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Geriatric cachexia: a role for magnesium deficiency as well as for cytokines?

Dear Sir:

Thank you for publishing the fine review of geriatric cachexia by Yeh and Schuster (1). They stated that prostaglandin E2 (PGE2) and the proinflammatory cytokines interleukin 1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α) are involved in biological processes related to the disorder. They implicated oxygen free radicals in the pathogenesis of cachexia by noting that TNF-α increases protein oxidation and that cachectic patients often experience a loss in body protein and an accelerated mobilization and oxidation of energy substrates. Cytokines have complex roles in the cause of cachexia because they rarely act alone, usually acting in conjunction with other cytokines (1), prostaglandins (1), or oxygen free radicals (2). Cytokines may inhibit feeding by causing nausea and vomiting and decreased gastric motility and gastric emptying (1).

Geriatric cachexia is associated with anorexia, involuntary weight loss, infections, decubitus ulcers, malnutrition, cognitive and psychiatric disorders, and even death (1). Yeh and Schuster stated that, of these conditions, only malnutrition is amenable to medical intervention. I propose that magnesium replacement therapy be considered as a therapy in geriatric cachectic patients found to be magnesium deficient.

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation (3). It is an activator in ≈300 enzyme systems that are critical to cellular metabolism (4). Magnesium is essential in reactions involving ATP, which is required for glucose utilization, muscle contraction, and the synthesis of fat, protein, nucleic acid, and coenzymes (4). Other functions of magnesium include neurochemical transmission, skeletal muscle contraction, cardiac homeostasis, and the maintenance of normal intracellular concentrations of other cations (3).

Magnesium depletion is associated with biochemical and clinical derangements (3–5), which include impaired anabolic processes manifested by low serum albumin and serum protein concentrations and a decreased growth rate (5). Magnesium deficiency may contribute to cardiac arrhythmias, skeletal and respiratory muscle weakness, and seizures (3). Several mediators associated with the pathogenesis of cachexia are increased in magnesium deficiency (1). These include the inflammatory cytokines IL-1, IL-6, and TNF-α (2); PGE2 (6); and oxygen free radicals (2). In magnesium deficiency, not only are free radical concentrations higher than normal, but tissue concentrations of the antioxidants vitamin E, ascorbate, and glutathione are lower than normal; thus, endogenous antioxidant capacity is reduced, predisposing magnesium-deficient tissues to subsequent oxidative stress (2). The cytokine substance P, which increases early in magnesium deficiency, may lead to oxidative injury and appetite suppression, possibly contributing to the reduced food intake and weight loss that characteristically occur in experimental animals within 2 wk of dietary magnesium restriction (2).

Two surveys showed suboptimal magnesium intake among free-living adults in the United States. One survey, sponsored by the US Department of Agriculture (7), showed magnesium intakes that were 61.7% of the recommended dietary allowance (RDA; 8) among elderly people from food-insufficient households. A second study was conducted among well-educated, middle-to-upper class, community-dwelling volunteers in the Baltimore Longitudinal Study of Aging (9). In both men and women, median daily dietary intakes of magnesium failed to meet the 1989 RDA. Forty percent of the men and ≈50% of the women consumed less than two-thirds of the RDA for magnesium. The consequences of these marginal intakes of magnesium on health status are unknown and require further study.

Other studies provided data concerning the incidence of hypomagnesemia and of its associated mortality among hospitalized patients. In their study of an inner-city, medically disadvantaged, indigent population, Rubeiz et al (3) detected hypomagnesemia at the time of admission in 18% of ward and in 20% of intensive-care-unit patients. The mortality rates of the 2 groups of patients were approximately twice (P < 0.01) the rates of the normomagnesemic groups. They cited one study that reported low serum magnesium concentrations in up to 65% of intensive-care-unit patients, and another study that showed a higher mortality rate in hypomagnesemic postoperative patients than in their normomagnesemic counterparts.

Cognitive disorders, psychiatric disorders, and mental depression are occasional features of cachexia (1) and may be associated with hypomagnesemia (10). Levine et al (10) showed that patients with acute depressive disorders had elevations in the ratio of calcium to magnesium in both serum and cerebrospinal fluid. Hypomagnesemic patients have reported confusion, disorientation, agitation, hallucinations, and depression. Magnesium has been effective in alleviating depressive and manic symptoms in rapidly cycling bipolar disorders (10).
Possibly, magnesium deficiency contributes to diminished host defenses in the elderly (1). Elin (5) showed profound immunosuppressive capability in magnesium-deficient mice that had low numbers of antibody-synthesizing cells and low serum immunoglobulin concentrations. He cited studies in magnesium-depleted rats with decreased serum γ globulin and immunoglobulin G concentrations.

I suggest that magnesium deficiency in elderly patients contributes to cachexia. Magnesium deficiency puts the patient at risk of increased activity of damaging mediators that contribute to cachexia (e.g., inflammatory cytokines, PGE₂, and oxygen free radicals) and it reduces the tissues’ antioxidant capacity. Magnesium deficiency may increase the risk for cognitive and psychiatric disorders, which may be amenable to magnesium therapy (10).

It may be prudent to evaluate the magnesium status of elderly patients with cachexia. If these subjects are magnesium deficient, magnesium supplementation may be beneficial because magnesium supplementation was shown to rapidly reverse the clinical symptoms (anorexia, apathy, weakness, and weight loss) of severely malnourished, magnesium-deficient children (11). However, numerous factors must be considered in geriatric cachexia. The chronicity of marginal or inadequate intakes of iron, calcium, magnesium, and zinc; the prolonged use of medications; and the reduced absorption or metabolism of nutrients may adversely affect the nutritional status of the elderly (9). The effects of magnesium supplementation late in the course of magnesium deficiency in the elderly are not known, but are worthy of investigation.

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Reply to JL Caddell

Dear Sir:

We thank Caddell for pointing out the important role of magnesium deficiency in cachexia. Although the focus of our review was on the cytokines themselves, we agree that there are numerous factors to be considered in geriatric cachexia (1). Inadequate food intake, reduced absorption, cytokine production, and medications can all affect the nutritional status of the elderly. Thiadizide diuretics and loop diuretics are among the most common medications taken by the elderly and they clearly can cause a loss of magnesium. This loss may be overlooked because of apparently normal serum magnesium concentrations. However, when skeletal muscle biopsies are performed, subnormal magnesium and potassium concentrations are found (2). Insufficient dietary supplies of magnesium may inhibit protein synthesis by decreasing serum insulin-like growth factor I (2). Therefore, minerals like magnesium and vitamins are important supplements in the treatment of cachexia.

We agree that magnesium deficiency may exacerbate the elevation of inflammatory cytokines caused by other etiologies. Furthermore, magnesium deficiency may decrease endogenous antioxidant capacity and diminish host defenses. Magnesium deficiency may play an essential role in cellular reactions and in immunoinflammatory processes (3). Magnesium deficiency can also affect mineral homeostasis, induce membrane damage, increase lipid peroxidation, and increase cytokine concentrations, thus reducing immunocompetence (4). Weglicki et al (5–7) found that dramatic elevations in interleukin 6, interleukin 1, and tumor necrosis factor α may promote cardiac lesions in magnesium-deficient rodents.

This activation of immune cells probably occurs early in magnesium deficiency because magnesium-deficient rats that received magnesium-replacement therapy before endotoxin challenge had significantly lower tumor necrosis factor α production than controls (3). It was also noted that vitamin E supplements can prevent the occurrence of myocardial reperfusion injury, possibly through the restoration of endogenous antioxidant defenses in the hypomagnesemic state (7).

Stress and chronic inflammation, under conditions of mineral or antioxidant deficiency, probably further stimulate the secretion of catecholamines and cortisol, which then stimulate the release of cytokines. As we emphasized in our review, cytokines rarely act alone because they stimulate a variety of cell types to produce and secrete a cascade of other cytokines (1). All of these interactions point to the complex roles of cytokines in causing cachexia (1). The effects of magnesium supplementation, the use of antioxidants, as well as the use