the plasma K^+ concentration that can become clinically important.

Alkalosis

Alkalemia, either metabolic or respiratory, can promote K^+ entry into the cells. In alkalemic states, H^+ ions are released from the cellular buffers and move into the extracellular fluid to minimize the elevation in pH. To preserve electroneutrality, extracellular K^+ and Na^+ enter the cells. In general, the plasma K^+ falls less than 0.4 meq/L per 0.1 unit increase in extracellular pH.

Although the effect of alkalemia per se is relatively small, hypokalemia is a common finding in metabolic alkalosis. The major reason for this association is that the causitive factors, including diuretics, vomiting, hyperaldosteronism, induce simultaneous losses of urinary K^+ and H^+. Key functional events along the nephron which stimulate excessive K^+ secretion include high distal luminal HCO_3^- concentration, reduced distal luminal Cl^- concentration, and increased intracellular K^+ concentration of tubular epithelial cells.

In contrast, renal K^+ wasting during chronic respiratory alkalosis is minimal. It is proposed that chronic hypocapnia inhibits distal Na^+ reabsorption, impairs K^+ secretion, and therefore offsets the kaliuretic effects of alkalemia.

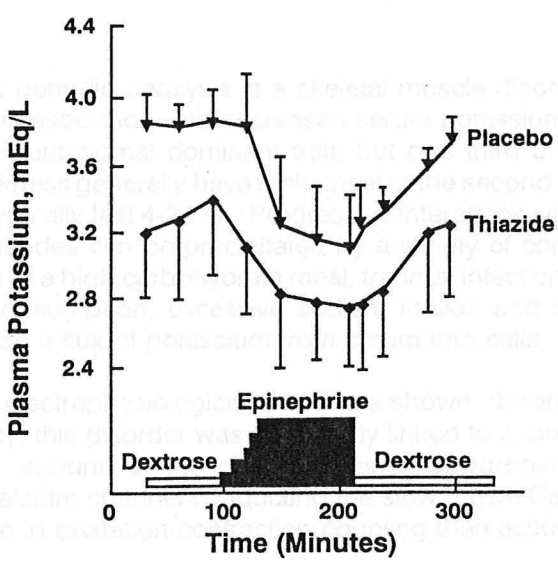
Increased Availability of Insulin

Insulin promotes the entry of K^+ into skeletal muscle and the liver. Patients with uncontrolled diabetes mellitus, especially when chronic, are markedly K^+ depleted, but the initial plasma K^+ concentration is usually normal or elevated, because the combination of insulin deficiency and hyperosmolality promotes the movement of intracellular K^+ into the ECF. These abnormalities are corrected by insulin, which then unmasks the underlying K^+ depletion.

Another common setting is when intravenous KCl is given in dextrose-containing solutions during the treatment of hypokalemia. In the setting the dextrose-induced stimulation of insulin may cause a transient further decrease in plasma K^+.

Increased ß-Adrenergic Activity

Catecholamines promote K^+ entry into the cells, which is mediated by the $ß_2$-adrenergic receptors, through stimulation of the activity of the Na, K-ATPase pump. Stress-induced epinephrine release, which occurs in a number of clinical conditions, can cause hypokalemia, which can become especially significant in the presence of prior hypokalemia, for example diuretic-induced hypokalemia.



The clinical conditions which are associated with increased epinephrine release include hypoglycemia, coronary ischemia, delirium tremens, post-cardiopulmonary resuscitation, acute head trauma, acute theophylline intoxication, and during the induction phase of anesthesia.

A similar effect, in which plasma K^+ concentration is lowered acutely, is also induced by the administration of ß-adrenergic agonist, such as albuterol or turbutaline to treat asthma, or dobutamine to treat heart failure. In heart failure patients, a rapid 0.4 meq/L fall in the plasma K^+ concentration following the administration of dobutamine may cause an exacerbation of ventricular arrhythmias.

Treatment of Anemia or Neutropenia

The administration of folic acid or vitamin B_{12} to patients with megaloblastic anemia frequently leads to a reduction in the plasma K^+ concentration to 3.0 meq/L or below, as an acute increase in red blood cell and platelet production by the bone marrow is associated with K^+ uptake by new cells.

Marked hypokalemia can also be induced by the administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) to correct neutropenia. The patients who respond by markedly increasing WBC production may have a significant hypokalemia.

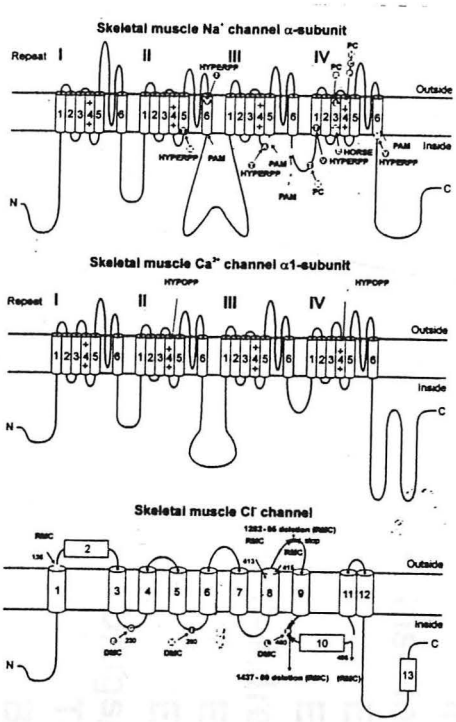
Hypokalemia can also occur following multiple transfusions with frozen, washed red cells. These cells lose up to 50% of their K^+ during storage. In the recipient, K^+ rapidly moves into the K^+-deficient RBC, thus causing hypokalemia.

Periodic Paralysis

Hypokalemic periodic paralysis is a skeletal muscle disorder in which episodic weakness occurs in association with decreased serum potassium levels. The disorder is transmitted as an autosomal dominant trait, but one third of cases are sporadic. Attacks of limb weakness generally have their onset in the second decade, usually begin during sleep, and typically last 4-24 hr. Progressive interattack weakness is common in these patients. Episodes can be precipitated by a variety of conditions, such as cold exposure, ingestion of a high carbohydrate meal, trauma, infections, rest after strenuous exercise, alcohol consumption, excessive sodium intake, and insulin administration, conditions that cause a flux of potassium from serum into cells.

Clinical and electrophysiological data have shown abnormalities of membrane excitability. Recently, this disorder was genetically linked to a muscle calcium channel, specifically the α-1 subunit of the skeletal muscle dihydropyridine (DHP) receptor (voltage-sensitive calcium channel conducting the slow L-type Ca^{2+} current), a channel involved much more in excitation-contraction coupling than action potentials. How the

inactivation of the L-type Ca^{2+} current is related to hypokalemia-induced attacks of muscle weakness is unknown. The working hypothesis is that the hypokalemia-induced membrane depolarization observed in excised muscle fibers may reduce Ca^{2+} release indirectly by inactivating Na^{+} channels.



At present time treatment consists of administration of K^{+} during attacks. In addition, the administration of the carbonic anhydrate inhibitor acetazolamide has been used successfully to treat severe attacks, and has been shown to be more effective than spironolactone.

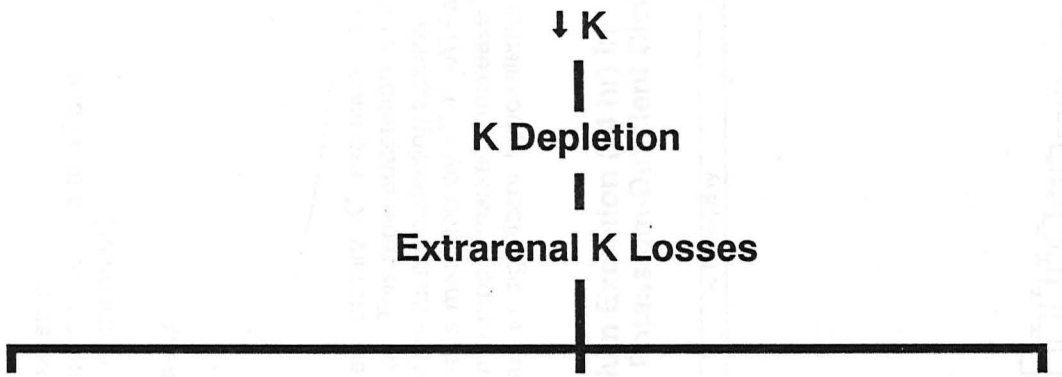
A variety of hypokalemic periodic paralysis, which is strongly associated with hyperthyroidism, occurs predominantly in orientals and manifests symptoms in the third and fourth decades. In addition, Sjogren's syndrome has been associated with hypokalemic periodic paralysis.

Hypokalemia

Spurious
- **High WBC count**

Redistribution
- **Acid-base alterations**
  - **Alkalemia**
  - **Increased plasma HCO_3**
- **Insulin excess**
  - **Endogenous**
  - **Exogenous**
- **∞ β–Adrenergic agonists**
  - **Endogenous**
  - **Exogenous**
- **Drugs/Toxins**
  - **Theophylline**
  - **Barium intoxication**
  - **Toluene intoxication**
  - **Calcium channel blockers (?)**
- **Hypokalemic periodic paralysis**
  - **Familial**
  - **Thyrotoxic**

Approach to the Hypokalemic Patient with Low Urinary Potassium



Metabolic Acidosis

- Diarrhea
- GI Fistulas
- Laxative Abuse

Normal Acid-Base Status

- Decreased Intake
- Cutaneous Losses
- Gastrointestinal Losses
- (Geophagia)
- Laxative Abuse

Metabolic Alkalosis

- Laxative Abuse
- Congenital
- Chloride Losing Diarrhea

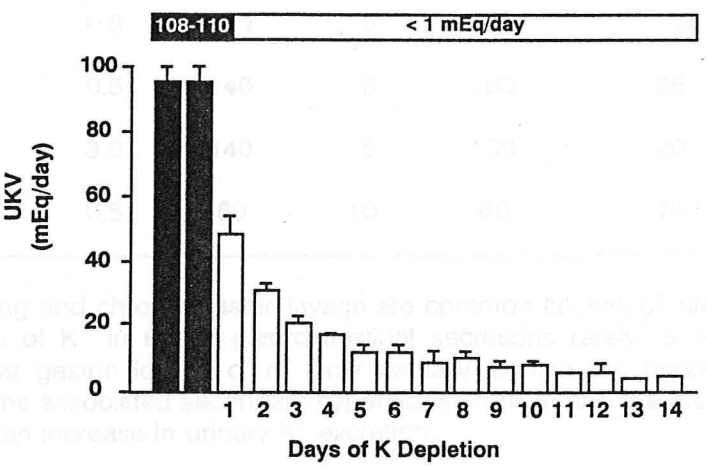
C) INADEQUATE DIETARY INTAKE

EXTRARENAL ETIOLOGIES OF POTASSIUM DEPLETION

Inadequate intake of potassium
Actual (fast, anorexia nervosa, tea and toast diet)
Relative (rapid increase in cell mass)
Copius perspiration
Gastrointestinal tract losses
Diarrhea
Geophagia
Laxative abuse
Rectal villous adenoma

If dietary K^+ intake is diminished, urinary K^+ excretion can be appropriately reduced to a minimum of 5 to 25 meq/day. This renal adaptation is mediated by tubular K^+ reabsorption in the cortical and outer medullary collecting tubules. The K^+ reabsorption occurs in the intercalated cells and is mediated by H^+-K^+-ATPase pumps in the luminal membranes; the activity of those pumps is markedly increased by hypokalemia. A low K^+ diet therefore does not result in significant hypokalemia unless intake is severely limited.

Urinary Potassium Excretion (24 hr) in Normal Men on a Potassium-Deficient Diet



Very low dietary K^+ intake can however occur in the poor and the elderly, who may have an average K^+ intake of only 25 meq/day (compared to 40-120 meq/day in the general population), partly because of the relatively high cost of K^+ containing foods. These patients are more likely to become hypokalemic if treated with diuretics, if they consume alcohol, or if they eat high carbohydrate containing foods.

Net K^+ intake can also be limited by chronic clay ingestion, which is especially common in certain areas in the Southwest. The clay appears to bind dietary K^+ and iron, diminishing their ability to be absorbed.

D) INCREASED GASTROINTESTINAL LOSSES

In normal subjects, approximately 3 to 6 liters of gastric, pancreatic, biliary, and intestinal secretions is secreted into the gastrointestinal lumen each day. Almost all of these fluids are then reabsorbed, as only 100 to 200 mL of water and 5 to 10 meq of K^+ are lost in the stool. Since each of these secretions contains K^+, the loss of any of them, either because of decreased reabsorption or increased secretion, can lead to K^+ depletion.

REPRESENTATIVE ELECTROLYTE CONTENTS AND VOLUMES OF UPPER GASTROINTESTINAL SECRETIONS

Site	Volume liters/day	$[Na^+]$ mmol/l	$[K^+]$ mmol/l	$[Cl^-]$ mmol/l	$[HCO_3^-]$ mmol/l
Gastric	1.5	20	10	130	0
Duodenal	3-8	110	15	115	10
Pancreas	0.5	140	5	30	115
Bile duct	0.5	140	5	100	25
Jejunal	3.0	140	5	100	20
Ileal	0.5	80	10	60	75

Vomiting and chronic gastric lavage are common causes of hypokalemia. The concentration of K^+ in upper gastrointestinal secretions rarely exceeds 10 meq/L, indicating that gastric losses of K^+ only partially explain the hypokalemia. More important is the associated secondary hyperaldosteronism and the metabolic alkalosis that result in an increase in urinary K^+ excretion.

The concentration of K^+ in lower gastrointestinal secretions exceed 80 meq/L. Diarrhea, due to a multitude of etiologies, can be associated with excessive stool K^+ losses and hypokalemia. Classically, profound K^+ depletion is seen in patients with diarrhea secondary to colonic villous adenomas, the Zollinger-Ellison syndrome, The Verner-Morrison syndrome or the VIPoma syndrome (pancreatic cholera), and of course cholera infection, where daily stool losses may average 8 liters of water, 1000 meq of Na^+, and 130 meq of K^+.

Laxative and enema abuse are also common causes of diarrhea and hypokalemia. The hypokalemia is worsened with committant diuretic abuse.

E) INCREASED RENAL LOSSES

Urinary K^+ excretion is primarily determined by K^+ secretion in the distal nephron, particularly the cortical collecting tubule. Inappropriate urinary K^+ loss leading to hypokalemia is most often due to conditions associated with **1)** mineralocorticoid excess, **2)** increased urinary flow of water and Na^+ to the distal secretory site, **3)** the reabsorption of Na^+ in the presence of a nonreabsorbable anion.

Renal Etiologies of Potassium Depletion

Diuretics
- Thiazide diuretics
- Loop diuretics

Renal tubular acidosis (RTA)
- Distal RTA (Type I)
- Proximal RTA (Type II)
- Carbonic anhydrase inhibitors

Diabetic ketoacidosis

Syndrome of chloride depletion
- Vomiting or gastric suction
- Diuretic therapy

Bartter's syndrome
- Classic Bartter's syndrome
- Gitelman's syndrome

Mineralocorticoid excess states
- Hyperaldosteronism
- Adrenogenital syndromes
- Exogenous mineralocorticoids
- Apparent mineralocorticoid excess
- Liddle's syndrome

Glucocorticoid excess states

Magnesium depletion

Antibiotic therapy

Leukemia

Approach to the Hypokalemic Patient with High Urinary K and Normal Acid-Base Status

↓ K

|

K Depletion

|

Renal K Losses

|

Normal Acid-Base Status

|

Acute Tubular Necrosis (Recovery)
Postobstruction Diuresis
Drugs (e.g., Aminoglycosides, cisplatin, high-dose Penicillin)
Leukemia
Magnesium Depletion

Approach to the Hypokalemic Patient with High Urinary K and Metabolic Acidosis

↓ K

K Depletion

Renal K Losses

Metabolic Acidosis

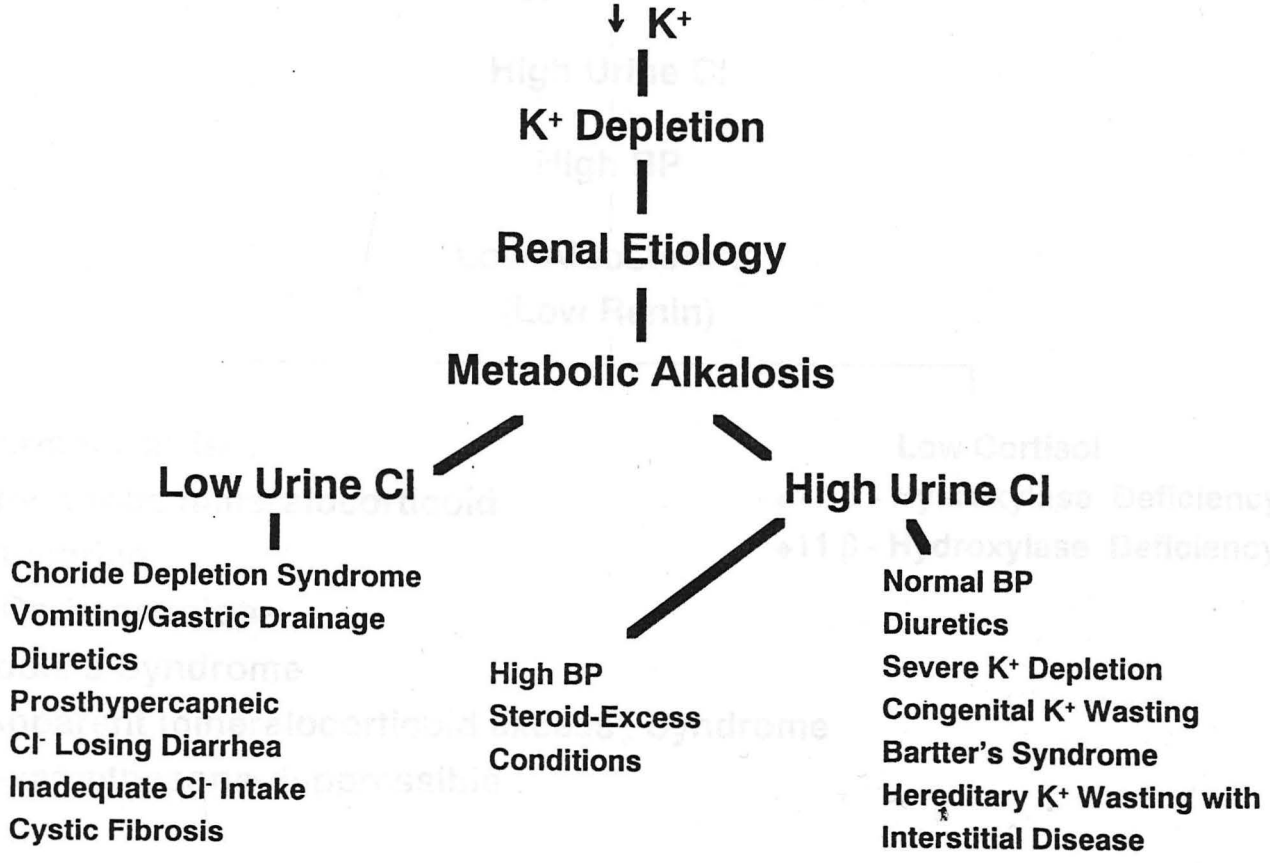
Normal Anion Gap

Renal Tubular Acidosis
(Proximal or Distal)
Carbonic Anhydrase Inhibitors
Ureterosigmoidostomy

Increased Anion Gap

Diabetic Ketoacidosis
Ethylene Glycol
Methanol

Approach to the Hypokalemic Patient with High Urinary K and Metabolic Alkalosis



↓ K^+

Renal Etiology/Metabolic Alkalosis

High Urine Cl

High BP

Low Aldosterone
(Low Renin)

Normal Cortisol

- **Exogenous mineralocorticoid**
  - **Licorice**
  - **Carbenoxolone**
- **Liddle's Syndrome**
- **"Apparent mineralocorticoid excess" Syndrome**
- **Dexamethasone-suppressible**

Low Cortisol

- **17 α - Hydroxylase Deficiency**
- **11 β - Hydroxylase Deficiency**

↓ K^+

|

Renal Etiology/Metabolic Alkalosis

|

High Urine Cl

|

High BP

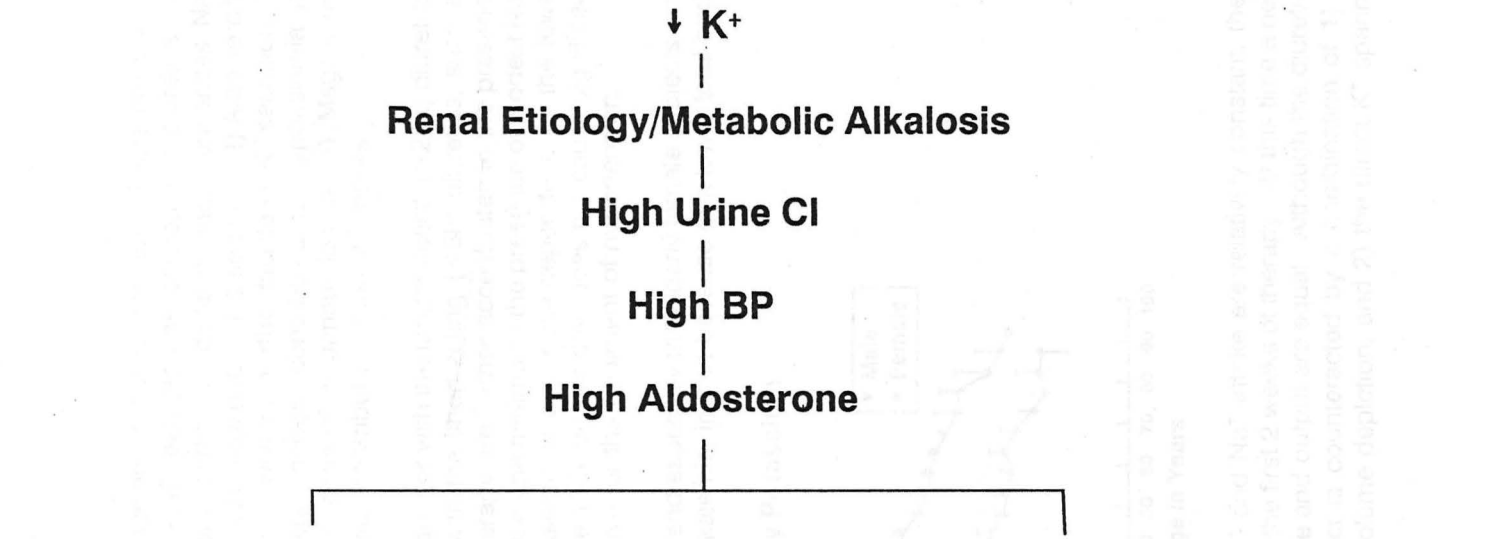
|

Normal Aldosterone

|

High Glucocorticoid

- **Cushing's Syndrome**
  - **Endogenous**
  - **Exogenous**
- **Ectopic ACTH**



High Renin

- **Secondary Hyperaldosteronism**
  - Renin-Secreting Tumor
  - Renovascular Disease
    - Main Renal Arteries
    - Small Vessels
  - Hereditary

Low Renin

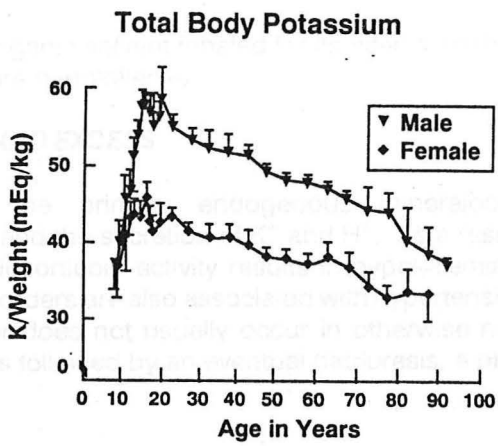
- **Primary Hyperaldosteronism**
  - Adenoma
  - Hyperplasia
  - Glucocorticoid-suppressible

DIURETICS

Hypokalemia is a potential complication of diuretic therapy. There are several mechanisms responsible for the increased K^+ excretion associated with diuretics: **1)** Inhibition of Na^+ reabsorption in the early portion of distal nephron enhances Na^+ delivery to K^+ secretory sites and increases the flow rate in this segment; **2)** Aldosterone released in response to diuretic-induced hypovolemia further facilitates K^+ secretion; **3)** Metabolic alkalosis resulting from diuretic therapy contributes to hypokalemia by promoting cellular uptake of K^+ and by enhancing urinary losses; **4)** Magnesium depletion complicating diuretic therapy may contribute to renal K^+ losses.

The magnitude of hypokalemia is greater with the longer acting (>24h) diuretics, such as chlorothalidone, as compared with the short-acting (<6h) diuretics, such as furosemide. K^+ losses during diuretic therapy are further accentuated in the presence of a high dietary Na^+ intake. The losses become minimal in the presence of modest Na^+ restriction. The diuretic-induced hypokalemia is also dose-dependent, as the lower doses of hydrochlorothiazide, for example 12.5 mg per day, does not cause significant K^+ depletion, but yet may be quite effective for the treatment of hypertension.

It should be noted that the elderly, and especially the elderly female subjects may be at increased risk for developing hypokalemia, in part because of a lower total body potassium.



If the diuretic dose and dietary K^+ and Na^+ intake are relatively constant, then almost all of the K^+ loss will occur during the first 2 weeks of therapy. At this time a new steady state is reached in which K^+ intake and output are equal. Although the diuretic-induced K^+ wasting continues, the effect is counteracted by a combination of **1)** a decrease in distal flow induced by the volume depletion, and **2)** the direct K^+ sparing effect of the hypokalemia per se.

ANTIBIOTICS AND OTHER DRUGS

The majority of penicillin derivatives, including sodium penicillin and carbenicillin have been implicated as potential causes of hypokalemia. Potential mechanisms include: **1)** Penicillin may act as an osmotic diuretic and, since it is a strong organic acid that is completely ionized at any urine pH, it may function as a nonreabsorbable anion; **2)** The administration of these antibiotics, especially carbenicillin, is often associated with a large Na^+ load that enhances distal tubule flow rate and potassium secretion.

Hypokalemia is also commonly seen in patients treated with amphotericin B. Increased membrane permeability due to an interaction of amphotericin with membrane sterols promotes distal K^+ secretion by increasing the K^+ permeability of the liminal membrane. In addition amphotericin also causes type 1 renal tubular acidosis which further contributes to the K^+ secretion. The tubular acidosis is probably related to increased membrane permeability to H^+ ions or to H_2C0_3, which allows the secreted acid to back-diffuse out of the tubular lumen.

Cis-dichlorodiammine platinum (cisplatinum), a chemotherapeutic agent, has been associated with hypokalemia, as well as hypomagnesemia. In this case the hypokalemia is usually resistant to K^+ replacement therapy until the magnesium deficiency is corrected.

Toluene, an organic solvent inhaled for its effects on the central nervous system, can also cause severe hypokalemia.

MINERALOCORTICOID EXCESS

Aldosterone, the primary endogenous mineralocorticoid, stimulates the reabsorption of Na^+ and the secretion of K^+ and H^+. As a result, increased aldosterone or any other mineralocorticoid activity results in hypokalemia and metabolic acidosis. In addition, these disorders are also associated with hypertension and mild hypernatremia. Edema, however does not usually occur in otherwise normal subjects, since the initial Na^+ retention is followed by an eventual natriuresis, a phenomenon referred to as aldosterone escape.

CAUSES OF PRIMARY MINERALOCORTICOID EXCESS

Primary hyperaldosteronism
A. Adenoma
B. Hyperplasia
C. Carcinoma

Cushing's disease

Congenital adrenal hyperplasia
A. 17a-hydroxylase deficiency
B. 11ß-hydroxylase deficiency

Chronic ingestion of exogenous mineralocorticoid
A. Fludrocortisone

Hyperreninism
A. Renal artery stenosis
B. Renin-secreting tumor

Hypersecretion of deoxycorticosterone or other mineralocorticoid including cortisol in the syndrome of apparent mineralocorticoid excess as induced by licorice.

PRIMARY HYPERALDOSTERONISM

The autonomous hypersecretion of aldosterone may result from a unilateral adrenal adenoma or carcinoma or from bilateral hyperplasia. An adenoma is responsible for about 60% of cases, with hyperplasia accounting for most of remaining patients.

The mechanism responsible for idiopathic adrenal hyperplasia is not well understood. Increased sensitivity of the adrenal zona glomerulusa to angiotensin II is one mechanism by which aldosterone secretion is elevated. Another potential mechanism involves the serotonergic pathways, as cyproheptadine, a serotonin antagonist, markedly lowers aldosterone secretion in some patients.

The diagnosis of primary hyperaldosteronism is established by showing **1)** urinary K^+ in excess of 25 meq/day, **2)** increased plasma or urine aldosterone, which is not suppressed by a high dietary Na^+ or intravenous saline administration, **3)** a plasma aldosterone PA to plasma renin (PRA) ratio in excess of 30 is also diagnostic, since the mean value for PA/PRA ratio in normotensive controls and patients with essential hypertension is 4 to 5.

The diagnosis of adenoma versus hyperplasia is established by **1)** obtaining 8 a.m. supine followed by 12:00 noon upright plasma aldosterone and renin values: because of increased sensitivity of hyperplasia to angiotensin II, and adenoma to ACTH, compared to 8 a.m. supine values the 12 noon upright aldosterone levels are higher in

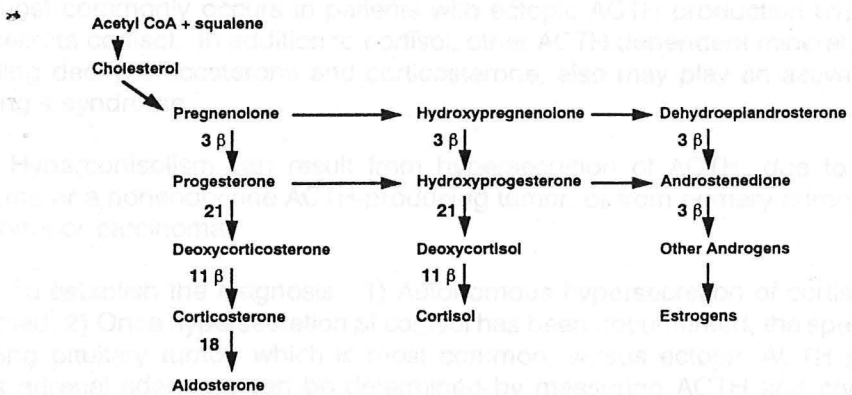
patients with hyperplasia, and lower in subjects with adenoma; **2)** CT scan or MR imaging; these test are useful in establishing the presence of an adenoma, or absence of carcinoma; **3)** although not widely available, scintillation scanning with 131-I-iodocholesterol, a precursor of aldosterone, may be more accurate than CT scanning or MRI in detecting a functioning unilateral lesion; **4)** adrenal vein aldosterone levels, measured by an experienced radiologist, can also be helpful in distinguishing between an adenoma and hyperplasia: Unilateral disease is associated with usually greater than 10 fold increase in aldosterone concentration on the side of the adenoma, whereas in bilateral hyperplasia there is little difference between the sides.

The treatment of choice for adenoma, when possible, is surgical removal, whereas for hyperplasia is medical, including amiloride or aldactone, angiotensin converting enzyme inhibitors, and calcium channel blockers.

GLUCOCORTICOID-REMEDIABLE HYPERALDOSTERONISM

Glucocorticoid-remediable hyperaldosteronism is a rare form of adrenal hyperplasia in which the hypersecretion of aldosterone can be reversed with glucocorticoid therapy. Normal subjects synthesize aldosterone in the zona glomerulosa, which lacks 17-hydroxylase required for cortisol synthesis, but not in the ACTH-sensitive zona fasciculata, which lacks the enzymes required to add the necessary aldehyde to corticosterone at the 18-carbon position. Patients with glucocorticoid-remediable hyperaldosteronism have ACTH-sensitive aldosterone production occurring in the zona fasciculata. The primary defect is a chimeric gene on chromosome 8 that contains the regulatory region of 11ß-hydroxylase and the coding sequences of the aldosterone synthase gene.

Schematic Pathways of Adrenal Steroid Biosynthesis



Glucocorticoid-remediable hyperaldosteronism is inherited as an autosomal dominant trait. The presence of this rare disorder as the cause of primary hyperaldosteronism should be suspected from the positive family history and the typical onset of hypertension before age 21. The diagnosis can be confirmed by documenting the increased secretion of 18-carbon oxidation products of cortisol - 18-hydroxycortisol and 18-oxocortisol - or, by direct genetic analysis.

Treatment consist of administration of glucocorticoids, dexamethasone or prednisone, which corrects the overproduction of aldosterone by diminishing ACTH release, and which usually also normalizes the blood pressure.

CONGENITAL ADRENAL HYPERPLASIA

17α-HYDROXYLASE DEFICIENCY impairs cortisol and androgen synthesis; the ensuing rise in ACTH release will increase the synthesis of the mineralocorticoids deoxycorticosterone and corticosterone, resulting in hypertension, hypokalemia, and metabolic alkalosis, but no virilization.

11ß-HYDROXYLASE DEFICIENCY, like 17-hydroxylase deficiency, is associated with ACTH-induced overproduction of the mineralocorticoid deoxycorticosterone, leading to hypertension and hypokalemia. This disorder, however, is virilizing, since there is also hypersecretion of adrenal androgens.

CUSHING'S SYNDROME (GLUCOCORTICOIS EXCESS)

Cortisol is synthesized in the zona fasciculata under the influence of ACTH. Cortisol binds as avidly as aldosterone to the mineralocorticoid receptor. Cortisol, however, normally has weak mineralocorticoid activity because it is inactivated to cortisone in the aldosterone-sensitive cells in the collecting tubules. In spite of this, some patients with Cushing's syndrome develop hypokalemia and metabolic alkalosis. This most commonly occurs in patients with ectopic ACTH production who markedly over secrete cortisol. In addition to cortisol, other ACTH dependent mineralocorticoids, including deoxycorticosterone and corticosterone, also may play an active role in the Cushing's syndrome.

Hypercortisolism can result from hypersecretion of ACTH, due to a pituitary adenoma or a nonendocrine ACTH-producing tumor, or from primary adrenal diseases (adenoma or carcinoma).

To establish the diagnosis: **1)** Autonomous hypersecretion of cortisol must be confirmed; **2)** Once hypersecretion of cortisol has been documented, the specific cause, including pituitary tumor, which is most common, versus ectopic ACTH production, versus adrenal adenoma can be determined by measuring ACTH and cortisol levels before and after a dexamethasone suppression test: **a)** pituitary disease is associated

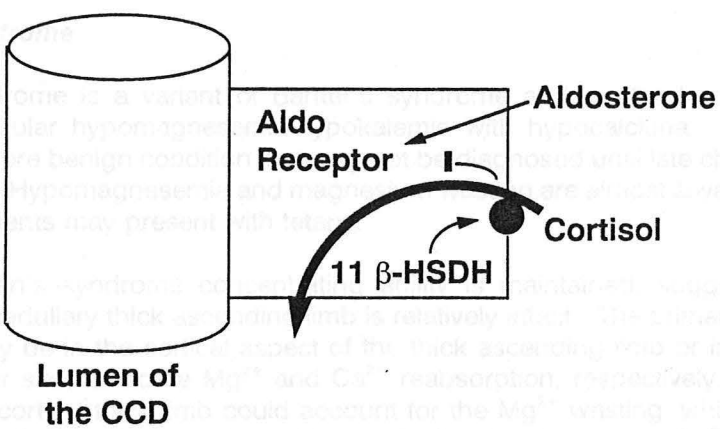
with normal to increased ACTH secretion, and both ACTH and cortisol levels are suppressed by more than 50% following dexamethasone; **b)** ACTH levels are markedly increased with ectopic production, and no suppression occurs following dexamethasone; **c)** in adrenal disease ACTH levels are very low, and cortisol secretion is not suppressed by dexamethasone.

Treatment consists of **a)** transsphenoidal microsurgery for pituitary disease; **b)** removal of a unilateral adrenal lesion; **c)** patients who are not surgical candidates can be treated with ketoconazole or metyrapone (both inhibit 11 ß-hydroxylase which converts deoxycorticol to cortisol), aminoglutethimide (inhibits the conversion of cholesterol to pregnenolone), or the adrenolytic agent mitotane.

Licorice and the Syndrome of Apparent Mineralocorticoid Excess

Subjects chronically ingesting large amounts of licorice, or licorice-containing chewing tobacco, or licorice-like compounds including carbonoxolone, can develop a reversible syndrome that acts like primary hyperaldosteronism. Glycyrrhenitic acid, a steroid in licorice has slight mineralocorticoid activity. In addition, this compound also impairs the action of the enzyme 11 ß-hydroxysteroid dehydrogenase that converts cortisol to cortisone in aldosterone target tissues such as the collecting tubules in the kidney. Increased levels of cortisol therefore activate the mineralocorticoid receptors and produce a syndrome similar to primary hyperaldosteronism. Endogenous aldosterone secretion is appropriately suppressed in this setting.

Influence of 11 β-hydroxysteroid Dehydrogenase on "Aldosterone-Like" Actions in the CCD



In the syndrome of apparent mineralocorticoid excess there is a genetic defect in which cortisol metabolism is impaired in the collecting tubules. Administration of dexamethasone suppresses endogenous cortisol production and corrects the hypokalemia. Alternatively, amiloride or spironolactone and a low Na^+ diet also corrects the hypokalemia in the syndrome of apparent mineralocorticoid excess.

Bartter's Syndrome

Bartter's syndrome generally presents early in life and is associated with growth retardation, hypokalemia, metabolic alkalosis, hyperaldosteronism, hyperreninemia, marked hypertrophy and hyperplasia of the juxtaglomerular apparatus, normal blood pressure, insensitivity to exogenous angiotensin II, polyuria, polydipsia, and decreased concentrating ability. Urinary calcium excretion is often increased and the plasma magnesium concentration is either normal or mildly reduced in most patients. The renal release of vasodilator prostaglandins (prostaglandin E_2 and prostacyclin) is also increased in this condition and may partially explain why the blood pressure remains normal.

The urinary findings described above are compatible with a primary defect in sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle. The activation of the renin-angiotensin-aldosterone system and the increased distal flow, both due to the reabsorptive defect, enhances K^+ and H^+ secretion in the collecting tubules, resulting in hypokalemia and metabolic alkalosis.

The diagnosis of the syndrome depends on establishing renal K^+ and Cl^- wasting. Repeated urinary screening for diuretics is particularly essential to exclude diuretic abuse. In addition, psychogenic vomiting presents with many features similar to Bartter's syndrome; distal fractional reabsorption of Cl^- however is high in this condition resulting in a low urinary Cl^-.

Treatment consists of **a)** replacement of KCl, **b)** correction of hypomagnesemia, **c)** use of prostaglandin synthase inhibitors, **d)** use of potassium-sparing diuretics, amiloride, spironolactone, or triamterene.

Gitelman's Syndrome

This syndrome is a variant of Bartter's syndrome and is also known as the syndrome of tubular hypomagnesemia-hypokalemia with hypocalciuria. Gitelman's syndrome is a more benign condition that may not be diagnosed until late childhood or even adulthood. Hypomagnesemia and magnesium wasting are almost always present and affected patients may present with tetany.

In Gitelman's syndrome concentrating ability is maintained, suggesting that function in the medullary thick ascending limb is relatively intact. The primary defect in this disorder may be in the cortical aspect of the thick ascending limb or in the distal tubule, the major sites of active Mg^{2+} and Ca^{2+} reabsorption, respectively. Impaired transport in the cortical thick limb could account for the Mg^{2+} wasting, while reduced Na^+ reabsorption in the distal tubule could account for the decrease in Ca^{2+} excretion (in contrast to the hypercalciuria seen in classic Bartter's syndrome).

Liddle's Syndrome

This is a rare autosomal dominant condition, in which there is a primary increase in collecting tubule Na^+ reabsorption and, in most cases, K^+ secretion. Correction of the hypokalemia and hypertension in one patient by renal transplantation suggested that enhanced activity of the luminal membrane Na^+ channels, rather than a circulating factor such as increased secretion of a nonaldosterone mineralocorticoid, is the underlying defect in this disorder. Recently Liddle's syndrome has been found to be caused by mutations in the ß subunit of the epithelial Na^+ channel. Functionally these mutations result in constitutive activation of the amiloride-sensitive distal renal tubular Na^+ channel.

Therapy in Liddle's syndrome consists of amiloride or triamterene, potassium-sparing diuretics which directly inhibit the Na^+ channel. Interestingly, the mineralocorticoid antagonist spironolactone is ineffective, since the increase in Na^+ channel activity is not mediated by aldosterone.

Renal Tubular Acidosis

Hypokalemia secondary to excessive urinary K^+ excretion is a common complication of both type I and type II renal tubular acidosis.

In type I (distal) RTA distal H^+ secretion is reduced. As a result Na^+ reabsorption must occur in exchange for K^+ in order for Na^+ balance to occur. Severe K^+ depletion with a plasma K^+ concentration below 2.0 meq/L may occur in this disorder. One of the more common causes of type I RTA in adults is Sjogren's syndrome. In most patients with distal RTA, K^+ supplements are not required to maintain normokalemia when correction of acidosis is achieved. In some patients K^+ losses however continue despite correction of the acidosis.

In type II (proximal) RTA increased quantities of Na^+ and $HC0^-_3$ are delivered to the distal nephron which enhances urinary K^+ excretion. This effect becomes even more prominent after the institution of alkali therapy, which raises the filtered $HC0^-_3$ load above proximal tubular reabsorptive capacity. These patients therefore require K^+ as well as $HC0_3^-$ replacement therapy.

Hypomagnesemia

Hypomagnesemia is a relatively common finding in hypokalemic patients. Hypomagnesemia of any cause can lead to K^+ depletion and hypokalemia. In addition, in some cases the underlying abnormality, including thiazide or loop diuretics, cisplatinum toxicity, or primary hyperaldosteronism, impair both K^+ and Mg^{2+} reabsorption by the kidney.

The mechanisms proposed for Mg^{2+} deficiency to cause increased K^+ secretion include: **a)** enhanced secretion of aldosterone, and **b)** enhanced opening of K^+ channels in the luminal membrane of the thick ascending limb of the loop of Henle.

Correction of the hypokalemia is usually not possible by K^+ repletion alone, unless magnesium balance is also corrected at the same time. Magnesium repletion in the presence of hypokalemia should preferably begin with magnesium oxide, as the use of magnesium sulfate can initially increase urinary K^+ losses since sulfate acts as a nonreabsorbable anion.

CONSEQUENCES OF POTASSIUM DEPLETION

Hypokalemia, whether produced by transcellular shifts or K^+ depletion, can alter the function of excitable tissues, including both nerve and muscle. The increase in the intracellular to extracellular K^+ ratio hyperpolarizes the membrane, which then increases the threshold for initiating an action potential, and also the subsequent repolarization process.

Clinical Sequelae of K^+ Depletion

Cardiac
- Ventricular arrhythmias
- Sensitivity to digitalis toxicity

Neuromuscular
- Weakness, paralysis
- Rhabdomyolysis
- Constipation, ileus

Renal
- Altered renal hemodynamics
- Interstitial nephritis
- Renal hypertrophy

Fluids and Electrolytes
- Polyuria
- Polydypsia
- ↑ NH_3 production
- Metabolic alkalosis
- Cl^- wasting
- Edema, Na^+ retention
- ↑ Citrate reabsorption
- ↓ Phosphate reabsorption

Metabolic Effects
- Glucose intolerance, ↓ insulin
- Growth Retardation

Hormonal Effects
- ↓ Aldosterone
- ↑ Plasma renin activity

Neuromuscular effects

K^+ levels below 3.0 meq/L are often associated with complaint of muscular weakness, generalized malaise, fatigue, the restless leg syndrome, and occasionally myalgias. Severe K^+ depletion can result in two major neuromuscular complications: paralysis and rhabdomyolysis.

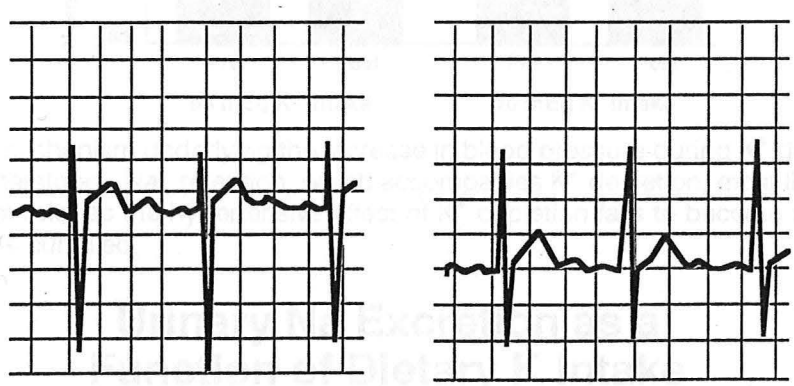
Skeletal muscle dysfunction is caused by several defects associated with K^+ depletion: **1)** a change in transmembrane ion transport, **2)** impaired muscle blood flow and absence of exercise-induced vasodilatation, **3)** a depletion of energy (glycogen) stores, **4)** total loss of cellular integrity which can result in muscle necrosis.

In addition, involvement of smooth muscle in the gastrointestinal tract can produce a paralytic ileus and the symptoms of abdominal distension, anorexia, nausea, vomiting, and constipation. Urinary bladder mobility is also decreased as a result of K^+ depletion.

Cardiac Effects

The cardiac manifestations of K^+ depletion include prominent abnormalities of electrophysiology. Hypokalemia is associated with hyperpolarization of the membrane potential at the end of repolarization, which could lead to increased automaticity, decreased conduction velocity, and shortened refractory period. The ECG changes in K^+ depletion include prolongation of the Q-U interval, widening, flattening, or inverting of the T wave, depression the S-T segment, prominent U waves, diminished QRS voltage, and increased A-V conduction time.

Prominent U Waves often Seen in Hypokalemia



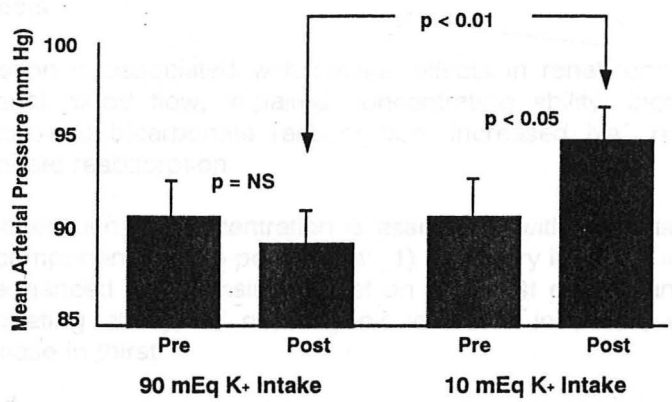
V2 **V3**

A variety of cardiac arrhythmias can be induced by hypokalemia. These include premature atrial and ventricular beats, sinus bradycardia, proxysmal atrial or junctional tachycardia, A-V block, ventricular tachycardia or fibrillation. The likelihood of inducing an arrhythmia with K^+ depletion is enhanced in a variety of clinical settings. These include coronary ischemia and left ventricular hypertrophy, and the use of digitalis. Digitalis-induced arrhythmias typically occur with toxic plasma levels if K^+ balance is normal, but can be seen with therapeutic plasma levels when hypokalemia is present.

Effects on Blood Pressure

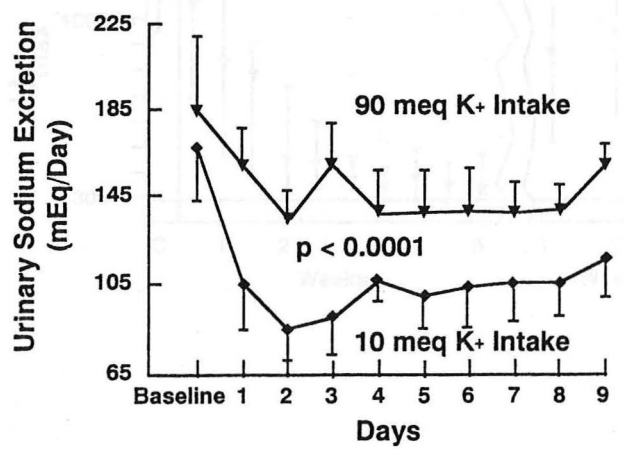
Experimental and clinical studies suggest that K^+ intake plays an important role in blood pressure regulation. K^+ depletion lowers blood pressure in most rat studies. In contrast, epidemiologic surveys suggest that populations ingesting diets low in K^+ are more susceptible to the development of hypertension. In fact, several clinical studies have demonstrated that K^+ depletion is associated with an increased in blood pressure, while K^+ supplementation exerts the opposite effect.

Blood Pressure on a Normal (90 mEq/d) or a Low (10mEq/d) K Diet



The mechanism underlying the increase in blood pressure during K^+ depletion is not well understood. Na^+ retention, which accompanies K^+ depletion, most likely plays an important role, as the hypertensive effect of K^+ depletion fails to become manifest if Na^+ intake is curtailed.

Urinary Na Excretion as a Function of Dietary K Intake



Renal Effects

K^+ depletion has both structural and functional effects on the kidney.

Morphologic Changes

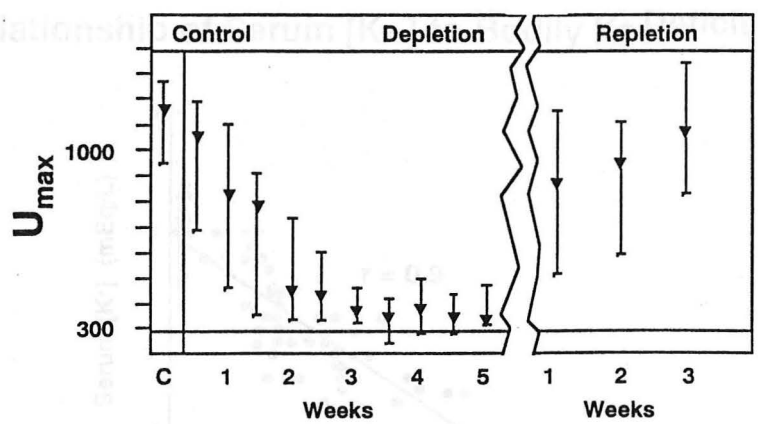
In humans the characteristic histological finding is vacuolization of proximal and distal tubular cells. In chronic K^+ depletion diffuse chronic interstitial nephritis and scaring has been observed. Furthermore, chronic hypokalemia from hyperaldosteronism is associated with renal cyst formation and interstitial scarring. The numbers and size of cyst in these patients decrease following correction of hypokalemia.

Functional effects

K^+ depletion is associated with several effects in renal function, including a decrease in renal blood flow, impaired concentrating ability, increased ammonia production, increased bicarbonate reabsorption, increased Na^+ reabsorption, and impaired phosphate reabsorption.

The impaired urinary concentration is associated with polyuria and polydipsia. There are two components to the polydypsia: **1)** a primary increase in thirst, probably secondary to enhanced angiotensin II effect on the thirst center, and **2)** diminished urinary concentrating ability, or nephrogenic diabetes insipidus, which causes a secondary increase in thirst.

Effects of Progressive K Depletion on Urinary Concentration Ability



Hypokalemia causes increased production of NH_3 and NH_4^+ by the renal tubular cells, resulting increases in urinary NH_4^+ excretion. In hypokalemia the ensuing intracellular acidosis most likely is responsible for the increased NH_4^+ production. The increase in ammonia production may be clinically important in patients with severe hepatic disease in whom hypokalemia can precipitate hepatic coma.

Metabolic Effects

Carbohydrate intolerance is the most common metabolic disorder associated with K^+ depletion. Impairment in glucose tolerance during K depletion results from a decrease in insulin secretion.

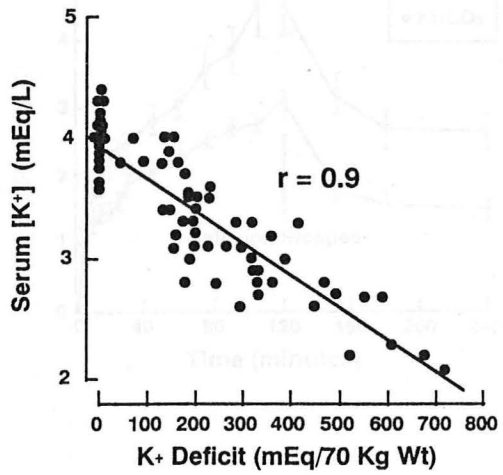
In addition, growth retardation is a known complication of K^+ deficiency states. The growth retardation may be a consequence of impaired growth hormone release, or altered protein synthesis due to relative insulin deficiency.

TREATMENT

The immediate objective of K^+ replacement is to prevent life-threatening cardiac and muscular complications, and the ultimate objective is to replenish total body K^+ stores.

The K^+ deficit can only be approximated, since there is no definite correlation between the plasma K^+ concentration and body K^+ stores. A reduction in the plasma K^+ concentration from 4.0 to 3.0 meq/L represents a loss of 200 to 400 meq of K^+. An additional 200 to 400 meq deficit will lower plasma K^+ concentration to 2.0 meq/L. However, continued K^+ loses may not produce much more hypokalemia, as the release of K^+ from the cells is usually able to maintain the plasma K^+ concentration near 2.0 mq/L.

Relationship of Serum [K^+] to Bodily K^+ Deficit



Transcellular shifts of K^+ may further complicate the estimation of a given K^+ deficit. In patients with periodic paralysis body K^+ stores are normal, as the hypokalemia is due to K^+ movement into the cells. In states associated with acidosis, for example renal tubular acidosis, and hyperosmolality, for example diabetic ketoacidosis, the serum K^+ concentration may underestimate K^+ losses. Initiation of bicarbonate therapy in renal tubular acidosis may rapidly lower serum K^+ concentration by enhancing cellular K^+ uptake. Initiation of therapy with saline and insulin in diabetic ketoacidosis may rapidly lower serum K^+ concentration by promoting urinary losses and cellular uptake of K^+.

Guidelines for K^+ replacement

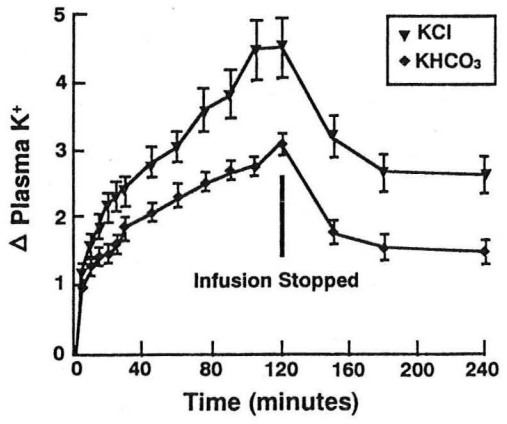
A variety of K^+ preparations are available for oral and intravenous use, including the Cl^-, HCO_3^-, citrate, phosphate, and gluconate salts.

a) In patients with metabolic alkalosis since there is also a simultaneous deficit in Cl^-, the administration of K^+ with Cl^- is essential for correction of both the alkalosis an the K^+ deficit.

b) In patients with metabolic acidosis $KHC0_3$ or K citrate is the preferred form of K^+ replacement therapy.

c) If equal doses of KCl and $KHC0_3$ are given, there will be a significantly greater increase in the plasma K^+ concentration with KCl than with $KHC0_3$. This difference is probably related to the ability of $HC0_3^-$ to enter the cells in comparison with that of Cl^-, which is mostly limited to the extracellular fluid.

Changes in Plasma [K+] of K-Depleted Dogs



When possible it is preferential to replace K^+ orally. The preferred preperations are KCl elixir (not very palatable), KCl tablets, or salt substitute which comes in crystalline form. It should be noted that K^+ replacement with K^+ rich foods such as bananas and orange juice is less effective since these foods contain citrate and phosphate rather than Cl^-, and therefore are not as effective especially in patients with hypokalemia in the presence of metabolic alkalosis.

In patients who are unable to eat, K^+ must be given intravenously. It is important to administer K^+ in solutions which do not contain dextrose, since the enhanced insulin secretion may result in a further lowering of plasma K^+ concentration.

Rate of K^+ repletion

In the majority of patients who have mild to moderate hypokalemia, plasma K^+ concentration ranging between 3.0 to 3.5 meq/L, unless the patients are on digitalis or have hepatic coma, the K^+ can be replaced slowly by oral route, at the rate of 30-60 meq/day.

In patients with severe hypokalemia, usually plasma K^+ less than 2.5 meq/L, plasma K^+ needs to be corrected rapidly, either by oral route, 60 meq KCl every hour, or intravenously, at a maximum rate of 10 to 20 meq/hr. The key is to continously monitor the electrocardiogram and to obtain frequent measurement of plasma K^+. Once again, since it is hard to estimate the exact degree of K^+ deficit, it is difficult to calculate the precise amount of K^+ which needs to be administered. They key to success is therefore frequent monitoring and assessment. It is also important to avoid over replacement which can result in hyperkalemia, a condition which is potentially as life threatening as severe hypokalemia.

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