New Guidelines for Potassium Replacement in Clinical Practice

A Contemporary Review by the National Council on Potassium in Clinical Practice

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T his article is the result of a meeting of the National Council on Potassium in Clinical Practice. The Council, a multidisciplinary group comprising specialists in cardiology, hypertension, epidemiology, pharmacy, and compliance, was formed to examine the critical role of potassium in clinical practice. The goal of the Council was to assess the role of potassium in terms of current medical practice and future clinical applications. The primary outcome of the meeting was the development of guidelines for potassium replacement therapy. These guidelines represent a consensus of the Council members and are intended to provide a general approach to the prevention and treatment of hypokalemia. *Arch Intern Med. 2000;160:2429-2436*

In recent years, studies of the potential pathogenetic role of potassium deficiency in various medical conditions have underscored the importance of preventing or correcting this deficiency. Although it has long been established that the maintenance of normal serum potassium is essential in reducing the risk of life-threatening cardiac arrhythmias, accumulating evidence suggests that the increased intake of potassium can also lower blood pressure and reduce the risk of stroke.

Few clinicians attempt to monitor and augment potassium stores on a routine basis. One reason may be the inconvenience of accurately measuring total body potassium, which entails a 24-hour urinary collection rather than a rapid laboratory serum measurement. Another reason is the practical difficulty of achieving and maintaining optimal potassium levels. Therefore, many clinicians may not attempt to remedy subnormal potassium levels except in high-risk patients.

The current lack of consensus on how to prevent and treat hypokalemia has led to the neglect of a wide range of situations in which increasing potassium intake might help prevent sequelae of cardiovascular disease. The multifactorial and interactive mechanisms that are stimulated by hypertension and even more so by heart failure, which mandate the introduction of drugs that disrupt electrolyte homeostasis, emphasize the serious role of potassium. This article reviews contemporary thinking on potassium in clinical practice.

Of the total body potassium content (about 3500 mmol [mEq]), 90% is sequestered within cells.[1] This compartmentalization depends on active transport through the cell membrane by a sodium-potassium pump, which maintains an intracellular cation ratio of 1:10. Normal serum potassium levels are considered to lie roughly between 3.6 and 5.0 mmol/L. The loss of just 1% (35 mmol) of total body potassium content would seriously disturb the delicate balance between intracellular and extracellular potassium and would result in profound physiologic changes. On the other hand, the presence of hypokalemia (ie, serum levels <3.6 mmol/L) is not necessarily synonymous with whole-body potassium deficiency, because such a small percentage of the total body stores is present in extracellular fluid. Whereas it is generally accepted that diuretic therapy can decrease serum potassium to hypokalemic levels, the subtler effects of inadequate dietary potassium are less well known.

Table 1. Foods High in Potassium*
Highest content
(>1000 mg [25 mmol]/100 g)
Dried figs
Molasses
Very high content
(>500 mg [12.5 mmol]/100 g)
Dried fruits (dates, prunes)
Nuts
Avocados
Bran cereals
Wheat germ
Lima beans
High content
(>250 mg [6.2 mmol]/100 g)
Vegetables: spinach, tomatoes, broccoli, winter squash, beets, carrots, cauliflower, potatoes
Fruits: bananas, cantaloupe, kiwis, oranges, mangos
Meats: ground beef, steak, pork, veal, lamb

Adapted from Gennari.[2]

Table 2. Potential Causes of Hypokalemia
Inadequate dietary potassium intake
Diuretic therapy
High dietary sodium intake
Hypomagnesemia
Prolonged diarrhea
Vomiting
Primary or secondary aldosteronism
Cushing syndrome or disease
Large doses of corticosteroids
Ectopic corticotropin
Bartter syndrome
Liddle syndrome
Urinary loss in congestive heart failure
Catecholamines
Others (excessive use of licorice, insulin, antibiotics)

For instance, although young adults may consume up to 3400 mg (85 mmol) of potassium per day, many elderly individuals, particularly those living alone or those who are disabled may not have a sufficient amount of potassium in their diet. People who eat large amounts of fruits and vegetables tend to have a high potassium intake of approximately 8000 to 11000 mg/d (200-250 mEq). Urban whites typically consume approximately 2500 mg (62.5 mEq) of potassium daily. In contrast, many African Americans have low intakes of about 1000 mg (25 mEq) per day.[1] The daily minimum requirement of potassium is considered to be approximately 1600 to 2000 mg (40-50 mmol or mEq). Factors that affect potassium intake include the type of diet consumed (**Table 1**), age, race, and socioeconomic status.

CLINICAL IMPLICATIONS OF POTASSIUM DEPLETION

Potassium depletion is one of the most common electrolyte abnormalities encountered in clinical practice. More than 20% of hospitalized patients have hypokalemia, widely defined as a serum potassium level of less than 3.5 mmol/L. Low serum (or plasma) concentrations of potassium may occur in up to 40% of outpatients treated with thiazide diuretics.[2]

Because the kidneys are the major regulators of external potassium homeostasis, accounting for approximately 80% of potassium transit from the body, renal dysfunction can result in gross abnormalities in serum potassium levels.[1] Transcellular potassium homeostasis depends to a large extent on acid-base balance.[1,3] Acidosis stimulates cellular efflux of potassium from cells, resulting in hyperkalemia, whereas alkalosis stimulates influx of potassium, resulting in hypokalemia, without a simultaneous alteration in total body potassium. Increases in insulin or catecholamines can also stimulate cells to import potassium and export sodium. In patients with type 2 diabetes, increases in glucose or insulin can affect potassium homeostasis. Stimulation of β_2-adrenergic receptors by sympathomimetic drugs (eg, decongestants and bronchodilators) can temporarily reduce serum potassium. A standard dose of nebulized albuterol reduces serum potassium by 0.2 to 0.4 mmol/L. A second dose administered within 1 hour reduces it by approximately 1 mmol/L.[2] β_2-Blockade, on the other hand, increases serum potassium.

Overt hypokalemia may be diagnosed when the serum potassium level is less than 3.6 mmol/L. Potential causes include diuretic therapy, inadequate dietary potassium intake, high dietary sodium intake, and hypomagnesemia (**Table 2**). In most cases, hypokalemia is secondary to drug treatment, particularly diuretic therapy (**Table 3**).[2] Diuretics inhibit chloride-associated sodium reabsorption in the kidney, creating a favorable electrochemical gradient for potassium secretion.[2,4] The degree of hypokalemia is directly related to the dose and half-life of the diuretic administered.[5] Hypokalemia occurs infrequently in patients with uncomplicated hypertension who take a diuretic but is more common in patients with congestive heart failure (CHF), nephrotic syndrome, or cirrhosis of the liver, who take an equivalent dose of a diuretic and consume approximately the same amount of potassium from food.[1]

Management of hypokalemia should begin with a thorough review of the patient's medical record. If potassium-wasting drugs are not implicated, hypokalemia is most commonly caused either by abnormal loss through the kidney induced by metabolic alkalosis or by loss in the stool secondary to diarrhea.[2]

Because potassium is a major intracellular cation, the tissues most severely affected by potassium imbalance are muscle and renal tubular cells. Manifestations of hypokalemia include generalized muscle weakness, paralytic ileus, and cardiac arrhythmias (atrial tachycardia with or without block, atrioventricular dissociation, ventricular tachycardia, and ventricular fibrillation). Typical electrocardiographic changes include flat or inverted T waves, ST-segment depression, and prominent U waves. In severe untreated hypokalemia, myopathy may progress to rhabdomyolysis, myoglobinuria, and acute renal failure. Such complications are most often seen in hypokalemia secondary to alcoholism.

PROTECTIVE EFFECT OF POTASSIUM

Data from animal experiments and epidemiologic studies suggest that high potassium may reduce the risk of stroke. Although part of the protective effect of potassium may be due to lowering of blood pressure, analysis of animal models suggests that potassium may have other pro-

tective mechanisms, including inhibitory effects on free radical formation, vascular smooth muscle proliferation, and arterial thrombosis.[6-9] It has also been shown experimentally that potassium may reduce macrophage adherence to the vascular wall (an important factor in the development of arterial lesions, oxidative stress of the endothelium, or vascular eicosanoid production).[10-12]

In 1987, the results of a 12-year prospective population study (N=859) showed that the relative risk of stroke-associated mortality was significantly lower with higher potassium intake.[13] In fact, multivariate analysis demonstrated that a 10-mmol higher level of daily potassium intake was associated with a 40% reduction in the relative risk of stroke mortality. This apparent protective effect of potassium was independent of other nutritional variables, including energy (caloric) intake; dietary levels of fat, protein, and fiber; and intake of calcium, magnesium, and alcohol. The authors also noted that the effect of potassium was greater than that which would have been predicted from its ability to lower blood pressure.[13]

More recently, Ascherio et al[6] reported the results of an 8-year investigation of the association between dietary potassium intake and subsequent risk of stroke in 43738 US men, aged 40 to 75 years, without previously diagnosed cardiovascular disease or diabetes. During the study follow-up, 328 strokes were documented. The relative risk of stroke for men in the top fifth of the range of potassium intake (median intake, 4.3 g/d) vs those in the bottom fifth (median, 2.4 g/d) was 0.62 (*P* for trend=.007). The inverse association between potassium intake and subsequent stroke was more marked in hypertensive men and was not significantly altered by adjustment for baseline level of blood pressure.[6]

Ascherio et al[6] also found that the use of potassium supplements was inversely related to the risk of stroke, particularly among hypertensive men. They speculated that this relationship might be due, at least in part, to a reduction in the risk for hypokalemia.[6,14,15] The authors recommended increasing the in-

take of potassium by substituting fruits, vegetables, and their natural juices for low-potassium processed foods and sodas and by considering potassium supplements for persons with hypertension.[6]

HYPOKALEMIA

Clinical Implications in Hypertension

Evidence from epidemiologic and clinical studies has implicated potassium depletion in the pathogenesis and maintenance of essential hypertension.[16] Increasing the intake of potassium appears to have an antihypertensive effect that is mediated by such mechanisms as increased natriuresis, improved baroreflex sensitivity, direct vasodilation, and lower cardiovascular reactivity to norepinephrine or angiotensin II.[17] Indirect support for this hypothesis comes from observations of the effects of primary aldosteronism (eg, aldosterone-producing hyperplasia or adenoma) or secondary aldosteronism (eg, excessive ingestion of licorice). These syndromes are characterized by abnormally low serum potassium levels and elevated blood pressure. Reversal of the underlying cause results in increased serum potassium levels and decreased blood pressure. Similarly, correction of diuretic or laxative abuse can also raise potassium level and lower blood pressure.

The large-scale Nurses' Health Study (N=41541) found that dietary potassium intake was inversely associated with blood pressure. Specifically, intake of

potassium-rich fruits and vegetables was inversely related to systolic and diastolic pressure.[18] Similarly, 24-hour urinary potassium excretion, 24-hour urinary sodium excretion, and the ratio of urinary sodium to potassium were found to be independently related to blood pressure in the INTERSALT study,[19] a 52-center international study of electrolytes and blood pressure. Additional information was provided by the Rotterdam Study,[20] which evaluated the relationship between dietary electrolyte intake and blood pressure in 3239 older people (age, ≥55 years). A 1 g/d higher level of dietary potassium intake was associated with a 0.9 mm Hg lower level of systolic blood pressure (*P*=.11) and a 0.8 mm Hg lower level of diastolic blood pressure (*P*=.01).

Whelton et al[21] recently conducted a meta-analysis of randomized controlled trials evaluating the effects of oral potassium supplementation on blood pressure. This analysis included 33 clinical trials involving 2609 participants. In these trials, the use of potassium supplementation was the only difference between the intervention and control arms. Dosages of potassium (mostly in the form of potassium chloride) ranged from 60 mmol/d to greater than 100 mmol/d. The results demonstrated that potassium supplementation was associated with a significant reduction in mean systolic and diastolic blood pressure (−4.4 mm Hg and −2.4 mm Hg, respectively; *P*<.001). The greatest effects were observed in participants who had a high concurrent sodium

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Table 3. Drugs That Induce Hypokalemia*

Hypokalemia Cause	Inducing Drugs
Transcellular potassium shift	β_2-Adrenergic agonists (epinephrine), decongestants, bronchodilators, tocolytic agents, theophylline, caffeine, verapamil intoxication, chloroquine intoxication, insulin overdose
Increased renal potassium loss	Diuretics (acetazolamide, thiazides, chlorthalidone, furosemide), mineralocorticoids (fludrocortisone acetate), substances with mineralocorticoid effects, high-dose glucocorticoids, high-dose antibiotics (penicillin, nafcillin), drugs associated with magnesium depletion (aminoglycosides, cisplatin, foscarnet sodium, amphotericin B)
Excess potassium loss in stool	Phenolphthalein, sodium polystyrene sulfonate

*Adapted from Gennari.[2]

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intake. This analysis suggests that low potassium intake may play an important role in the genesis of high blood pressure. Thus, the authors recommended increased potassium intake for the prevention and treatment of hypertension.[21] Based on the strength of the available data, the Joint National Committee for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) included increased potassium intake as a core recommendation for the prevention and treatment of hypertension.[22]

Among hypertensive patients, certain subgroups would derive special benefit from increased potassium intake. Best recognized are African Americans.[23] In the meta-analysis by Whelton et al,[21] the reduction of systolic blood pressure after potassium supplementation was approximately 3 times greater in blacks compared with whites. In addition, several studies have revealed lower urinary potassium excretion in blacks than in whites.[23] Watson et al[24] reported that 24-hour urinary excretion of potassium was 28 mmol in black females and 36 mmol in white females. The urinary sodium-to-potassium ratio was 4.1 in blacks and 2.9 in whites, a difference that was statistically significant.[24] The Veterans Administration Cooperative Study Group on Antihypertensive Agents (N=623) found potassium excretion to be 62% higher in whites than in blacks (73±41 vs 45±40 mmol); in addition, serum potassium levels were negatively associated with systolic blood pressure. The study concluded that the difference in urinary potassium excretion and in serum potassium levels between blacks and whites reflected a difference between the 2 groups in the intake of dietary potassium. Such a difference may be an important factor in the greater prevalence of hypertension in blacks.[25]

Clinical Implications in CHF

Not surprisingly, potassium depletion is commonly seen in patients with CHF, a condition that is characterized by several physiologic abnormalities that predispose to the development of electrolyte disturbances.

Among the pathogenetic factors associated with CHF are renal dysfunction and neurohormonal activation, which embrace stimulation of the renin-angiotensin-aldosterone axis, enhanced sympathetic nervous tone, and hypersecretion of catecholamines.[26]

A common misperception regarding angiotensin-converting enzyme (ACE) inhibitor therapy is that these drugs enhance potassium retention, thereby eliminating the need to add potassium or potassium-sparing diuretics to ACE inhibitor therapy. In many cases, the prescribed dosages of ACE inhibitors in patients with CHF are insufficient to protect against potassium loss. Serum potassium levels, therefore, must be closely monitored in all patients with CHF—even those taking ACE inhibitors—to minimize the life-threatening risk of hypokalemia in these patients.

The arrhythmogenic potential of digoxin is enhanced by hypokalemia in patients with heart failure. When using digoxin in combination with a loop diuretic and an ACE inhibitor, the decision of whether to administer potassium supplements can be complex. Leier et al[26] recommend maintaining serum potassium levels in the range between 4.5 and 5.0 mmol/L. They suggest that "effective potassium management with properly targeted serum potassium concentrations . . . probably represents the most effective and safe antiarrhythmic intervention" in heart failure. Magnesium may also be administered to facilitate the reversal of refractory hypokalemia.

The importance of preventing hypokalemia is underscored by the finding that the risks of dysrhythmias, syncope, cardiac arrest, or death are greater in patients with heart failure.[26] This result may be due in part to the cells of hypertrophied and failing hearts often having prolonged action potential duration, which in most cases is due to a decrease in outward potassium currents.

Nolan et al[27] found that low serum potassium levels were related to sudden cardiac death in the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (N=433). Grobbee and Hoes[28] re-

ported similar results in an examination of published randomized trials and recent case-control studies; patients with hypertension who were prescribed non–potassium-sparing diuretics had approximately twice the risk of sudden cardiac death compared with users of potassium-sparing therapy. The authors recommended using thiazide diuretics at a low dose only, and adding a potassium-sparing diuretic drug when higher diuretic doses are needed.[28] They estimated that the protective effect of antihypertensive treatment on mortality might be halved by the induction of sudden death following potassium loss.

Leier et al[26] suggested that virtually all patients with CHF should receive potassium supplementation, a potassium-sparing diuretic, or an ACE inhibitor. This is a prudent management strategy in light of the potentially dire consequences of hypokalemia in these patients.

Clinical Implications in Patients With Arrhythmias

In the absence of underlying heart disease, major abnormalities in cardiac conduction secondary to hypokalemia are relatively unusual. However, mild-to-moderate hypokalemia can increase the likelihood of cardiac arrhythmias in patients who have cardiac ischemia, heart failure, or left ventricular hypertrophy.[2,29] As mentioned earlier, this occurrence is not surprising in light of the important role that potassium plays in the electrophysiologic properties of the heart. The relation between extra and intracellular potassium levels is the primary determinant of the resting membrane potential (RMP). Changes in potassium level modify the electrophysiologic properties of the membrane and can have profound effects on impulse generation and conduction throughout the heart.[30]

Potassium deficiency, as well as potassium channel blockade or down-regulation, can cause prolonged repolarization, the pathogenic factor in the genesis of torsades de pointes. The effects of hypokalemia on repolarization are magnified in many disease states, including left ventricular hypertro-

phy, CHF, myocardial ischemia, and myocardial infarction. Such effects, in turn, are compounded by agents with class III antiarrhythmic effects, such as sotalol.[31]

The Nernst equation describes how the ratio of intracellular to extracellular potassium affects the RMP of myocardial cells: $RMP = -61.5 \log [K^+_i/K^+_e]$. Changes in this ratio, such as those induced by diuretic therapy, affect cardiac conduction and automaticity. As a result, low intracellular potassium levels can increase spontaneous depolarization, automaticity, and the emergence of ectopic foci.[32]

Despite this compelling basic information, the link between hypokalemia and clinical arrhythmogenesis is not a strong one. Caralis et al[32] studied 17 hypertensive men to determine the relationship of diuretic-induced hypokalemia with ventricular ectopic activity. They found that the risk for ventricular ectopic activity was marked in a group of patients who were older and had clinical evidence of organic heart disease. Patients with these characteristics had increased frequency and complexity of ventricular ectopic activity during diuretic therapy. In these patients, normalization of serum potassium levels with oral potassium supplements or potassium-sparing agents reduced the complexity and frequency of arrhythmias by 85%, even after discontinuation of diuretic therapy. Therefore, the authors recommended that clinical and laboratory observation should be used to identify those patients susceptible to diuretic-induced ventricular ectopic activity (eg, older patients with organic heart disease) and that steps should be taken to normalize serum potassium levels. Caralis et al speculated that the finding of electrocardiographic abnormalities in a specific population suggested that modest disturbances of potassium metabolism alone may not induce arrhythmia; rather, abnormalities of heart rhythm are most likely when underlying heart disease and low potassium occur together.[32,33]

Although the relation between complex ventricular arrhythmia and hypokalemia remains uncertain, there is evidence that hypokalemia can trigger sustained ventricular tachycardia or ventricular fibrillation, particularly in the setting of acute myocardial infarction. However, the exact mechanism by which hypokalemia provokes ventricular fibrillation or sudden cardiac death in the absence of an acute myocardial infarction is unclear. In patients with a history of serious arrhythmias receiving antiarrhythmic drugs, hypokalemia may reverse the beneficial effects of these agents and render the patient vulnerable to a recurrence of arrhythmia.[34,35] It is probably important, therefore, to impose a stricter standard for treatment (potassium <4.0 mmol/L) especially in patients with heart disease who are at risk for serious ventricular tachyarrhythmias. For example, the risk of early ventricular fibrillation in acute myocardial infarction is strikingly increased in patients with serum potassium levels less than 3.9 mmol/L.[34-37] However, there are no data to prove that aggressive replenishment of potassium in patients with heart disease necessarily leads to a better clinical outcome.

POTASSIUM SUPPLEMENTATION STRATEGIES: PREVENTION VS REPLETION

Increasing potassium intake should be considered when serum potassium levels are between 3.5 and 4.0 mmol. Although treatment of asymptomatic patients with borderline or "low normal" concentrations is controversial, very low levels (<3.0 mmol) are universally regarded as undesirable. Efforts to increase potassium intake are appropriate in certain populations who are vulnerable to cardiac arrhythmias (such as patients with heart failure, those taking digoxin, and patients with a history of myocardial infarction or ischemic heart disease). When the serum potassium level is below 3.5 mmol, potassium supplementation may be warranted even in asymptomatic patients with mild-to-moderate hypertension.[32]

Strategies to minimize the risk of potassium depletion include minimizing the dosage of non–potassium-sparing diuretics and restricting sodium intake. Increasing dietary potassium is the most straightforward means of enhancing potassium intake, but the high content of some potassium-rich foods is a potential drawback to dietary potassium supplementation (Table 1). Moreover, dietary potassium is almost entirely coupled with phosphate, rather than with chloride; therefore, it is not effective in correcting potassium loss that is associated with chloride depletion, such as in diuretic therapy, vomiting, and nasogastric drainage.[2] For patients receiving diuretic therapy, an attempt should be made to reduce the dose or to discontinue therapy. If the potassium depletion is not due to diuretic therapy, the patient should be evaluated for other causes of potassium loss.[1] When diuretic therapy is necessary, potassium balance should be protected by using low-dose diuretics and by using diuretics in combination with drugs that have the potential for sparing potassium (such as β-blockers, potassium-sparing diuretics, ACE inhibitors, or angiotensin receptor blockers). Repletion strategies also should include eating foods high in potassium, using salt substitutes, or taking prescription potassium supplements (**Table 4**).[2]

Potassium salts include potassium chloride, potassium phosphate, and potassium bicarbonate. Potassium phosphate is found primarily in food, and potassium bicarbonate is typically recommended when potassium depletion occurs in the setting of metabolic acidosis (pH <7.4). In all other settings, potassium chloride should be used because of its unique effectiveness against the most common causes of potassium depletion. Moreover, hypochloremia may develop if citrate, bicarbonate, gluconate, or another alkalinizing salt is administered, particularly in patients adhering to diets that restrict the intake of chloride. Potassium chloride is available in either liquid or tablet formulations (Table 4),[2] and all potassium formulations are readily absorbed. Although liquid forms may be less expensive, they have a strong, unpleasant taste and often are not well tolerated.

Table 4. Potassium Supplements

Supplement	Attributes
Controlled-release microencapsulated tablets	Disintegrate better in stomach than encapsulated microparticles; less adherent and less cohesive[38]
Encapsulated controlled-release microencapsulated particles	Fewer erosions than wax-matrix tablets[38-42]
Potassium chloride elixir	Inexpensive, tastes bad, poor compliance; few erosions; immediate effect[43,44]
Potassium chloride (effervescent tablets) for solution	Convenient, but more expensive than elixir; immediate effect
Wax-matrix extended-release tablets	Easier to swallow; more gastrointestinal tract erosions compared with microencapsulated formulations[39-42]

COMPLIANCE ISSUES AND POTASSIUM REPLACEMENT THERAPY

As with many long-term therapies, compliance can be a challenge with potassium supplementation. Specific characteristics of a medication, such as appearance, color, taste, size, ease of swallowing, and cost can all influence patient compliance.[45] Studies demonstrate that drug regimens should be simplified to the greatest extent possible to enhance compliance.[46] For instance, compliance rates can be improved by requiring the fewest doses of medication per day. An examination of automated pharmacy records by Halpern et al[45] documented this hypothesis. In their study of more than 2000 patients, the investigators determined the mean adherence ratios for 1 pill vs 2 or more pills daily with an equivalent dosage of potassium supplementation. At 1 year, the mean adherence ratio was significantly higher for patients taking 1 pill compared with those taking multiple pills per day. The worst ratios were observed in patients who were treated with liquid potassium supplements, which the authors speculated may have been due to increased side effects, poor taste, and the inconvenience of liquid supplements.[45] In their conclusion, the authors emphasized that "patient adherence is vitally important in the successful treatment of disease, especially in asymptomatic long-term diseases. . . . Since potassium supplements are typically indicated for long-term use, it is important to optimize patient adherence."[45]

Reported adverse effects of potassium supplements affect primarily the gastrointestinal tract, and they include nausea, vomiting, diarrhea, flatulence, and abdominal pain or discomfort. Ulcerations of the small bowel have been reported after the administration of enteric-coated potassium chloride tablets. A few cases of small bowel ulceration, stricture, and perforation have been associated with wax-matrix formulations.[47] Although slow-release tablets have been associated with gastrointestinal tract ulcerations and bleeding, the risk of these complications is low and seems to be lowest with the use of microencapsulated preparations.[2]

POTASSIUM REPLETION AND THE ROLE OF MAGNESIUM

Magnesium is an important cofactor for potassium uptake and for the maintenance of intracellular potassium levels. Recent studies using cellular models confirm the critical role of magnesium in maintaining intracellular potassium and indicate that the mechanisms are multifactorial.[48] Whang and colleagues[48] demonstrated that coexisting magnesium and potassium depletion could lead to refractory potassium repletion, which is the inability to replete potassium in the presence of unrecognized and continuing magnesium deficiency.

Many patients with potassium depletion may also have magnesium deficiency. In particular, loop diuretics (eg, furosemide) produce substantial serum and intracellular potassium and magnesium loss. Digoxin accelerates the excretion of magnesium by reducing its reabsorption at the renal tubules. The role of magnesium in maintaining intracellular potassium is particularly important in cardiac myocytes because it desensitizes them to the calcium-induced arrhythmogenic actions of cardiac glycosides.

Routine determination of serum magnesium levels should be considered whenever the measurements of serum electrolytes are necessary in a patient. Whang et al[48] recommend considering the repletion of both magnesium and potassium for patients with hypokalemia. Dietary sources of magnesium include whole-grain cereals, peas, beans, nuts, cocoa, seafood, and dark green vegetables.

CONSENSUS GUIDELINES FOR THE USE OF POTASSIUM REPLACEMENT IN CLINICAL PRACTICE

Low serum potassium concentration is perhaps the most common electrolyte abnormality encountered in clinical practice. Strategies aimed at achieving and maintaining normokalemia must take into account such factors as (1) baseline potassium values, (2) the presence of underlying medical conditions (eg, CHF), (3) the use of medications that alter potassium levels (eg, non–potassium-sparing diuretics) or that lead to arrhythmias in the presence of hypokalemia (eg, cardiac glycosides), (4) patient variables such as diet and salt intake, and (5) the ability to adhere to a therapeutic regimen.

Because of the multiple factors involved, guidelines therefore should be directed toward patients with specific disease states, such as those with cardiovascular conditions, and toward the general patient population. The following list encompasses our general practices for the use of potassium. The guidelines were developed at a 1998 meeting of the National Council on Potassium in Clinical Practice. It is clear that controlled clinical studies are necessary to determine the specific recommendations.

General Guidelines

1. *Dietary consumption of potassium-rich foods should be supplemented with*

potassium replacement therapy. Often, increasing dietary potassium intake is not completely effective in replacing the potassium loss associated with chloride depletion (eg, that which occurs in diuretic therapy, vomiting, or nasogastric drainage) because dietary potassium is almost entirely coupled with phosphate, rather than with chloride. In addition, the consumption of potassium-rich foods in amounts that are sufficient to increase the level of serum potassium level to acceptable concentrations may be costly, and it may lead to weight gain.

2. *Potassium replacement is recommended for individuals who are sensitive to sodium or who are unable or unwilling to reduce salt intake; it is especially effective in reducing blood pressure in such persons.* A high-sodium diet often results in excessive urinary potassium loss.

3. *Potassium replacement is recommended for individuals who are subject to nausea, vomiting, diarrhea, bulimia, or diuretic/laxative abuse.* Potassium chloride has been shown to be the most effective means of replacing acute potassium loss.

4. *Potassium supplements are best administered orally in a moderate dosage over a period of days to weeks to achieve the full repletion of potassium.*

5. *Although laboratory measurement of serum potassium is convenient, it is not always an accurate indicator of total body potassium.* Measurement of 24-hour urinary potassium excretion is appropriate for patients who are at high risk (eg, those with CHF).

6. *Patient adherence to potassium supplementation may be increased with compliance-enhancing regimens.* Microencapsulated formulations have no unpleasant taste and are associated with a relatively low incidence of gastrointestinal side effects.

7. *Potassium supplementation regimens should be as uncomplicated as possible to help optimize long-term compliance.*

8. *A dosage of 20 mmol/d of potassium in oral form is generally sufficient for the prevention of hypokalemia, and 40 to 100 mmol/d sufficient for its treatment.*

Patients With Hypertension

1. *Patients with drug-related hypokalemia (ie, therapy with a non–potassium-sparing diuretic) should receive potassium supplementation.*

2. *In patients with asymptomatic hypertension, an effort should be made to achieve and maintain serum potassium levels of at least 4.0 mmol/L.* Low serum potassium levels (eg, 3.4 mmol/L) in asymptomatic patients with uncomplicated hypertension should not be regarded as inconsequential. Dietary consumption of potassium-rich foods and potassium supplementation should be instituted as necessary.

Patients With CHF

Potassium replacement should be routinely considered in patients with CHF, even if the initial potassium determination appears to be normal (eg, 4.0 mmol/L). The majority of patients with CHF are at increased risk for hypokalemia. In patients with CHF or myocardial ischemia, mild-to-moderate hypokalemia can increase the risk of cardiac arrhythmia. In addition, diuretic-induced hypokalemia can increase the risk of digitalis intoxication and life-threatening arrhythmias.

In light of the above information and the potential for hyperkalemia to occur secondary to drug therapy with ACE inhibitors or angiotensin II receptor blockers, regular monitoring of the serum potassium level is essential in these patients. At any time, stress can trigger the secretion of aldosterone and the release of catecholamine in response to low cardiac output, thereby precipitating a fall in the serum potassium level.

Patients With Cardiac Arrhythmias

Maintenance of optimal potassium levels (at least 4.0 mmol/L) is critical in these patients and routine potassium monitoring is obligatory. Patients with heart disease are often susceptible to life-threatening ventricular arrhythmias. In particular, such arrhythmias are associated with heart failure, left ventricular hypertrophy (characterized by an abnormal QRS complex), myocardial ischemia, and myocardial infarction (both in the acute phase and after remodeling). The coadministration of magnesium should be considered to facilitate the cellular uptake of potassium.

Patients Prone to Stroke

It is prudent to maintain optimal potassium levels in patients at high risk for stroke (including those with a history of atherosclerotic or hemorrhagic cerebral vascular accidents). Although the effectiveness of potassium supplementation in reducing the incidence of stroke in humans has not been demonstrated in randomized controlled trials, prospective studies suggest that the incidence of fatal and nonfatal stroke correlates inversely with dietary potassium intake. In addition, the association of stroke with hypertension is well known.

Patients With Diabetes Mellitus

Potassium levels should be closely monitored in patients with diabetes mellitus and potassium replacement therapy should be administered when appropriate. Data underscore the adverse effects of glucose and insulin on potassium levels and the high incidence of cardiovascular and renal complications in patients with diabetes mellitus. These factors are specific to patients with type 2 diabetes who have poorly controlled serum glucose levels.

Patients With Renal Impairment

Data suggest a link between potassium levels and lesions of the kidneys in patients with renal disease or diabetes. Animal studies have demonstrated that potassium may offer a protective effect on the renal arterioles. The clinical implications of these findings are not yet clear.

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REFERENCES

1. Mandal AK. Hypokalemia and hyperkalemia. *Med Clin North Am.* 1997;81:611-639.
2. Gennari FJ. Hypokalemia. *N Engl J Med.* 1998;339:451-458.
3. Halperin ML, Kamel KS. Potassium. *Lancet.* 1998;352:135-140.
4. Tannen RL. Potassium disorders. In: Kokko JP, Tannen RL, eds. *Fluids and Electrolytes.* 3rd ed. Philadelphia, Pa: WB Saunders; 1996:chap 3.
5. Hoes AW, Grobbee DE, Peet TM, Lubsen J. Do non–potassium-sparing diuretics increase the risk of sudden cardiac death in hypertensive patients? recent evidence. *Drugs.* 1994;47:711-733.
6. Ascherio A, Rimm EB, Hernán MA, et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation.* 1998;98:1198-1204.
7. McCabe RD, Backarich MA, Srivastava K, Young DB. Potassium inhibits free radical formation. *Hypertension.* 1994;24:77-82.
8. McCabe RD, Young DB. Potassium inhibits cultured vascular smooth muscle proliferation. *Am J Hypertens.* 1994;7:346-350.
9. Lin H, Young DB. Interaction between plasma potassium and epinephrine in coronary thrombosis in dogs. *Circulation.* 1994;89:331-338.
10. Ishimitsu T, Tobian L, Sugimoto K, Everson T. High potassium diets reduce vascular and plasma lipid peroxides in stroke-prone spontaneously hypertensive rats. *Clin Exp Hypertens.* 1996;18:659-673.
11. Ishimitsu T, Tobian L, Sugimoto K, Lange JM. High potassium diets reduce macrophage adherence to the vascular wall in stroke-prone spontaneously hypertensive rats. *J Vasc Res.* 1995;32:406-412.
12. Ishimitsu T, Tobian L, Uehara Y, Sugimoto K, Lange JM. Effect of high potassium diets on the vascular and renal prostaglandin system in stroke-prone spontaneously hypertensive rats. *Prostaglandins Leukot Essent Fatty Acids.* 1995;53:255-260.
13. Khaw K-T, Barrett-Connor E. Dietary potassium and stroke-associated mortality: a 12-year prospective population study. *N Engl J Med.* 1987;316:235-240.
14. Young DB, Lin H, McCabe RD. Potassium's cardiovascular protective mechanisms. *Am J Physiol.* 1995;268:R825-R837.
15. Cohen JD, Neaton JD, Prineas RJ, Daniels KA, for the Multiple Risk Factor Intervention Trial Research Group. Diuretics, serum potassium and ventricular arrhythmias in the Multiple Risk Factor Intervention Trial. *Am J Cardiol.* 1987;60:548-554.
16. Krishna GG, Kapoor SC. Potassium depletion exacerbates essential hypertension. *Ann Intern Med.* 1991;115:77-83.
17. Barri YM, Wingo CS. The effects of potassium depletion and supplementation on blood pressure: a clinical review. *Am J Med Sci.* 1997;314:37-40.
18. Ascherio A, Hennekens C, Willett WC, et al. Prospective study of nutritional factors, blood pressure, and hypertension among US women. *Hypertension.* 1996;27:1065-1072.
19. INTERSALT Cooperative Research Group. INTERSALT: an international study of eletrolyte excretion and blood pressure: results for 24-hour urinary sodium and potassium excretion. *BMJ.* 1988;297:319-328.
20. Geleijnse JM, Witteman JCM, den Breeijen JH, et al. Dietary electrolyte intake and blood pressure in older subjects: The Rotterdam Study. *J Hypertens.* 1996;14:737-741.
21. Whelton PK, He J, Cutler JA, et al. Effects of oral potassium on blood pressure: meta-analysis of randomized controlled clinical trials. *JAMA.* 1997;277:1624-1632.
22. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med.* 1997;157:2413-2446.
23. Langford HG. Dietary potassium and hypertension: epidemiologic data. *Ann Intern Med.* 1983;98:770-772.
24. Watson RL, Langford HG, Abernethy J, Barnes TY, Watson MJ. Urinary electrolytes, body weight, and blood pressure: pooled cross-sectional results among four groups of adolescent females. *Hypertension.* 1980;2(suppl I):I93-I98.
25. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Urinary and serum electrolytes in untreated black and white hypertensives. *J Chron Dis.* 1987;40:839-847.
26. Leier CV, Dei Cas L, Metra M. Clinical relevance and management of the major electrolyte abnormalities in congestive heart failure: hyponatremia, hypokalemia, and hypomagnesemia. *Am Heart J.* 1994;128:564-574.
27. Nolan J, Batin PD, Andrews R, et al. Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart). *Circulation.* 1998;98:1510-1516.
28. Grobbee DE, Hoes AW. Non–potassium-sparing diuretics and risk of sudden cardiac death. *J Hypertens.* 1995;13:1539-1545.
29. Schulman M, Narins RG. Hypokalemia and cardiovascular disease. *Am J Cardiol.* 1990;65:4E-9E.
30. Podrid PJ. Potassium and ventricular arrhythmias. *Am J Cardiol.* 1990;65:33E-44E.
31. Näbauer M, Kääb S. Potassium channel downregulation in heart failure [review]. *Cardiovasc Res.* 1998;37:324-334.
32. Caralis PV, Materson BJ, Perez-Stable E. Potassium and diuretic-induced ventricular arrhythmias in ambulatory hypertensive patients. *Miner Electrolyte Metab.* 1984;10:148-154.
33. Steiness E, Olesen KH. Cardiac arrhythmias induced by hypokalemia and potassium loss during maintenance digoxin therapy. *Br Heart J.* 1976;38:167-172.
34. Duke M. Thiazide-induced hypokalemia: association with acute myocardial infarction and ventricular fibrillation. *JAMA.* 1978;239:43-45.
35. Solomon RJ, Cole AG. Importance of potassium in patients with acute myocardial infarction. *Acta Med Scand.* 1981;647:87-93.
36. Dyckner T, Helmers C, Lundman T, Wester PO. Initial serum potassium level in relation to early complications and prognosis in patients with acute myocardial infarction. *Acta Med Scand.* 1975;197:207-210.
37. Hulting J. In-hospital ventricular fibrillation and its relation to serum potassium. *Acta Med Scand.* 1981;647(suppl):109-116.
38. Graham DY, Smith JL, Bouvet AA. What happens to tablets and capsules in the stomach? endoscopic comparison of disintegration and dispersion characteristics of two microencapsulated potassium formulations. *J Pharm Sci.* 1990;79:420-424.
39. McMahon FG, Ryan JR, Akdamar K, Ertan A. Upper gastrointestinal lesions after potassium chloride supplements: a controlled clinical trial. *Lancet.* 1982;2:1059-1061.
40. Pietro DA, Davidson L. Evaluation of patients' preference of two potassium chloride supplements: Slow-K and K-Dur. *Clin Ther.* 1990;12:431-435.
41. Sinar DR, Boyzmski EM, Blackshear JL. Effects of oral potassium supplements on upper gastrointestinal mucosa: multicenter clinical comparison of three formulations and placebo. *Clin Ther.* 1986;8:157-163.
42. Strom BL, Carson JL, Schinnar R, et al. Upper gastrointestinal tract bleeding from oral potassium chloride: comparative risk from microencapsulated vs wax-matrix formulations. *Arch Intern Med.* 1987;147:954-957.
43. McMahon FG, Ryan JR, Akdamar K, Ertan A. Effect of potassium chloride supplements on upper gastrointestinal mucosa. *Clin Pharmacol Ther.* 1984;35:852-855.
44. Melikian AP, Cheng LK, Wright GJ, Cohen A, Bruce RE. Bioavailability of potassium from three dosage forms: suspension, capsule, and solution. *J Clin Pharmacol.* 1988;28:1046-1050.
45. Halpern MT, Irwin DE, Brown RE, Clouse J, Hatziandreu EJ. Patient adherence to prescribed potassium supplement therapy. *Clin Ther.* 1993;15:1133-1145.
46. Becker MH. Understanding patient compliance: the contributions of attitudes and other psychosocial factors. In: Cohen SJ, ed. *New Directions in Patient Compliance.* Lexington, Mass: Lexington Books; 1979:16.
47. Graham DY. Effectiveness and tolerance of "solid" vs. "liquid" potassium replacement therapy. In: Cameron JS, Glussock RJ, Whelton A, eds. *Kidney Disease.* New York, NY: Marcel Dekker Inc; 1986:6:chap 36.
48. Whang R, Whang DD, Ryan MP. Refractory potassium repletion: a consequence of magnesium deficiency. *Arch Intern Med.* 1992;152:40-45.