MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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THE MAGNESIUM DEPLETION SYNDROME

Magnesium is the fourth most common cation in the human body. The entire body of a human adult contains 21-28 grams (approximately 2000 mEq). Approximately 66% of the body magnesium is present in bones. Second to the osseous tissue liver and muscle have the next highest concentrations. Erythrocyte magnesium concentration varies between 4.4 and 6.0 mEq/L. Using an accurate and sensitive method for magnesium determination, atomic absorption spectrophotometry, serum values have been found to vary between 1.6 and 2.1 mEq/L. Approximately 35% of the magnesium in plasma is protein bound and not ultrafiltrable. Percent protein bound appears to be constant with changing plasma magnesium levels.

1. Aikawa, J.K. The role of magnesium in biologic processes. Springfield, Illinois: Thomas 1963.

2. Wacker, W.E.C., and Parisi, A.F. Magnesium Metabolism. New Eng. J. Med. 278:658-661, 712-717, 772-776, 1968.

3. Valber, L.S., Holt, J.M., Paulson, E. and Szivek, J. Spectrochemical analysis of sodium, potassium, calcium, magnesium, copper and zinc in normal human erythrocytes. J. clin. Invest. 44:379, 1965.

4. Rasmussen, H. The parathyroids. Textbook of Endocrinology, Ed. Williams, W.B. Saunders Co. Phila. Pa. 859, 1968.

5. Wallach S., Cahill, L.N., Rogan, F.H., Jones, H.L. Plasma and erythocyte magnesium in health and disease. J. Lab. Clin. Med. 59:195, 1962.

6. Silverman, S.H. and Gardner, L.L. Ultrafiltrable studies of serum magnesium. New Eng. J. Med. 200:938, 1954.

Magnesium Absorption:

The usual American diet contains approximately 300 mg (25 mEq) of magnesium. Much of the magnesium present in the diet is derived from eating green vegetables - chlorophyll being rich in magnesium. Other food sources high in magnesium include cocoa, nuts, seafood and grains (7). Because of the high content of soybeans, vegetables, rice and seafood in the oriental and Indian diets magnesium intake in these population groups is approximately twice that of the average American. The minimum magnesium intake felt to be required to maintain a positive magnesium balance is 0.3-0.35 mEq/Kg (21 mEq/day) (7). This suggests that people in the western countries would be particularly prone to the development of magnesium depletion.

Magnesium absorption from the gastrointestinal tract appears to be poorly controlled. Normally 30-40% of the ingested magnesium is absorbed. Percent absorption is related to the amount of magnesium present in the diet. Using oral ^{28}Mg 23.7% of the magnesium in a diet containing 47 mEq of magnesium was absorbed. In contrast 44.3% of the magnesium in a diet containing 20 mEq of magnesium and 75.8% of the magnesium in a diet containing 1.9 mEq of magnesium was absorbed. (8) Hypermagnesemia has developed following magnesium containing enemas which suggests that some absorption may occur in the colon. (9) Following oral radio-calcium peak plasma levels are reached within 1-2 hours. (10) In contrast peak plasma radiomagnesium levels occur 2-8 hours following oral administration. (11) Maximum magnesium absorption would appear to take place more distal in the small bowel than maximum calcium absorption. The area of maximum calcium absorption, which is vitamin D dependent, is in the duodenum. (12) Studies performed in sheep demonstrate little magnesium absorption in the proximal small bowel. (13) The maximum absorption of magnesium occurs in the mid-ileum. At this distal site magnesium and calcium appear to share a common absorptive mechanism and are competive. (13,14,15) Magnesium absorption is always down an electro-chemical gradient. There appears to be a limiting value which suggests a carrier mechanism. In most studies physiological dosages of vitamin D have had minimal if any effect on magnesium absorption. (16,17,18) In patients with vitamin D resistant rickets, where calcium absorption is markedly impaired, magnesium absorption appears to be normal. (18) In chronic uremia magnesium absorption is minimally if at all impaired in contrast to the marked impairment of calcium absorption. (19)

Pharmacological dosages of vitamin D increases magnesium absorption. However, under the influence of large vitamin D dosage serum magnesium falls, urinary magnesium increases and a negative magnesium balance occurs. (20,21,22,23)

7. Seelig, M.S. Requirement of magnesium by normal adult: Summary and analysis of published data. Am. J. Clin. Nutrition 14:242-290, 1964.

8. Graham, L.A., Caesar, J.J. and Burger, A.S.V. Gastrointestinal absorption and excretion Mg^{28} in man. Metabolism 9:646, 1960.

9. Fawcett, D.W. and Gens, J.P. Magnesium poisoning following enema of epsom salt solution. J.A.M.A. 123:1028, 1943.

10. Avioli, L.V., McDonald, J.E., Singer, R.A. and Henneman, P.H. A new oral isotopic test of calcium absorption. J. clin. Invest. 44:128, 1965.

11. AiKawá, J.K., Rhodes, E.L. and Gordan, G.S. Urinary and fecal excretion of orally administered Mg^{28}. Proc. Soc. Exp. Biol. and Med. 28:29, 1958.

12. Kimberg, D.V., Schacter, O.D. and Schenker, H. Active transport of calcium by intestine: Effect of dietary calcium. Am. J. Physiol. 200:1256, 1961.

13. Care, A.D. and Vant Klooster, A.T. In vivo transport of magnesium and other cations across the wall of the gastrointestinal tract of the sheep. J. Physiol. 177:174, 1965.

14. Alcock, N. and MacIntyre, I. Interrelation of calcium and magnesium absorption. Clin. Sci. 22:185, 1962.

15. Smith, R.H. Net exchange of certain inorganic ions and water in the alimentary tract of the milk-fed calf. Biochemical J. 83:151, 1962.

16. Meintzer, R.B. and Steenbock, H. Vitamin D and magnesium absorption. J. Nutrition 56:285, 1955.

17. Miller, E.R., Ullrey, D.E., Zutant, C.L., Hoeter, J.A. and Luecke, R.W. Mineral balance studies with the baby pig: Effect of dietary vitamin D_2 level upon calcium, phosphorus and magnesium balance. J. Nutrition 85:255, 1965.

18. Anast, C.S. Mg studies in relation to vitamin D resistant rickets. Pediatrics 40:425, 1967.

19. Clarkson, E.M., McDonald, S.J., DeWardener, and Warren, R. Magnesium metabolism in chronic renal failure. Clin. Sci. 28:107, 1965.

20. Hanna, S. Influence of large doses of vitamin D on magnesium metabolism in rats. Metabolism 10:735, 1961.

21. Richardson, J.A. and Welt, L.G. The hypomagnesemia of vitamin D administration. Proc. Soc. Exp. Biol. Med. 118:512, 1965.

22. Richardson, J.A. and Welt, L.G. The hypomagnesemia of vitamin D administration. Clin. Res. 11:250, 1963.

23. George, W.K., George, W.D., Jr., Haan, C.L. and Fisher, R.G. Vitamin D and magnesium. Lancet 1:1300, 1962.

The Renal Handling of Magnesium:

In view of the poorly defined and what appears to be poorly controlled G.I. absorption of magnesium it has been suggested that magnesium balance is largely determined by renal mechanisms. On a normal diet the urine contains approximately 100 mg of magnesium or about 30-40% of the dietary intake. (24) With oral magnesium supplementation in the form of antacids, urinary magnesium may increase to 400-600 mg/day. (25) Similarly when dietary magnesium restriction is imposed urinary magnesium falls in 4-6 days to less than 12 mg (1 mEq) day. (26) Magnesium appears to be primarily regulated by the kidney by a combination of filtration and reabsorption. Although tubular secretion of magnesium undoubtedly occurs in the aglomerular fish (27) there has been little evidence to support the presence of tubular secretion of magnesium in mammals. Gin et al using stop-flow studies with radiomagnesium suggested that the filtered material was completely reabsorbed and urinary magnesium was the result of tubular secretion in a manner similar to potassium. (28) However, numerous studies in a variety of mammals including man have failed to demonstrate direct proof of tubular secretion. (29,30,31) Only one study in rats has shown urinary magnesium excretion to be greater than filtered load. (32) However, other authors raising serum magnesium concentrations to equal or higher levels have failed to confirm this observation. (33)

Filtered magnesium is determined by the amount of the plasma magnesium present in the ultrafiltrable fraction (approximately 65% of the plasma level). Recent micropuncture studies show that TF/PUfMg ratio in the proximal tubule under conditions of volume expansion, mannitol diuresis and magnesium loading is always unity. (33) These studies suggest that the majority of magnesium reabsorption occurs in the proximal tubule (up to 60%) and is probably passive. During saline loading urinary magnesium increased from 6.1% of the filtered load to 12.6%. During magnesium loading GFR and TF/Pinulin fell. Magnesium delivery to the end of the accessible portion of the proximal tubule increased from 45 to 70% and urinary excretion rose from 10.1 to 56.2% of the filtered load. Using stop-flow techniques minimum urinary concentrations of magnesium are found in the distal samples. Studies in rats, sheep, cattle and dogs suggests that there is a renal Tm for reabsorption of magnesium that is near the normal filtered load. The threshold value in rats was found to be 1.5-1.7 mg/100 ml, (32) 2.0 mg/100 ml in sheep (34) and 1.9 mg/100 ml in cattle. (35) A recent study in dogs suggested a Tm of 140 μg/min/kg body weight. (36)

Because of stop-flow data showing minimal magnesium and calcium concentrations in the same distal urine collections it has been suggested that magnesium and calcium share a common reabsorptive pathway. (37,38) Acute calcium loads are associated with increased urinary calcium and magnesium excretion. (38) However, under some conditions calcium and magnesium excretion can be dissociated. Thiazide diuretics markedly reduce urinary calcium excretion in the face of unchanged or increased magnesium excretion. Following acetozolamide urinary calcium increases while both GFR and Mg excretion fall. (30)

Parathyroid hormone has also been implicated in the urinary handling of magnesium. (39) In rats urinary calcium and magnesium fall following the administration of parathyroid hormone. (40) This has also been shown in dogs. (36) Approximately 35% of hypoparathyroid patients have reduced serum magnesium concentrations. (39) Urinary magnesium wasting has been reported in two patients with hypoparathyroidism. (26,41) However, both of these patients were receiving vitamin D therapy. As previously stated, urinary magnesium increases and serum magnesium falls with the administration of large dosages of vitamin D which may have contributed to the development of hypomagnesemia in these two patients.

Aldosterone has also been suggested as an additional factor controlling magnesium handling. (42) Patients with adrenal insufficiency during crisis, have hypermagnesemia. (43) Also, hypomagnesemia has been found in patients with primary aldosteronism. Horton and Biglieri demonstrated increased urinary magnesium and reduced serum magnesium in five patients with primary hyperaldosteronism. (42) They were also able to show that spirnolactone and surgical removal of the adenoma decreased urinary magnesium excretion. Similarly aldosterone given to an adrenalectomized subject increased urinary magnesium excretion. (42)

24. Sutton, R.A.L. and Watson, L. Urinary excretion of calcium and magnesium in primary hyperparathyroidism. Lancet 1:1000, 1969.

25. Randall, R.E., Jr., Cohen, M.D., Spaas, C.C., Jr., Rossmeial, E.C. Hypermagnesemia in renal failure. Etiology and toxic manifestations. Ann. Int. Med. 61:73, 1964.

26. Gitelman, H.J., Graham, J.B. and Welt, L.G. A new familial disorder characterized by hypokalemia and hypomagnesemia. Trans. Assoc. of American Physicians. 79:221, 1966.

27. Berglund, F., and Forster, R.P. Renal tubular transport of inorganic divalent ions by the aglomerular marine teleost, Lophius Americanus. J. gen. Physiol. 41:429, 1958.

28. Ginn, H.E., Smith, W.O., Hammarsten, J.F. and Snyder, D. Renal tubular secretion of magnesium in dogs. Proc. Soc. Exp. Biol. 101:691, 1959.

29. Murdaugh, H.V. and Robinson, R.R. Magnesium excretion in the dog studied by stop-flow analysis. Amer. J. Physiol. 198:571, 1960.

30. Barker, E.S., Elkinton, J.R. and Clark, J.K. Studies of the renal excretion of magnesium in man. J. clin. Invest. 38:1733, 1959.

31. Chesley, L.C. and Tepper, I. Some effects of magnesium loading upon renal excretion of magnesium and certain other electrolytes. J. clin. Invest. 37:1362, 1958.

32. Averill, C.M. and Heaton, F.W. The renal handling of magnesium. Clin. Sci. 31:353, 1966.

33. Brunette, M., Wen Sung-Feng, Evanson, R.L. and Dirks, J. Micropuncture study of magnesium reabsorption in the proximal tubule. Am. J. Physiol. 216:1510, 1969.

34. Wilson, A.A. Magnesium homeostasis and hypomagnesaemia in ruminants. Vet. Rev. 6:39, 1960.

35. Storry, J.E. and Rook, J.A.F. The magnesium nutrition of the dairy cow in relation to the development of hypomagnesaemia in the grazing animal. J. Sci. Fed. Agric. 13:621, 1962.

36. Massry, S.G., Coburn, J.W. and Kleeman, C.R. Renal handling of magnesium in the dog. Am. J. Physiol. 216:1460, 1969.

37. Walser, M. Calcium clearance as a function of sodium clearance. Am. J. Physiol. 200:1099, 1961.

38. Wesson, L.G., Jr. Magnesium, calcium and phosphate excretion during osmotic diuresis in the dog. J. Lab. Clin. Med. 60:422, 1962.

39. Jones, K.H. and Fourman, P. Effects of infusions of magnesium and of calcium in parathyroid insufficiency. Clin. Sci. 30:138, 1966.

40. MacIntyre, I., Boss, S. and Troughton, V.A. Parathyroid hormone and magnesium homeostasis. Nature 198:1058, 1963.

41. Massry, S.G., Coburn, J.W. and Kleeman, C.R. Hypomagnesemia due to an acquired renal defect in magnesium reabsorption. Am. Soc. Neph. (Abst.) October, 1967 page 45.

42. Horton, R. and Biglieri, E.G. Effect of aldosterone on the metabolism of magnesium. J. Clin. Endo. Metab. 22:1187, 1962.

43. Hills, A.G., Parsons, D.W., Rosenthal, O. and Webster, G.D., Jr. Observations of magnesium metabolism in man. J. clin. Invest. 34: 940, 1955.

Summary:

Renal handling of magnesium is dependent on filtration and tubular reabsorption. Proximal tubular reabsorption of magnesium is interrelated to sodium and water reabsorption-factors such as volume expansion which reduces proximal reabsorption of sodium would be expected to increase distal delivery of magnesium. Distal reabsorption of magnesium appears to be a threshold mechanism. Tm for reabsorption of magnesium in the distal site appears to be very near the usual delivery to this site and normal plasma levels in a number of mamillian species including man. PTH and calcium appear to have an opposite effect on urinary magnesium excretion. The effect of aldosterone on urinary magnesium excretion may be a result of volume expansion.

Experimental Magnesium Depletion Syndromes:

The classical features of magnesium deficiency in rats was described in 1932 by Kruse, Orent and McCollum. (44) Five to seven days on a magnesium deficient diet the rats developed vasodilation as manifested by erythema and hyperemia. This is followed by the development of palor and cyanosis. The animal exhibits signs of increasing neuromuscular hyper-irritability and finally generalized seizures. With chronic magnesium deficiencyalopecia, hematomas of the ear lobes and hyperemic gums occur.

A more interesting disease called "Grass Staggers" is of considerable importance and probably more closely resembles the magnesium depletion syndrome in man. (45,46) This disease is particularly common in Australia, New Zealand, England, Holland and some areas of this country. It usually occurs within 1-2 weeks, sometimes as early as 2 days, after cattle have been allowed to graze on the early spring pastures. The disease is characterized by nervousness, anorexia, muscular twitching, unsteady gait and convulsions which may lead to death. Probably results from reduced magnesium absorption secondary to excess soil ammonium content which results in the formation of magnesium ammonium phosphate. The animals typically have hypomagnesemia and frequently hypokalemia and hypocalcemia.

The experimental production of magnesium deficiency in man has been attempted by several authors. (47,48,49,50,51,52) Most studies have induced minimal magnesium depletion and little if any change in serum magnesium. Dunn and Walser were able to cause serum Mg and RBC Mg concentrations to fall but the only other abnormality noted was hypokalemia in one subjects. Probably the best study was that of Shils. (52) Six of seven subjects developed symptoms; Trosseau sign occurred in five and the Chovstek sign in two. Lethargy, generalized weakness, anorexia, nausea and apathy were also noted. Biochemical abnormalities included hypomagnesemia, hypocalcemia and hypokalemia. Urinary calcium fell and all patients developed a positive calcium balance. With one exception, urinary K increased, K balance became negative, and total exchangeable potassium decreased. All abnormalities reverted to normal with magnesium supplementation. With the exception of this study most of the knowledge concerning magnesium deficiency in man has been acquired through the study of diseases associated with magnesium deficiency.

44. Knuse, H.D., Orent, E.R., McCollum, E.L. Studies on magnesium deficiency in animals. I. Symptoms and loss resulting from magnesium deprivation. J. Biol. Chem. 96:518, 1932.

45. Blayter, K.L. and Shurman, B.A.M. Hypermagnesemia tetany in beef cattle. Vet. Rec. 67:108, 1955.

46. Allcroft, R. Hypomagnesemia of cattle and sheep in Britian. J. Brit. Grassland Soc. 2:119, 1956.

47. Barnes, B.A., Cope, O. and Harrison, T. Magnesium conservation in the human being on a low Mg diet. J. clin. Invest. 37:430, 1958.

48. Fitzgerald, M.G. and Fourman, P. An experimental study of magnesium deficiency in man. Clin. Sci. 15:635, 1956.

49. Barnes, B.A., Cope, O. and Gordon, E.B. Magnesium requirements and deficiency: An evaluation in two surgical patients. Ann. Surg. 152:518, 1960.

50. Shils, M.L. Experimental human magnesium depletion. I. Clinical observation and blood chemistry alteration. Am. J. Clin. Nutr. 15:133, 1964.

51. Dunn, M.J. and Walser, M. Magnesium depletion in normal man. Metabolism. 15:884, 1966.

52. Shils, M.E. Experimental human magnesium depletion. Medicine 48:61, 1969.

Clinical Conditions Associated with Hypomagnesemia

I. Inadequate Intake:

Protein-calorie malnutrition of childhood (including Kwashiorkor)

53. Caddell, Joan L. and Goddard, Daniel R. Studies in protein-calorie malnutrition. I. Chemical evidence for magnesium deficiency. New Eng. J. Med. 276:533, 1967.

II. Defective Gastro-intestinal Absorption:

Primary hypomagnesemia

54. Paunier, L., Radde, I.C., Kooh, S.W., Cowen, P.E. and Fraser, D. Primary hypomagnesemia with secondary hypocalcemia in an infant. Pediatrics 41:385, 1968.

Malabsorption syndromes:

Intestinal resections

55. Heaton, F.W. and Fourman, P. Magnesium deficiency and hypocalcemia in intestinal malabsorption. Lancet 2:50, 1965.

Nontropical sprue

56. Hanna, S. Harrison, M., MacIntyre, I. and Fraser, R. Syndrome of magnesium deficiency in man. Lancet 2:172, 1960.

Intestinal and Biliary fistulas

57. Fishman, R.A. Neurological aspects of magnesium metabolism. Arch. Neurology 12:562, 1965.

III. Parathyroid Disease

Pre- and Post-operative for hyperparathyroidism

58. Hanna, S., North, K.A.K., MacIntyre, I. and Fraser, R. Magnesium metabolism in parathyroid disease. Brit. Med. J. 2:1253, 1961.

39. Jones, K.H. and Fourman, P. Effects of infusions of magnesium and of calcium in parathyroid insufficiency. Clin. Sci. 30:138, 1966.

IV. Diabetic Keto-acidosis

59. Wacker, W.E.C. and Vallee, B.L. Magnesium metabolism. New Eng. J. Med. 259:431-438 and 475-482, 1958.

60. Martin, H.E. and Wertman, M. Serum K, Mg, and Ca levels in diabetic acidosis. J. clin. Invest. 26:217, 1947.

V. Hyperthyroidism

61. Rizek, J.E., Dimich, A. and Wallach, S. Plasma and erythrocyte magnesium in thyroid disease. J. Clin. Endocrinol. Metab. 25: 350, 1965.

VI. Vitamin D Therapy (20,21,22)

VII. Excess Lactation

62. Greenwald, J.H., Dubin, A. and Cardon, L. Hypomagnesemic tetany due to excess lactation. Am. J. Med. 35:854, 1963.

VIII. Diuretic Therapy

Mercurial diuretics

63. Smith, W.O., Kyriakopoulous, A.A. and Hammarsten, J.F. Magnesium depletion induced by various diuretics. J. Okla. Med. Assoc. 55: 248, 1962.

IX. Inappropriate secretion of antidiuretic hormone

64. Hellman, E.S., Tschudy, D.P. and Bartter, F.C. Abnormal electrolyte and water metabolism in acute intermittent porphyria; transient inappropriate secretion of antidiuretic hormone. Am. J. Med. 32: 734, 1962.

X. Alcoholism: (51)

65. Kalbfleisch, J.M., Lindemann, R.D., Ginn, H.E., and Smith, W.O. Effects of ethanol administration on urinary excretion of magnesium and other electrolytes in alcoholic and normal subjects. J. clin. Invest. 42:1471, 1963.

66. McCollister, R.J., Flink, E.B. and Lewis, M.D. Urinary excretion of magnesium in man following the ingestion of ethanol. Am. J. Clin. Nutr. 12:415, 1963.

67. Heaton, F.W., Pyrah, L.N., Bernesford, C.C., Bryson, R.W. and Martin,D.F. Hypomagnesemia in chronic alcoholism. Lancet 2:802, 1962.

Excess Renal Losses:

Azotemic Renal Disease

68. Kleeman, C.R., Better, O., Massry, S.G. and Maxwell, M.H. Divalent ion metabolism and osteodystrophy in chronic renal failure. Yale J. Biol. Med. 40:1, 1967.

Reduced proximal tubule reabsorption (excess volume)

Primary Aldosteronism (42)

Bartter's Syndrome

69. Bartter, F.C. So-called Bartter's syndrome (Editorial) New Eng. J. Med. 281:1483, 1969.

Abnormal distal reabsorptive site (26,41)

70. R.M. Freeman and E. Pearson. Hypomagnesemia of unknown etiology. Amer. J. Med. 41:645, 1966.

Renal Tubular acidosis

71. Hanna, S. Plasma magnesium in health and disease. J. Clin. Path. 14:410, 1961.

Diagnosis of Magnesium Depletion:

Serum Magnesium

72. Montgomery, R.D. Magnesium metabolism in infantile protein malnutrition. Lancet 2:74, 1960. Described normal serum magnesium in patients with reduced muscle magnesium.

During vitamin D administration, hypomagnesemia occurs in the face of normal tissue magnesium concentration.

Erythrocyte Magnesium

73. Ginsburg, S. Smith, J.G., Ginsburg, F.M., Reardon, J.Z. and Aikawa, J.K. Magnesium metabolism of human and rabbit erythrocytes. Blood 20:722, 1966. Magnesium concentration higher in Reticulocytes.

Erythrocyte magnesium concentration in deficiency and repletion occurs less rapidly than blood changes, suggests that erythrocyte magnesium reflects plasma concentration which existed earlier during erythropoiesis, rather than current magnesium deficit.

Muscle Magnesium:

74. MacIntyre, I. and Davidson, D. The production of secondary potassium depletion, sodium retention, nephrocalcinosis and hypercalcaemia by magnesium deficiency. Biochem. J. 70:456, 1958.

Appears to correlate best with state of magnesium deficiency in animal studies.

Bone Magnesium:

75. Heaton, F.W. The parathyroid glands and magnesium metabolism in the rat. Clin. Sci. 28:543, 1965.

Although the above author demonstrated a correlation between plasma Mg and bone Mg in rats; there is no sound data to support such a correlation in man.

76. P. Fourman and D.B. Morgan. Chronic magnesium deficiency. Proc. of the Nutr. Soc. 21:34, 1962.

77. McCrudden, H.F. Chemical analysis of bone from a case of human adolescent osteomalacia. J. Biol. Chem. 7:199, 1909.

Bone magnesium content appears to be greater than normal in vitamin D resistant rickets but less than normal in rickets associated with steatorrhea.

Intravenous Magnesium loading

76. Normal subjects excrete over 80% of an IV Mg infusion in 48 hours whereas magnesium defient patients usually excrete less than 50% of the load. This test is only valid when renal mechanisms are intact.

Effect of magnesium on calcium homeostasis

Experimentally induced magnesium deficiency is associated with hypocalcemia in:

Cattle

78. Smith, R.H. Calcium and magnesium metabolism in calves. Plasma levels and retention in milk fed calves. Biochem. J. 67:472, 1957.

Sheep

79. L'Estrange, J.L. and Axford, R.F.E. A study of magnesium and calcium metabolism in lactating ewes fed a semi-purified diet low in magnesium. J. Agric. Sci. 62:353, 1964.

Pigs

17. Miller, E.R., Ullrey, D.E., Zutant, C.L., Baltzer, B.V., Schmidt, D.A., Hoefer, J.A. and Leiecke, R.W. Magnesium requirement of the baby pig. J. Nutr. 85:13, 1965.

and Dogs

80. Chiemchaisri, Y. and Phillips, P.H. Certain factors including fluoride which affect magnesium calcinosis in the dog and rat. J. Nutr. 86: 23, 1965.

In contrast hypercalcemia has usually occurred in the magnesium deficient rat.

75. Heaton, F.W. The parathyroid glands and magnesium metabolism in the rat. Clin. Sci. 28:543, 1965.

Whang, R. and Welt, L.G. Observations in experimental magnesium depletion. J. Clin. Invest. 42:305, 1963.

81. Gitelman, H.J., Kukol, J. and Welt. L.G. The influence of the parathyroid glands on the hypercalcemia of experimental magnesium depletion in the rat. J. clin. Invest. 47:118, 1968.

82. MacManus, J. and Heaton, F.W. The effect of magnesium deficiency on calcium homeostasis in the rat. Clin. Sci. 36:297, 1969.

These authors showed hypercalcemia in the magnesium deficient rat is a result of augmentation of calcium absorption from the G.I. tracts. If a low calcium diet was given, magnesium deficiency produced hypocalcemia.

Case Report

The presented report lends further support to the fact that magnesium depletion also causes hypocalcemia in man. Hypocalcemia appears to result from deranged internal control mechanisms. External balance was positive during the induction of hypocalcemia and actually became slightly negative during the phase of magnesium repletion. These findings are similar to those reported by Smith in calves.

83. Smith, R.H. Importance of magnesium in the control of plasma calcium in the calf. Nature 191:181, 1961.

84. Larvor, P., Girard, A., Brochant, M. Etude de la carence experimentale en magnesium ches le veau I. Observations cliniques biochimiques et anatomopatholog ques & II Interference entre la carence en magnesium et le metabolisme du calcium. Ann. Biol. Anim. Biochem. Biophys. 4:345 & 371, 1964.

Kinetic studies demonstrating reduced bone turnover during magnesium depletion. Also noted parathyroid hyperplasia in magnesium defient animals.

Suggested mechanism is parathyroid hormone resistance.

85. Estep, H., Shaw, W.A., Watlington, C., Hobe, R., Holland, W. and Tucker, S.G. Hypocalcemia due to hypomagnesemia and reversible parathyroid hormone unresponsiveness. J. clin. Endocrin. 29:842, 1969.

Studied 8 hypomagnesemic alcoholics - absent calcemic and phosphaturic effect of PTH until magnesium replacement.

86. Muldowney, F.P., McKenna, T.J., Kyle, L.H., Freaney, R. and Swan, M. Parathormone-like effect of magnesium replenishment in steatorrhea. New Eng. J. Med. 282:61, 1970.
In 2 patients PTH infusion in the magnesium depletion state caused no calcemic effect but did induce increased phosphaturia. Magnesium replenishment relieved tetany, elevated the serum calcium, renal phosphate clearance and serum alkaline phosphatase - bone disease was not present in the magnesium depleted patient.

82. MacManus, J. and Heaton, F.W. The effect of magnesium deficiency on calcium homeostasis in the rat. Clin. Sci. 36:297, 1969.

Magnesium depletion further reduced serum calcium in parathyroidectomized rats suggests a direct effect on bone. Urinary hydroxyproline found to increase with magnesium repletion.

Effect of Magnesium on parathyroid hormone secretion.

No studies during magnesium depletion.

87. Care, A.D., Sherwood, L.M., Potts, J.T. and Aurbach, G.D. Perfusion of the isolated parathyroid gland of the goat and sheep. Nature 209:55, 1966.

Isolated perfusion with high magnesium content shown to lower rate of hormone secretion.

Gitelman, Kukolj and Welt (81) showed that the hypercalcemia and hypophosphatemia of magnesium deficiency in the rat demands parathyroid hormone. However, magnesium deficiency produced phosphaturia in the parathyroidectomized as well as parathyroid intact rats. Furthermore the magnesium depleted parathyroidectomized rats had lower serum calcium levels than their matched controls.

Paunier et al (54) were able to show a normal response to PTH in a hypomagnesemic child.

Nephrocalcinosis in magnesium depleted rats.

88. Oliver, J., MacDowell, M., Whang, R. and Welt, L.G. The renal lesions of electrolyte imbalance. J. Exp. Med. 124:263, 1966.

Magnesium depleted rats developed intranephronic calculi which had their orgins in the thin limb of Henle's loop. Characterized by a PAS positive matrix and $Ca\text{-}PO_3$ precipitation.

89. Heaton, F.W. and Anderson, C.K. The mechanism of renal calcification induced by magnesium deficiency. Clin. Sci. 28:99, 1965.

Able to show that even on a low calcium diet that kidney calcium concentration increased during magnesium deficiency. Parathyroidectomy prevented renal calcium deposition.

Hypokalemia in Magnesium Deficiency:

The development of tetany following the administration of potassium to depleted patients has been previously described.

90. Engel, F.L., Martin, S.P. and Taylor, H. On the relation of potassium to the neurological manifestations of hypocalcemic tetany. Bull. Johns Hopkins Hosp. 84:285, 1949.

91. Fourman, P. and McCance, R.A. Tetany complicating the treatment of potassium deficiency in renal acidosis. Lancet 1:329, 1955.

Potassium depletion in association with magnesium depletion has also been repeatedly observed. The reported patient had renal potassium wasting, hypokalemia, reduced RBC, muscle and total body potassium (total body counter). Shils demonstrated renal potassium wasting, hypokalemia and reduced exchangeable potassium pools during experimental magnesium depletion in man. These findings were corrected with magnesium repletion.

Potassium depletion also occurs in the magnesium depleted rat.

Whang, R. and Welt, L.G. Observations in experimental magnesium depletion. J. clin. Invest. 4:40, 1961.

92. Ginn, H.E. and Cade, R. Aldosterone in magnesium deficient rats. Physiologist 4:40, 1961.

93. Martin, H.E. and Wilson, M.L. Effect of magnesium deficiency on serum and carcus electrolyte levels in the rat. Metabolism 9:484, 1959.

Rats have been shown to have reduced muscle and total carcus potassium content. In the face of reduced total body and muscle potassium serum levels may be normal. Whang and Welt were able to show that potassium loss occured from muscle when bathed with a magnesium free bath.

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Suggests that magnesium and potassium share a common transport mechanism across the mitochondrial membrane and are competive. PTH increases permeability to both Mg and K. Also PTH resistance may be related to failure of Mg to activate Pyrophosphatase.

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CASE STUDY:

18 year old male first admitted November, 1967. The patient's family related that their son had episodes of muscle pain and cramps since 5 years of age. These usually occurred when the patient was overly tired or emotionally disturbed. Polyuria and polydipsia had been present for as long as the parents could remember. The patient had been a poor student, had few outside interests and was difficult to manage at home.

Physical examination revealed a poorly developed male, 5 ft. 1/2 inch tall and weighing 106 lbs (lower 3 percent). BP was 106/70. Trosseau and chovstek's signs were not present.

Family history was negative and serum Mg and K were normal in the patient's mother, father and two sisters.

Abdominal x-ray revealed nephrocalcinosis.

Lab Studies:

Serum Na	132 mEq/L	Arterial	pH	7.41	Serum	Mg	1.0 mg/100 ml
K	2.0 mEq/L		pCO_2	34 mm/Hg		Ca	9.7 mg/100 ml
Cl	102 mEq/L		St. HCO_3	23			

Creatinine clearance - 79 ml/min

Standard acid load - urine pH 6.9 (minimum)

Concentration Test - pitressin and dehydration - 260 mOsm/L

H_2O loading - minimum osmolality - 126 mOsm/L

Curic acid - 8 ml/min
CPO_4- 12 ml/min
Glucose - neg.
Amino acids - normal pattern and amount

		Lower Normal
RBC Mg	2.6 mEq/L	(4.4) mEq/L
Muscle Mg	12.5 mEq/L	(16) mEq/L
RBC K	60 mEq/L	(90) mEq/L