Renal Damage Caused by Magnesium Deficiency

Metastatic calcification, frequently involving the kidneys, is not infrequent in patients with hypercalcemia, whether of dietary or metabolic derivation, because of osteolytic processes, or as a result of therapy. The study by B. S. W. Smith and Nisbet (1968), which showed that magnesium-deficient rats develop nephrocalcinosis, and later osteoporosis, is an appropriate reference for the transition from bone damage to renal damage of magnesium deficiency.

13.1. Experimental Magnesium Deficiency

The diets contrived to be magnesium deficient are almost always imbalanced in other constituents as well. The early diets were usually rich in fats, calcium, phosphorus, and vitamin D, which were effective in producing acute signs of magnesium depletion rapidly (Kruse et al., 1932) and also produced severe renal glomerular and tubular damage that was most extensive at the junction of the cortex and medulla (Cramer, 1932; Brookfield, 1934). Modifications of that diet (designed specifically to produce hypercholesterolemia and atherosclerosis) also produced renal damage (Hellerstein et al., 1957; Gottlieb et al., 1959; Vitale et al., 1959). There was deposition of calcium microliths in the lumina of the collecting tubules that was accompanied by tubular dilatation, and flattened epithelium. High dietary magnesium (96 mg Mg/100 g of diet) abolished the renal tubular calcification, regardless of the amount of calcium fed, in the animals not loaded with cholesterol and cholic acid, and decreased it in fat-loaded rats.

With less imbalanced diets, designed to produce subacute magnesium deficiency (Watchorn and McCance, 1937), rats developed occasional to more frequent calcareous deposits scattered throughout the renal cortex and medulla. Those with most severe damage had extensive calcareous casts and obliteration of the epithelium of the straight and collecting tubules, but no glomerular changes. Greenberg et al. (1938), also using a less imbalanced diet that did not produce signs of acute
deficiency and that contained neither excess phosphate nor very high doses of vitamin D, but was high in calcium (Tufts and Greenberg, 1937), found that prolonged magnesium deprivation of rats produced corticomedullary necrosis and calcinosis involving both the tubular cells and lumina. They attributed the renal calcinosis to the high calcium/magnesium ratio. Greenberg (1939) later attributed part of the severe manifestations of the magnesium-deficiency syndrome (including the renal calcinosis) in the early studies to the inadequacy of vitamins B₂ and B₆ in the vitamin-B-complex supplements then available. The concomitant magnesium and pyridoxine deficiencies might be relevant to calcium oxalate deposition in the kidneys, magnesium being a cofactor in vitamin B₆ metabolism (Review: Durlach, 1969b), oxalate excretion increasing in vitamin B₆ deficiency (Gershoff et al., 1959), and a combination of high magnesium and vitamin B₆ being useful in decreasing calcium oxalate and apatite nephrocalcinosis and urolithiasis (Gershoff and Andrus, 1961; Gershoff and Prien, 1967). Gershoff and Andrus (1961) also showed that the amount of magnesium usually provided control rats (400 ppm) did not completely prevent formation of apatite salts in the kidneys. Tenfold higher intakes were completely protective.

Most of the magnesium-deficiency data derived from rat studies have been obtained with diets rich in calcium and phosphorus, although the marked imbalances in dietary Ca/Mg and P/Mg are rarely noted. Usually they provided from 600/1 to 60/1 ratios of Ca/Mg. For example, rats reported by Hess et al. (1959) were fed a diet delivering 18 mmol Mg/kg of diet and 150 mmol Ca; the deficient group were given 0.25 mmol Mg. They had mitochondrial swelling of tubular cells (observed as early as 3 days of magnesium deprivation) in the distal segment of the convoluted tubule and extending to the thick descending limb. By 6 days, Henle’s loop was also involved. Tubular necrosis was noted by 12 to 20 days, and there were calcium deposits intracellularly and in the lumina, forming calcareous casts. The semisynthetic magnesium-deficient diet provided by Mishra (1960a,b) provided a similar Ca/Mg ratio, and caused decreased renal mitochondrial count and increased tubular calcinosis. With an approximately tenfold less disparity between dietary calcium and magnesium, tubular lesions developed in the renal cortex and at the cortico-medullary junction by the day 8 of magnesium deficiency (Kashiwa, 1961). Some of the tubular cells were hypertrophied and had vacuolated cytoplasm, others were flattened, and there were numerous calcareous deposits, especially at the cortico-medullary junction. Comparable changes, with clumping of renal tubular mitochondria, were correlated with functional renal defects after as little as a week of magnesium depletion (W. O. Smith et al., 1962). The rats exhibited a decreased ability to concentrate and acidify urine and a marked phosphaturia.

Sauberlich and Baumann (1949) found that mice fed diets deficient in thiamine, pyridoxine, or magnesium had aminoaciduria. In a study of chicks and rats (with a Ca/Mg ratio, even in the magnesium-deficient group of rats that was less imbalanced, about 40/1; Bunce et al. (1963) showed that sixfold higher intakes of magnesium were necessary to prevent nephrocalcinosis and aminoaciduria that were seen in the deficient groups. Progressively increased aminoaciduria was also produced in rats on the usual high Ca/Mg dietary ratios of magnesium deficiency studies as the depletion developed (Mazzocco et al., 1966).

Noted in most of the cited magnesium-deficiency studies were the intraluminal