Magnesium and the pancreas[1, 2]

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Magnesium, essential for life, is present in all living tissues. It is the fourth most abundant cation in the body, whereas intracellularly, magnesium content of cells is second to potassium. Of the total body magnesium content of approximately 2,000 mEq, approximately one-half is present in bone and the remainder is inside body cells; only 1% of the total body magnesium is in the extracellular fluid (1). In plasma, the concentration of magnesium is relatively constant within narrow limits and in sera, nearly three-fourths of it is ultrafilterable. Magnesium participates in many enzymatic reactions, including acting as a cofactor in ATP transference of enzymes for protein synthesis and in oxidative phosphorylation (2). Because the main exocrine function of the pancreas is the elaboration of pancreatic enzymes essential in the digestion of foodstuffs, derangements in magnesium metabolism may thereby affect pancreatic function. In turn, magnesium levels are often altered in diseases of the pancreas. The symptoms and metabolic aberrations of hypomagnesemia are prominent in some patients with pancreatitis (3–5). This paper reviews the relationships of magnesium and the exocrine pancreas.

Magnesium depletion has been reported as a complication of diseases of the small intestine, including massive resection of the gut, celiac disease, and regional enteritis (6–8). The deficiency occurs mainly from a rapid intestinal transit and increased fecal losses of magnesium (5–7). Hypomagnesemia also follows the prolonged use of magnesium-free parenteral fluids (9), childhood malnutrition (10, 11), chronic renal disease (9), and disorders of the parathyroids (9). In some children, magnesium deficiency is associated with a diarrheal syndrome and hypocalcemia, possibly resulting from a selective defect in magnesium absorption (12). Experimental human magnesium depletion has reproduced the symptoms of magnesium deficiency that are akin to those of hypocalcemia (13, 14).

Clinical features of magnesium deficiency consist mainly of signs of neuromuscular hyperexcitability, including paresthesia, muscle cramps, carpopedal spasm, tetany, and convulsions (9, 13). Serum magnesium levels may correlate poorly with manifestations of the deficiency because serum levels are maintained at the expense of the intracellular stores of the cation. Urinary magnesium values in these deficiency states are markedly diminished, attesting to the vital role of the kidney in conserving magnesium in the presence of magnesium deficiency (5, 9).

Growth is markedly impaired in young animals placed on experimental protein or magnesium deficiency diets (15, 16). Dietary protein deficiency in animals and man is followed by pancreatic exocrine insufficiency (17–19). The ensuing decrease of pancreatic enzymes for digestion further complicates the syndrome of protein malnutrition. The pancreas, however, may recover the ability to synthesize its enzymes, and body growth resumes during dietary protein repletion. One study, however, has shown that protein-depleted rats fail to regain weight or grow compared with control animals being deprived of magnesium during the period of protein repletion (15). Thus, magnesium replacement is a necessary supplement for recovery of organ function in protein malnu-

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trition (20). Because the pancreas synthesizes more protein per gram than other tissues and requires metabolic energy to secrete bicarbonate, another study has focused on pancreatic function in experimental magnesium depletion of rats (16). In both groups of young and adult rats placed on magnesium-deficient diets, pancreatic function, measured by volume, nitrogen output, and amylase content of the pancreatic secretion, was studied in the resting state and after secretin and pancreozymin stimulation. There were no significant differences between the pancreatic secretions of the magnesium-depleted animals and their controls (16). Even when low levels of magnesium were attained in the serum and in red blood cells of many of the animals, the magnesium content of the pancreas was similar to the values obtained in the control animals and in the magnesium-supplemented rats. In contrast to animals with combined protein and magnesium deficiency and impaired pancreatic function, magnesium content of the pancreas remains normal in experimental magnesium deficiency. Preservation of magnesium content in the pancreas may account for the test animals' normal pancreatic functions. The animals likely die of other complications of magnesium deficiency before inducing alterations in the pancreas. In magnesium-deficient animals, neuromuscular symptoms may be related to significant decreases in the magnesium content of skeletal muscle (15–16) and nervous tissue (21) and may account for death while on the experimental diet (16).

Pancreatic insufficiency and magnesium deficiency also occur in human protein–calorie malnutrition (19, 20). As malnutrition progresses in these patients, the associated diarrhea becomes more severe. There is a rapid intestinal transit and passage of undigested food particles (20). The diarrhea increases fecal losses of magnesium. Dietary protein repletion ordinarily reverses the exocrine pancreatic deficiency during the recovery phase. In controlled studies, children with protein–calorie malnutrition had a more prompt and significant and sustained clinical improvement when their diets were supplemented with magnesium (20). Although the effect of magnesium repletion on pancreatic function has not been evaluated in these children, the marked beneficial effect of magnesium administration in this syndrome may in part be related to a prompt reversal of the diarrhea. Improvement in absorption and a normal intestinal transit time follow magnesium repletion (20). Because there is enhanced protein synthesis in the recovery phase of malnutrition, magnesium needs to be replaced to participate in these metabolic functions. Similar effects of magnesium supplements have been noted in patients with hypomagnesemia from diarrhea and malabsorption (22, 23).

One of the severe complications of acute pancreatitis is hypocalcemia, manifested clinically by tetany and carpopedal spasm (3, 4). These symptoms may also result from hypomagnesemia (4, 13). In acute pancreatitis, hypocalcemia and hypomagnesemia may occur either alone or in combination (3, 4, 9). In 20 patients with acute pancreatitis, low serum magnesium levels occurred in four cases in the first 5 days of the acute episode. The hypomagnesemia did not appear to be related to a fall in the serum levels of calcium or potassium (3, 4). In two patients who expired from acute hemorrhagic pancreatitis, large amounts of magnesium were present in areas of fat necrosis (3). Deposition of magnesium in areas of fat necrosis may contribute to the hypomagnesemia of pancreatitis. In order to correct the neuromuscular manifestations of hypocalcemia or hypomagnesemia complicating acute pancreatitis, the particular cation deficiency needs to be corrected promptly.

In dogs with experimentally induced pancreatitis, the serum levels of both calcium and magnesium were found to be depressed (24). There was a concomitant increase in the urinary excretion of phosphorus in these dogs, suggesting an increased parathyroid response to the hypocalcemia of pancreatitis. In other dogs with a previous parathyroidectomy, the experimental pancreatitis was associated with a more pronounced and prolonged fall in both serum calcium and magnesium levels. In these parathyroidectomized dogs, there was no increase in the urinary excretion of phosphorus. Administration of exogenous parathyroid hormone in the dogs

with pancreatitis and hypomagnesemia was associated with a return of serum magnesium to normal levels. Radiolabeled magnesium, infused during the induction of pancreatitis, showed an eightfold increase in content of magnesium in fat from the peritoneal cavity of the animals with pancreatitis compared with that in fat tissue found in control animals (24). Increased radioactivity from the labeled magnesium was also noted in specimens of subcutaneous fat from the abdominal wall in the test animals. Thus, in animals and humans with acute pancreatitis, hypomagnesemia may result in part from deposition of magnesium, like calcium, in areas of fat necrosis.

In intact animals treated with magnesium infusions after induction of pancreatitis, the hypocalcemia and hypomagnesemia that usually followed the pancreatitis was less pronounced than in the untreated dogs with pancreatitis (24). When hypocalcemia coexists with hypomagnesemia of any etiology, neuromuscular symptoms may be only transiently alleviated with administration of calcium alone. During hypomagnesemia in humans, exogenous parathyroid hormone also does not fully correct the hypocalcemia (12, 25). When the hypomagnesemia is corrected alone, both serum magnesium and calcium levels rise, and there is amelioration of the clinical features. Once magnesium levels have been restored to normal, parathyroid hormone can exert its calcemic and phosphaturic effects on the respective end organs (12, 25). Thus, responsiveness to parathyroid hormone is dependent on the state of magnesium. In acute pancreatitis, complicated by hypomagnesemia and hypocalcemia, administration of parenteral magnesium is vital in the treatment of symptoms resulting from deficiency of these cations.

Diarrhea and steatorrhea occur in chronic pancreatitis and pancreatic insufficiency. Magnesium deficiency complicates these malabsorption syndromes (5, 23). In patients with chronic diarrhea, magnesium losses in stool are increased over daily output, resulting in a decrease in body stores. Magnesium depletion was noted in six of seven cases with chronic diarrhea, one of whom had chronic pancreatitis (5). Inadequate dietary intake appears to enhance the magnesium deficiency in these patients. Clinical manifestations of magnesium deficiency that correlated best with skeletal muscle magnesium content for magnesium levels in serum and in the erythrocytes tended to be normal. Symptomatic hypomagnesemia was corrected by parenteral magnesium administration including the patient with chronic pancreatitis (5). Hypocalcemia, when present, was similarly corrected by magnesium alone. The magnesium deficiency of pancreatic insufficiency may result in part from the increased fecal losses; balance studies in patients with pancreatic insufficiency need to be performed to evaluate magnesium metabolism in these patients.

Magnesium and calcium production by the pancreas has been evaluated in 25 patients with and without pancreatic disease (26). Pancreatic function tests were done in the resting state and after secretin stimulation. The pancreatic secretion in normal humans has a mean magnesium concentration of 3.5 mg/100 ml; after secretin stimulation, the concentration falls to 0.8 mg/100 ml. In normal subjects, there is an inverse relationship between the concentration of bicarbonate and of magnesium in the duodenal aspirates after secretin administration. In patients with chronic pancreatitis, however, there is a higher mean concentration of magnesium after secretin stimulation (26). Similar findings were observed for calcium concentration in the duodenal aspirates. Increased concentration of calcium and magnesium in pancreatic secretion in chronic pancreatitis may play a role in the etiology of the pancreatitis and in pancreatic calcification (26, 27).

Alcoholism is a frequent inciting factor in the pathogenesis of acute pancreatitis. Because magnesium deficiency may be present in the patient with chronic alcoholism (28), hypomagnesemia may be more pronounced when the alcoholic patient develops an attack of pancreatitis.

In the alcoholic, the decrease in body magnesium may occur irrespective of the presence of liver disease, as hypomagnesemia occurs at various stages of the alcoholic syndromes (29). Magnesium depletion in the

alcoholic may exist independent of other factors such as poor caloric intake, vomiting, or diarrhea. These latter factors alone can decrease magnesium body stores. Hypomagnesemia has been reported in the immediate alcohol withdrawal period (29), a fact of importance in the alcoholic patient who develops acute pancreatitis complicated by neuromuscular symptoms. The fall in serum magnesium after alcohol ingestion is often associated with a decrease in other serum electrolytes, particularly potassium. These changes may coincide with the onset of the neuromuscular excitation of the alcohol withdrawal syndrome.

In chronic alcoholics, the hypomagnesemia may be aggravated by an increased renal excretion of magnesium (29). This renal factor occurs mainly when the levels of alcohol are rising in blood but not when the serum levels are high, but steady. Evidence for a decrease in total body magnesium in alcoholics with or without cirrhosis is provided by a demonstration of low skeletal muscle content of magnesium (31) and by retention of significant amounts of intravenously administered magnesium (30). Thus, the chronic alcoholic, with or without cirrhosis, tends to be magnesium depleted (28, 31). When an attack of acute pancreatitis supervenes in these patients, the neuromuscular manifestations of hypomagnesemia may become more pronounced and be further complicated by an alcohol-withdrawal syndrome. In this group of patients, chronic diarrhea and pancreatic insufficiency occur as further complications of alcoholism. These also tend to reduce the body magnesium stores. Magnesium replacement is thus important in the patient with alcoholism and concomitant disease of the pancreas.

Summary

In summary, magnesium participates in the protein synthesis of pancreatic enzymes. There is no impairment in pancreatic function in animals with experimental magnesium deficiency as these succumb to the neuromuscular and cardiovascular complications of magnesium deficiency. Magnesium content in pancreatic cells was not decreased in these animals. In protein deficiency in humans and animals, however, recovery of function and growth during dietary protein repletion is enhanced by concomitant magnesium supplementation.

In acute pancreatitis, hypomagnesemia and hypocalcemia may occur alone or in combination, presumably due in part to deposition of these cations in areas of fat necrosis. Magnesium deficiency also occurs in patients with diarrhea and pancreatic insufficiency. Because chronic alcoholics tend to be magnesium depleted, pancreatic disease in these cases will aggravate the deficiency. Correction of hypomagnesemia alone allows parathyroid hormone to act on bone and thereby also to correct the accompanying hypocalcemia in patients with inflammatory pancreatic disease. Magnesium and calcium concentrations are increased in secretin-stimulated pancreatic juice in patients with chronic pancreatitis. The significance of these findings are not known, but this may have some relevance in deposition of pancreatic calculi and recurrence of attacks of pancreatitis. Magnesium should be evaluated in serum and urine in patients with acute and chronic pancreatitis, particularly in cases with chronic alcoholism.

References

1. MacIntyre, I. Magnesium metabolism. *Advan. Internal Med.* 13: 143, 1967.
2. Wacker, W. E. C., and A. F. Parisi. Magnesium metabolism. *New Engl. J. Med.* 278: 658, 1968.
3. Edmondson, A. H., C. J. Berne, R. E. Homann and M. Wertman. Calcium, potassium, magnesium and amylase disturbances in acute pancreatitis. *Am. J. Med.* 12: 34, 1952.
4. Wills, M. R. Hypocalcemia and hypomagnesemia in acute pancreatitis. *Brit. J. Surg.* 53: 174, 1966.
5. Lim, P., and E. Jacob. Tissue magnesium level in chronic diarrhea. *J. Lab. Clin. Med.* 80: 313, 1972.
6. Opie, L. M., B. G. Hunt and J. M. Finlay. Massive small bowel resection with malabsorption and negative magnesium balance. *Gastroenterology* 47: 415, 1964.
7. MacIntyre, I., and C. J. Robinson. Magnesium and the gut: experimental and clinical observations. *Ann. N.Y. Acad. Sci.* 162: 865, 1969.
8. Neilsen, J. A., and E. Hess Thaysen. Acute

and chronic magnesium deficiency following extensive small gut resection. *Scand. J. Gastroenterol.* 6: 663, 1971.
9. MARTIN, H. E. Clinical magnesium deficiency. *Ann. N.Y. Acad. Sci.* 162: 891, 1969.
10. MONTGOMERY, R. D. Magnesium metabolism in infantile protein malnutrition. *Lancet* 2: 70, 1960.
11. LINDER, G. C., J. D. L. HANSEN AND C. D. KARABUS. The metabolism of magnesium and other inorganic cations and of nitrogen in acute kwashiorkor. *Pediatrics* 31: 552, 1963.
12. WOODWARD, J. C., P. D. WEBSTER AND A. A. CARR. Primary hypomagnesemia with secondary hypocalcemia, diarrhea, and insensitivity to parathyroid hormone. *Am. J. Digest. Diseases* 17: 612, 1972.
13. VALLE, B. L., W. E. C. WACKER AND D. D. ULMER. The magnesium-deficiency tetany syndrome in man. *New Engl. J. Med.* 262: 155, 1960.
14. SHILS, M. E. Experimental human magnesium depletion. *Medicine* 48: 61, 1969.
15. MENAKER, W., AND I. S. KLEINER. Effect of deficiency of magnesium and other minerals on protein synthesis. *Proc. Soc. Exptl. Biol. Med.* 81: 377, 1952.
16. SARNER, M., AND P. J. SNODGRASS. Preservation of exocrine pancreatic function in the magnesium-deficient rat. *J. Nutr.* 96: 275, 1968.
17. VEGHELYI, P. U., AND T. T. KEMENY. Protein metabolism and pancreatic function. In: *Ciba Found. Symp. Exocrine Pancreas.* London: Churchill, 1962, p. 329.
18. HERSKOVIC, T. The exocrine pancreas in intestinal malabsorption syndromes. *Am. J. Clin. Nutr.* 21: 520, 1968.
19. GOMEZ, F., R. RAMOS, J. CRAVIOTO AND S. FRENK. Estudios Sobre el niño desnutrido. *Pediatrics* 13: 544, 1954.
20. CADDELL, J. L. Magnesium deficiency in protein–calorie malnutrition: a follow-up study. *Ann. N.Y. Acad. Sci.* 162: 874, 1969.
21. CHUTKOW, J. G. Distribution of magnesium and calcium in brains of normal and magnesium-deficient rats. *Mayo Clin. Proc.* 47: 647, 1972.
22. FLETCHER, R. F., A. A. HENLY, H. G. SAMMONS AND J. R. SQUIRE. A case of magnesium deficiency following massive intestinal resection. *Lancet* 1: 522, 1960.
23. BOOTH, C. C., S. HANNA, N. BABOURIS AND I. MACINTYRE. Evidence of hypomagnesemia in intestinal malabsorption. *Brit. Med. J.* 2: 141, 1963.
24. HERNANDEZ, I. A., S. R. POWERS AND T. F. FRAWLEY. The role of the parathyroid glands in calcium and magnesium metabolism in acute hemorrhagic pancreatitis. *Surgery* 50: 113, 1961.
25. ESTEP, H., W. A. SHAW, C. WATTINGTON, R. HOBE, W. HOLLAND AND ST. G. TUCKER. Hypocalcemia due to hypomagnesemia and reversible parathyroid hormone unresponsiveness. *J. Clin. Endocrinol. Metab.* 29: 842, 1969.
26. NIMMO, J., N. D. C. FINLAYSON, A. F. SMITH AND D. J. C. SHEARMAN. The production of calcium and magnesium during pancreatic function tests in health and disease. *Gut* 11: 163, 1970.
27. HERSKOVIC, T., L. G. BARTHOLOMEW, J. C. CAIN AND J. D. JONES. Relationship of calcium in the serum to that in the pancreatic secretion in normal and hypercalcemic states. *Surgery* 58: 530, 1965.
28. SULLIVAN, J. F., P. W. WOLPERT, R. WILLIAMS AND J. D. EGAN. Serum magnesium in chronic alcoholism. *Ann. N.Y. Acad. Sci.* 162: 947, 1969.
29. MENDELSON, J. H., M. OGATA AND N. K. MELLO. Effects of alcohol ingestion and withdrawal on magnesium states of alcoholics: clinical and experimental findings. *Ann. N.Y. Acad. Sci.* 162: 918, 1969.
30. JONES, J. E., S. R. SHANE, W. H. JACOBS AND E. B. FLINK. Magnesium balance studies in chronic alcoholism. *Ann. N.Y. Acad. Sci.* 162: 934, 1969.
31. LIM, P., AND E. JACOB. Magnesium deficiency in liver cirrhosis. *Quart. J. Med.* 41: 291, 1972.