care by medical staff and compliance by patients. Additionally, monitoring has secondary benefits; it reinforces the risks associated with warfarin, and it provides further opportunities to educate the patient.

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What are the causes of hypomagnesemia?

EVIDENCE-BASED ANSWER

The causes of magnesium depletion and hypomagnesemia are decreased gastrointestinal (GI) absorption and increased renal loss. Decreased GI absorption is frequently due to diarrhea, malabsorption, and inadequate dietary intake. Common causes of excessive urinary loss are diuresis due to alcohol, glycosuria, and loop diuretics.

Medical conditions putting persons at high risk for hypomagnesemia are alcoholism, congestive heart failure, diabetes, chronic diarrhea, hypokalemia, hypocalcemia, and malnutrition (strength of recommendation: **C**, based on expert opinion, physiology, and case series). Evidence suggests that magnesium deficiency is both more common and more clinically significant than generally appreciated.

EVIDENCE SUMMARY

Prevalence and incidence. In general, studies are limited by variations in analytic techniques and differences in defining the lower limit for normal serum magnesium.[1] Estimates of the prevalence of hypomagnesemia in the general population range from 2.5% to 15%. A study of 11,000 white urban Americans aged 45 to 64 years (probability sampling) found 2.5% with magnesium <0.7 mmol/L and 5% with magnesium <0.75 mmol/L; rates for 4000 African Americans were twice as high.[2]

Some authors have proposed a higher range for normal serum magnesium, asserting that dietary magnesium deficiency is endemic in developed countries where acid rain reduces the magnesium content of crops and food processing causes further large reductions in the magnesium content of the diet.[1] Moreover, common diseases are associated with hypomagnesemia and likely contaminate studies of "normal" populations. Thus, a study of 16,000 German subjects (including blood donors, outpatients, and children) found a 14.5% prevalence of hypomagnesemia using a lower limit of 0.76 mmol/L[1]; however, applying the more commonly cited lower limit of 0.70 mmol/L (1.7 mg/dL) to the same data yielded a prevalence of 2%.

Numerous studies agree that the prevalence of hypomagnesemia is much higher (10%–65%) in subpopulations defined by severity of illness (hospitalization, in intensive care unit [ICU] or pediatric ICU), increasing age (elderly/in nursing home), or specific diseases. For example, of 94 consecutive patients admitted to the ICU, 65% had hypomagnesemia.[3] Likewise, for 127 consecutive patients admitted with a diagnosis of alcoholism, the prevalence was 30%.[4]

Because of limitations noted above, as well as the lack of control groups, the relative prevalence in these groups (compared with the general population) is uncertain, but the studies do identify high-risk populations. A single study, which included a control group, demonstrated an 11% prevalence of hypomagnesemia among 621 randomly selected hospitalized patients compared with 2.5% among 341 hospital employees.[5] Other diseases associated with a high prevalence of hypomagnesemia include cardiovascular disease (hypertension, congestive heart failure, coronary artery disease), diabetes, diarrhea, diuretics use, hypokalemia, hypocalcemia, and malabsorption.[6–9]

Common causes. We found no high-quality studies to establish the relative probabilities of various causes in the general population or any subpopulation.[10] The most common causes of significant hypomagnesemia in developed coun-

TABLE

Causes of hypomagnesemia

Gastrointestinal
Diarrhea, dietary deficiency (including protein-calorie malnutrition, parenteral and enteral feeding with inadequate magnesium, alcoholism, and pregnancy), familial magnesium malabsorption, gastrointestinal fistulas, inflammatory bowel disease, laxative abuse, malabsorption (sprue, steatorrhea, chronic pancreatitis), nasogastric suction, surgical resection, vomiting
Renal
Alcoholism, diabetes, diuretics (thiazide, loop, and osmotic/hyperglycemia), other medications, hormones (hypoparathyroidism, hyperthyroidism, hyperaldosteronism, SIADH (syndrome of inappropriate antidiuretic hormone secretion), excessive vitamin D, ketoacidosis, renal disease (acute tubular necrosis, interstitial nephritis, glomerulonephritis, post-obstructive diuresis, post-renal transplantation), hypercalcemia/hypophosphatemia, tubular defects (primary magnesium wasting, Welt's syndrome, Gitelman's syndrome, renal tubular acidosis)
Shifts from extracellular to intracellular fluid
Acidosis (correction of), blood transfusions (massive), epinephrine, hungry bone syndrome, insulin/glucose/refeeding syndrome, pancreatitis (acute)
Transdermal losses
Excessive sweating, massive burns

tries are said to be diabetes, alcoholism, and the use of diuretics. In a group of 5100 consecutive patients (predominantly outpatient, middle-aged, and female) presenting to a diagnostic lab, the most common diagnoses associated with hypomagnesemia were diabetes (20% of cases) and diuretic use (14% of cases); however, other potential causes, including alcoholism, were not identified.[11] A complete list of causes is in the **Table**.

Serious causes. A critical serum magnesium level is less than 0.5 mmol/L and is associated with seizures and life-threatening arrhythmias.[6] Very low magnesium levels typically result when an acute problem is superimposed on chronic depletion. For example, critical levels can occur among patients with diabetes during correction of ketoacidosis or alcoholics who develop vomiting, diarrhea, or pancreatitis.

Magnesium in the 0.5 to 0.7 mmol/L range may be life-threatening in certain disease contexts, such as acute myocardial infarction or congestive heart failure, where there is already a risk of fatal arrhythmia.[8]

Impact. The impact of hypomagnesemia is underestimated largely because clinicians fail to measure magnesium.[12] Since magnesium is a cofactor for more than 300 enzymes and is involved in numerous transport mechanisms, it is not surprising that hypomagnesemia is associated with significant morbidity.

For example, in a study of 381 consecutive admissions at an inner-city hospital,[13] approximately half the admissions went to ICUs and half to regular wards. Despite similar Acute Physiology and Chronic Health Evaluator (APACHE) scores at admission, hospital mortality was twice as high for hypomagnesemic patients in both care settings.

RECOMMENDATIONS FROM OTHERS

Several review articles include a comprehensive differential diagnosis for causes of

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magnesium deficiency based on physiologic principles as listed in the Table, but none provide data on the relative frequency of the various causes in the general population or specific subgroups.[6–9]

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CLINICAL COMMENTARY

We need to know when magnesium replacement improves patient outcomes

Treating the underlying cause of hypomagnesemia makes sense. However, even though clinicians often treat "the numbers," it is not clear that magnesium replacement therapy is beneficial in the absence of symptoms caused by the hypomagnesemia. For example, hypomagnesemia is common for patients with acute myocardial infarction, but magnesium replacement therapy has not been shown to improve outcomes in 2 large randomized trials, the Fourth International Study of Infarct Survival (ISIS 4)[14] and Magnesium in Coronaries (MAGIC).[15] We need better-designed randomized trials to know for what clinical conditions magnesium replacement leads to improved patient-oriented outcomes.

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What are effective therapies for *Clostridium difficile*–associated diarrhea?

EVIDENCE-BASED ANSWER

Oral metronidazole and oral vancomycin are equally effective treatments for *Clostridium difficile*–associated diarrhea (CDAD) (strength of recommendation [SOR]: **A**, based on randomized trials). Oral vancomycin is considerably more expensive and may select for colonization with vancomycin-resistant enterococci, leading the American College of Gastroenterology to recommend oral metronidazole as preferred therapy (SOR: **C**, expert opinion). They recommend therapy with vancomycin for those who are pregnant, breast feeding, less than 10