The Relationship Between Disorders of K^+ and Mg^+ Homeostasis

By Richard Solomon

POTASSIUM AND MAGNESIUM are the two most abundant intracellular cations, respectively, and there are many observations which suggest that some relationship between them exists. For example, correlations between extracellular levels[1-4] and intracellular levels[4] of these cations have been described. However, these correlations do not provide any insight into the physiologic relationship of these two cations. To establish a physiological role of one cation in the homeostasis of the other, this report will focus on the experimental observations that support such a relationship. The clinical relevance of this relationship will then be addressed.

Let us start with an overview of magnesium homeostasis. Less than 1% of the total body magnesium content exists in the extracellular fluid. Fifty percent of the intracellular magnesium is in bone, and of the remaining intracellular magnesium, 85% to 90% is bound in the form of metaloenzyme complexes. Although the total intracellular concentration of magnesium can be easily determined, the concentration of free magnesium is not well defined. Based on various estimates, Mg^{2+} sensitive electrodes, and ^{31}P nuclear magnetic resonance, the intracellular concentration of free magnesium is between 0.2 to 3.0 mmol/L and varies considerably in different tissues, the heart muscle having one of the highest levels.[5-7] The extracellular concentration of magnesium is .7 to 1.3 mmol/L, of which 20% to 35% is bound to circulating proteins. The similarity between the free intracellular and extracellular concentrations of magnesium suggest that magnesium distribution across the cell membrane is largely determined by passive forces,[8] although a carrier mediated transport of magnesium across the membrane of some cells has recently been described.[5]

Magnesium balance is determined by gastrointestinal absorption of approximately 30% of ingested magnesium (average intake of 15 mmol/d) and the renal excretion of 4 to 6 mmol/d of magnesium.[9] The renal handling of magnesium is determined by the filtered load of 120 mmol/d and the tubular reabsorption of magnesium, such that only 3% to 5% appears in the final urine. The filtered magnesium is reabsorbed in the proximal tubule (25%), in the thick ascending limb of Henle (60%), and the remainder in distal segments of the nephron. There is little evidence for magnesium secretion in mammals.[9] Reabsorption, particularly in the proximal nephron, is characterized by a transport maximum that can be reduced by saline infusion and volume expansion. Additional components of the regulatory system for magnesium balance include the following: magnesium excretion is increased by an increase in plasma magnesium or calcium, suggesting a possible role for parathyroid hormone or a competitive transport site; diuretics (loop active agents, osmotic, and thiazides), phosphate depletion, digitalis, ethanol, and glucose all increase magnesium excretion variably; glucocorticoids and mineralocorticoids also increase magnesium excretion, although the role of extracellular volume expansion and the subsequent "escape" from the sodium retaining effects of mineralocorticoids, in particular, plays a preeminent role.[10] On the other hand, dietary restriction of magnesium results in the almost complete elimination of magnesium from the final urine (unlike the situation for calcium). The avidity of the nephron for magnesium in the face of magnesium depletion provides the basis for the use of the renal excretion of a magnesium load as a test for subclinical magnesium deficiency.[11]

Many of the factors that influence magnesium balance are also capable of independently affecting potassium balance (Table 1). Notable in this regard are diuretics, mineralocorticoids, and gastrointestinal function. The fact that magnesium balance and potassium balance may both be influenced by changes in common physiologic variables, may provide an explanation for the correlations in serum and tissue levels described above.

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0270-9295/87/0703-0007$5.00/0

Table 1. Factors Affecting Both Magnesium and Potassium

Intake
Alcoholism
Starvation
Hyperalimentation and IV fluids
Loss
Gastrointestinal
malabsorption
fistuli
N/G suction
laxatives
Renal
primary hyperaldosteronism
secondary hyperaldosteronism
CHF, cirrhosis, nephrosis
diuretics
toxins—gentamicin, cis-platinum
post obstructive diuresis
primary renal Mg wasting

THE EFFECTS OF MAGNESIUM DEPLETION ON POTASSIUM BALANCE

In Vivo Studies

The removal of magnesium from the diet of experimental animals produces consistent changes in serum and tissue electrolytes (Table 2). Within a week or two, serum magnesium levels decrease. A decrease in skeletal muscle magnesium is usually seen by 3 weeks.[12,29] Similar decreases in magnesium content have been observed in lymphocytes,[30] RBCs,[21,24,27] cardiac muscle,[12,15,18,24,25] liver,[22,25,27] and kidney.[14,18,22]

Most importantly, tissue content of potassium also decreases with magnesium depletion. This potassium depletion occurs rapidly and may or may not be accompanied by a decrease in serum potassium. The degree of potassium depletion and the effect on serum potassium depends in part on the amount of potassium provided in the diet of the magnesium deficient animals. A concomitant deficiency of both dietary potassium and magnesium results in the greatest potassium depletion (greater than that seen with a potassium deficient diet alone) and the most consistent hypokalemia.[12,21] However, even in the presence of an excess of potassium in the diet, tissue depletion of potassium is seen.

Studies in humans have generally confirmed the observations in animals. Dunn et al, using a low

Table 2. Magnesium Depletion Studies

Duration (days)	Magnesium		Potassium		Sodium	Calcium		References
	Serum	Tissue*	Serum	Tissue*	Tissue	Serum	Tissue	
Animals								
10	ND	–	ND	dec	ND	ND	ND	12
10	dec	dec	–	dec	–	–	–	13
14	dec	ND	–	dec	–	–	–	14
19-20	dec	–†	dec	dec†	ND	ND	ND	15
21	dec	dec	–	dec	–	ND	ND	16
28	dec	dec	–	–	–	inc	–	17
28	dec	dec	dec	dec	inc	–	inc	18
28	dec	dec	–	dec	ND	inc	inc	19
28-35	ND	dec	–	dec	inc	–	–	20
31	dec	dec	–	dec	inc	inc	–	21
38-44	dec	dec	–	dec	–	inc	–	22
43	dec	ND	–	dec	inc	inc	inc	23
56	dec	ND	dec	dec	inc	–	inc	24
60	dec	dec	–	dec	inc	inc	–	21
62	dec	dec	ND	dec	inc	inc	inc	25
75	dec	ND	–	dec	inc	inc	–	14
190-210	dec	ND	dec	ND	ND	ND	ND	26
270	dec	dec	–	dec	inc	–	–	27
Humans								
39-49	dec	–	dec	dec	–	–	–	28
42-266	dec	dec‡	dec	dec§	ND	dec	–	29

Abbreviations: dec, decrease; inc, increase; –, no change; ND, not done.
*Skeletal muscle unless otherwise stated.
†Cardiac muscle.
‡RBC.
§^{42}K.

magnesium diet (1 to 2.5 mmol/d), studied two normal subjects. Negative magnesium balance was observed (approximately 61 and 88 mmol total at the time of tissue analysis) and serum magnesium and RBC magnesium decreased. In the subject maintained for 45 days on the deficient diet, hypokalemic alkalosis developed and depletion of tissue potassium occurred.[28]

Similar observations were made by Shils in seven patients using a diet containing only 0.25 to 0.4 mmol/d of magnesium. Serum magnesium decreased in all individuals within the first week. Skeletal muscle magnesium was not measured, but RBC magnesium decreased significantly. Serum potassium decreased in six of the seven patients, and total body potassium, measured by ^{42}K, also decreased significantly in the four patients in which it was measured.[29]

Thus, in the experimentally induced magnesium deficient state, in which intake of potassium is kept adequate, a loss of potassium from the body occurs that is variably associated with hypokalemia. This appears to be a consequence of the magnesium deficient state per se, as repletion of magnesium alone corrects the potassium deficit.[16,31]

A reduction in total body potassium and tissue content of potassium in the presence of hypokalemia must reflect negative potassium balance. The negative balance results from persistent urinary losses of potassium in excess of dietary intake.[14,21,29,32] In this regard, the potassium depletion and hypokalemia associated with magnesium deficiency is unlike primary hypokalemia resulting from an inadequate intake of potassium. In the latter condition, urinary potassium excretion is reduced so as to conserve potassium. In contrast, magnesium deficiency is associated with urinary potassium wasting.

The inappropriate kaliuresis during magnesium deficiency is similar to the findings in states of mineralocorticoid excess. A number of observations suggest that there is a relationship between magnesium and potassium homeostasis and adrenal function. For example, states of adrenal insufficiency are usually associated with elevations in both serum magnesium and potassium.[33] Conversely, concomitant magnesium and potassium depletion is found in primary hyperaldosteronism.[34,35] Treatment of adrenal insufficiency with florinef[36] and treatment of primary hyperaldosteronism with spironolactone or surgery, corrects both the magnesium and potassium abnormalities.[34] Finally, aldosterone is known to increase renal excretion of magnesium.[34,37]

In the magnesium depletion studies noted above, adrenal function was evaluated only in the study of Ginn.[23] After 6 weeks of magnesium deficiency, at a time of increased urinary potassium excretion, aldosterone secretory rates were twofold higher in the experimental group compared with controls, despite the absence of change in serum potassium. Similar observations were made by Francisco, who noted that plasma aldosterone levels increased during magnesium depletion in the rat during the period of negative potassium balance, and that the addition of spironolactone concurrent with the magnesium depletion prevented the development of potassium depletion.[38] In humans, Shils also noted that urinary sodium decreased and urinary potassium increased during magnesium depletion, an effect consistent with enhanced mineralocorticoid activity.[29] Why mineralocorticoid stimulation should occur in the face of magnesium deficiency is speculative. Perhaps altered systemic hemodynamics resulting from a depression in cardiac function secondary to magnesium depletion activates the renin-angiotensin system. Support for this hypothesis is suggested by the observation that magnesium deficiency results in an increase in the juxtaglomerular cell granulation index (reflecting increased renin synthesis) and the width of the adrenal zona glomerulosa (reflecting increased mineralocorticoid synthesis).[39]

However, a number of observations are discordant with a primary role of mineralocorticoids in mediating the kaliuresis of magnesium deficiency. The infusion of magnesium salts into normal subjects,[40-42] and those with renal potassium wasting of diverse etiologies,[43,44] reduces urinary excretion of potassium. This effect is associated with an increase[43] or no change[44] in plasma aldosterone. If the effects of magnesium on potassium excretion were mediated by aldosterone, a decrease in plasma aldosterone levels should be observed during the magnesium infusion. Finally, the increase in plasma aldosterone that followed magnesium replacement in three patients with hypokalemia, was not accompanied by changes in plasma renin and was probably secondary to the positive potassium balance and increase in serum potassium levels.[43] Thus, although enhanced secretion

of aldosterone may be found during some magnesium depletion states, this alone is not sufficient to explain the inappropriate kaliuresis that accompanies magnesium depletion.

Another possible mechanism for the inappropriate kaliuresis during magnesium deficiency involves renal tubular dysfunction secondary to hypercalcemia. Hypercalcemia and increases in tissue calcium, particularly within the kidney, are a frequent finding in animal models of magnesium depletion.[17,19,21,25] These renal histological lesions, which include nephrocalcinosis, are also observed in vitamin D intoxication in which renal potassium wasting is also observed.[45] While hypercalcemia has been noted in some but not all animal studies, hypocalcemia appears to be the rule in magnesium deficiency in humans.[29] Functional hypoparathyroidism has been proposed as the mechanism for this hypocalcemia.[46] Therefore, it is unlikely that the changes in calcium balance and renal tubular damage, which appear to depend on the experimental model, could account satisfactorily for the kaliuresis seen in magnesium deficiency.

A more likely explanation for the kaliuresis involves the inability of cells to retain potassium in the face of magnesium depletion. For example, following the intraperitoneal injection of ^{42}K in animals on a magnesium deficient diet, there is an increase in both urinary ^{42}K and serum ^{42}K compared with control animals.[47] The investigators interpret this finding to indicate that potassium is unable to get into cells adequately and, therefore, the increase in potassium excretion represents "overflow" kaliuresis secondary to this endogenous load. The mechanism by which this load is ultimately excreted in the urine is unclear. During magnesium depletion, cellular depletion of potassium also occurs in renal tissues and this might be expected to decrease rather than increase potassium excretion. On the other hand, an increase in apical membrane permeability to potassium (vide infra) might decrease potassium reabsorption in proximal tubules and increase potassium secretion in the cortical collecting tubules. To date, such membrane effects have not been directly investigated. Such studies would extend the evidence for a direct effect of magnesium depletion on cellular handling of potassium.

In Vitro Studies

Studies of isolated tissues provide a means for eliminating the confounding effects of hemodynamic changes and various hormonal influences. In such systems, the direct effect of changes in the magnesium concentration of the extracellular or intracellular compartment can be evaluated. In general, these studies indicate that potassium is lost from the cells in the presence of a low extracellular magnesium concentration. Both enhanced efflux of potassium from cells[21,48] and diminished influx[49-51] have been described. For example, in ascites tumor cells, passive K^+ efflux, measured by ^{86}Rb, is increased 40% when cells are incubated in the absence of magnesium in the bath.[48] Elevation of extracellular magnesium decreases ^{42}K efflux from rat interventricular septa.[52] However, based on substitution studies with cesium, which competes for potassium transport into the cell, but not for potassium conductance channels out of the cell, magnesium deficiency also inhibits the active transport of potassium into the cell.[53]

The effects of magnesium on membrane transport of potassium are probably twofold. Changes in extracellular magnesium may produce alterations in the surface (zeta) potential of cell by complexing with charged proteins and phospholipids in the membrane.[48] These effects are not specific for magnesium, but can be observed with other divalent cations.[51] In addition, these effects are usually seen at levels of extracellular magnesium above the physiologic range, eg, greater than 5 mmol/L. Raising extracellular magnesium to these levels inhibits the bidirectional movement of potassium across the cell membrane.

On the other hand, changes in intracellular magnesium directly influence potassium transport via effects on Na^+-K-ATPase. The requirement of Na^+-K-ATPase for magnesium has been demonstrated with a Km between 0.8 to 1.2 mmol/L and an intracellular binding site has been proposed.[54,55] As indicated previously, the concentration of free intracellular magnesium is normally at or below 1 mmol/L.[5-8] Further support for the role of Na^+-K-ATPase in mediating the effects of magnesium depletion derives from studies of red cell transport, which indicate that the ouabain-sensitive component of potassium influx is extremely sensitive to changes in internal magnesium precisely within this concentration range.[49-51]

These two mechanisms of action do not exclude other potential effects of magnesium, either intracellular or extracellular, on potassium transport across the cell membrane. For example, the central role of magnesium in the maintenance of

energy supplies within the cell, through activation of the enzymes of oxidative phosphorylation and the coupling with AMP, ADP, and ATP, may be additional sites of action.[7] Finally, additional direct effects of magnesium on K^+ channels in the membrane may occur. Magnesium has recently been shown to increase the sensitivity of calcium activated potassium channels studied by the patch clamp technique.[56]

Until further studies reveal physiologically relevant actions of magnesium, a reasonable hypothesis suggests that changes in internal magnesium concentration, within the range noted during experimental magnesium deficiency, interfere with the ability of the cell to actively transport potassium into the cell because of inhibition of Na^+-K-ATPase. As noted in Table 2, many, but not all of the experimental studies of magnesium deficiency also noted an increase in cellular sodium and/or calcium, effects consistent with inhibition of Na^+-K-ATPase.

THE EFFECTS OF MAGNESIUM EXCESS ON POTASSIUM BALANCE

Because of the efficiency of the kidney in eliminating magnesium from the body following an acute load, dietary increases in magnesium do not result in positive magnesium balance in the absence of renal dysfunction or prior magnesium depletion. Therefore, animal studies have used models of acute and chronic renal insufficiency to evaluate the effects of elevations in serum magnesium levels and/or tissue magnesium on potassium homeostasis. For example, Whang et al studied rats with 5/6 nephrectomy maintained for 4 months on "normal" rat diets.[57] Mild hypermagnesemia was noted (.81 *v* .61 mmol/L), but skeletal muscle magnesium was unaffected. There were no perturbations of serum or muscle potassium. When acute renal failure was superimposed by removal of the remnant kidney, significant hypermagnesemia and hyperkalemia were both observed. However, tissue levels of magnesium remained normal while tissue potassium increased. These results suggest that the cell is not affected by mild hypermagnesemia. Whether the absence of an increase in tissue magnesium is a result of the slower mobility of magnesium into cells compared with potassium[58] or a reflection of saturated intracellular binding sites is unknown. Since 85% to 90% of the intracellular magnesium is bound to ligands, it might be beyond the limits of sensitivity to detect small increases in the free intracellular level of magnesium that would follow mild to moderate hypermagnesemia.

Similar observations have been made in humans under a variety of chronic disease states. Baldwin examined five patients with chronic renal disease with mild hypermagnesemia (mean = 1.1 mmol/L) and hyperkalemia (6.1 mEq/L). Again, tissue levels of magnesium were similar to control populations. Potassium levels in tissue were actually low, probably reflecting protein malnutrition.[59]

Repletion studies in previously magnesium or magnesium and potassium depleted animals and humans provide an additional physiologic perspective on the relationship between magnesium and potassium homeostasis. Such studies demonstrate that urinary potassium excretion is diminished and positive potassium balance occurs following magnesium infusions.[16,29,31] Serum and tissue potassium increase to normal levels, despite minimal changes in extracellular magnesium. Similar electrolyte shifts have been described in magnesium treated patients with congestive heart failure.[60] It is not clear whether the positive potassium balance is a result of a decrease in urinary potassium excretion or a primary increase in potassium uptake into cells in which the kidney also participates. Based on the in vitro studies cited above, the latter seems most likely. The results are consistent with a stimulatory effect of increasing intracellular magnesium levels on Na^+-K-ATPase. However, an additional direct effect of magnesium on the renal excretion of potassium is not excluded. Indeed, acute IV infusions of magnesium in humans without previous magnesium deficiency will also decrease urinary potassium excretion. Heller infused six men with a total of 21 mmol of magnesium sulfate over 45 minutes. Hypermagnesemia was produced in all subjects. Urinary potassium excretion decreased 44%, remaining low as long as the magnesium infusion was continued. The antikaliuresis was observed in the face of an increase in urinary sodium and chloride excretion.[40] Other acute infusion studies in humans have indicated that the chloride, sulfate, acetate, and lactate salts of magnesium are equally effective in reducing urinary excretion of potassium.[42] A similar effect of magnesium infusion has been noted in three siblings with familial hypokalemia and a patient with Bartter's syndrome.[44] Although serum magnesium was normal in all these studies, magnesium depletion was not ruled out by either tissue analysis or magnesium loading studies. Finally, with marked increases in extracellular

magnesium to 6 mmol/L in the dog, enhanced potassium excretion is observed.[61] The unphysiologic nature of these studies is evident and all animals needed artificial ventilation to complete the study.

In summary, magnesium affects potassium homeostasis primarily by its effects on intracellular processes of which the regulation of Na^+-K-ATPase is most central. A reduction in intracellular magnesium that follows experimentally induced negative magnesium balance is associated with kaliuresis and negative potassium balance. Serum potassium decreases when the duration and extent of the magnesium depletion and consequent potassium depletion is greatest. Repletion of magnesium stimulates cellular uptake of potassium. Urinary potassium excretion is reduced and positive potassium balance occurs. Both serum and tissue potassium increase. In contrast, mild hypermagnesemia is not accompanied by an increase in intracellular magnesium. No effects on potassium homeostasis can be attributed directly to this mild increase in total body magnesium load.

THE EFFECTS OF POTASSIUM ON MAGNESIUM BALANCE

The details of potassium balance have been reviewed in this journal by Wright. Potassium depletion does not have a consistent effect on magnesium balance (Table 3). Potassium depletion resulting from dietary restriction results in hypokalemia and a decrease in tissue potassium, with an increase in tissue sodium. Intracellular magnesium is unchanged and occasionally mild hypermagnesemia is observed. The etiology of this hypermagnesemia is probably dependent on the effects of potassium depletion on renal function and/or mineralocorticoid suppression.[62]

Similarly, chronic hyperkalemia secondary to renal insufficiency does not affect tissue magnesium, even in the face of mild hypermagnesemia.[57,59] These studies suggest that perturbations of potassium balance per se do not affect magnesium levels in serum or tissue. The mild hypermagnesemia observed in both potassium depletion and chronic hyperkalemia models is probably a reflection of changes in renal function.

CLINICAL ASSOCIATIONS BETWEEN MAGNESIUM AND POTASSIUM

There are a number of reasons to consider the relationship between magnesium and potassium a clinically important one. Table 4 summarizes a number of survey studies on the frequency of magnesium depletion in various clinical populations.

It is apparent that many patients, particularly those with cardiovascular diseases, are magnesium depleted. In the clinical setting, the serum level is a poor predictor of total body magnesium stores,[73] although hypomagnesemia, in a patient at risk for magnesium depletion, is usually confirmatory. The lack of correlation between serum and tissue levels observed in clinical studies contrasts with the experimental studies in animals. While this discrepancy may relate to species differences, it is more likely a reflection of the fact that clinical disorders often involve simultaneous depletion of potassium and magnesium. In such combined disorders, lesser degrees of magnesium depletion may not be associated with hypomagnesemia, yet still contribute to significant depletion of intracellular potassium. For example, in patients receiving diuretics, digoxin, or who have a predisposition to magnesium depletion such as chronic alcohol abuse, the incidence of magnesium depletion (de-

Table 3. Potassium Depletion Studies

Duration (days)	Magnesium		Potassium		Sodium	Calcium		References
	Serum	Tissue*	Serum	Tissue*	Tissue	Serum	Tissue	
Animals								
13	inc	dec	dec	dec	inc	–	–	62
15	–	ND	dec	dec	inc	ND	ND	14
20	–	dec	dec	dec	inc	ND	ND	15
28	inc	–	dec	dec	inc	–	–	18
28-72	ND	–	dec	dec	inc	ND	–	20
31	–	–	dec	dec	inc	–	–	21
60	inc	ND	dec	ND	ND	ND	ND	26
40-60	ND	inc	ND	dec	inc	ND	ND	63

*Skeletal muscle unless otherwise stated.

Table 4. Frequency of Hypomagnesemia in Clinical Populations

Clinical Population	N	Hypomagnesemic (%)	Tissue Depletion (%)	References
Outpatient hypertensive	1,000	5	–	64
Outpatient hypertensive	198	–	42	65
Hospitalized patients	2,300	7	–	66, 68
Hospitalized	621	11	–	67
Hospitalized	421	26	–	2
Hospitalized	974	26	–	87
Individuals taking digoxin	136	19	–	69
Elderly, no drugs	45	16	–	4
Elderly, with drugs	45	48	–	4
Coronary care unit	104	8	53	70
Intensive care unit	94	53	–	71
Congestive heart failure	98	–	63	65
Alcoholic admissions	30	60	–	72

termined by tissue analysis) may be as high as 50%, although only half of these patients have concomitant hypomagnesemia. These patients also have a predisposition to potassium depletion independent of magnesium balance. This fact contributes to the frequent association of potassium and magnesium disturbances in clinical practice. For example, in a study by Whang et al, 42% of hypokalemic patients also had hypomagnesemia, although the incidence of hypomagnesemia in normokalemic patients was only 24%.[68] Boyd also reported a 38% incidence of hypomagnesemia in patients with concomitant hypokalemia.[1] Similarly, the incidence of hypokalemia is higher in hypomagnesemic patients compared with normomagnesemic patients.[1] However, these studies are looking only at the tip of the iceberg. As noted above, magnesium depletion without hypomagnesemia is probably the more common situation and the incidence of accompanying potassium depletion is unknown.

Finally, are these relationships between potassium and magnesium of clinical importance? The reader is referred to the review by Altura[7] for a general overview of this issue. Perhaps one of the most debated issues concerns the role of potassium and magnesium depletion in the genesis of cardiac arrhythmias, particularly in patients treated with diuretics. The basis of this debate is the fact that diuretics, both loop active and thiazides, produce potassium and magnesium depletion throughout the dose range used in clinical medicine. The magnesium loss induced by diuretics may involve inhibition of magnesium reabsorption in the loop of Henle and increased magnesium loss distally induced by the secondary hypermineralocorticoid state.[74] While the magnitude of the depletion is small, the fact that both magnesium and potassium are lost from the body during diuretic treatment and that large numbers of patients are treated with these agents increases the likelihood that even infrequent adverse effects may come to the attention of the clinician. The concern with cardiac arrhythmias is pertinent because the heart muscle does not lose potassium when there is total body potassium depletion.[75] This would tend to magnify any effect that extracellular potassium changes would have on the electrical properties of the myocardial cell that depend on the ratio of intracellular to extracellular potassium.[76] Thus, it is not surprising that some investigators have found an increase in ventricular ectopic beats that correlated with the changes in serum potassium and magnesium produced by diuretic treatment.[74,77,78] Although this has not been a universal finding,[79,80] it is of interest that in those studies in which replacement therapy was effective in correction of the arrhythmia, changes in magnesium balance also occurred. Such changes were effected by either administration of supplemental magnesium[74] or the use of "K-sparing" diuretics such as spironolactone, amiloride, and triamterine.[77,80-82] The mechanism by which these drugs produce positive magnesium balance is unclear, but may involve alkalinization of the distal urine[83] and a reduction in the transepithelial potential gradient that would favor magnesium reabsorption.[84] In contrast, potassium replacement alone was ineffectual in correction of the arrhythmias.

The frequency of more serious arrhythmias, such as ventricular tachycardia and ventricular fibrillation, has also been correlated with the level

of serum potassium in patients with overt ischemic heart disease.[85 87] Refractory ventricular arrhythmias, which respond to magnesium treatment, have also been reported[88] and, most recently, a reduction in arrhythmias and mortality following myocardial infarction has been noted with magnesium therapy.[89]

While these studies suggest some relationship between cardiac arrhythmias and potassium and magnesium balance, a causal relationship has not been established. Potassium and magnesium levels can be acutely affected by circulating catecholamines that may independently affect cardiac rhythm.[90] Thus, the changes in potassium and magnesium may simply be markers for the arrhythmogenic effects of catecholamines. All of the intervention studies with potassium and magnesium have involved small numbers of patients and have not been blinded or had a concurrent nontreatment control group.

This controversy has been fueled further by the results of large clinical trials involving the treatment of essential hypertension. Most studies have demonstrated either no effect or a minimal improvement in coronary heart disease morbidity and mortality in diuretic treated patients with essential hypertension, particularly mild hypertension.[91] This contrasts with the impressive and consistent benefit that diuretic treatment has on the development of cerebrovascular complications of hypertension. This raises the possibility that diuretics may have an adverse effect on the natural history of coronary heart disease, which negates the benefit that might be expected from a reduction in blood pressure. In addition to effects on carbohydrate balance and circulating lipids, the effects of diuretics on potassium and magnesium balance have been implicated in this adverse effect.[92]

SUMMARY

Potassium and magnesium balance are frequently altered by common pathological conditions. Isolated disturbances of potassium balance do not produce secondary abnormalities in magnesium homeostasis. In contrast, primary disturbances in magnesium balance, particularly magnesium depletion, produce secondary potassium depletion. This appears to result from an inability of the cell to maintain the normally high intracellular concentration of potassium, perhaps as a result of an increase in membrane permeability to potassium and/or inhibition of Na^+-K-ATPase. As a result, the cells lose potassium, which is excreted in the urine. Repletion of cell potassium requires correction of the magnesium deficit.

Are such magnesium dependent alterations in potassium balance of any clinical significance? Within the context of electrolyte disturbances, magnesium replacement is often necessary before hypokalemia and potassium depletion can be satisfactorily corrected with potassium supplements. The hyponatremia often seen with chronic diuretic usage may also be related to depleted intracellular potassium stores. In a small group of patients with chronic congestive heart failure, magnesium replacement alone was sufficient to correct this hyponatremia.[93] Finally, magnesium and potassium depletion may play an important role in the development of cardiac arrhythmias in certain select groups of patients, such as those with overt ischemic heart disease. The frequency of magnesium depletion in some clinical disease states warrants renewed interest in the relationship between magnesium and potassium homeostasis.

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