Perspectives in Nutrition

Renal Aspects of Nutritional Disease

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IT IS hoped that Perspectives in Nutrition will review the literature selectively, interpret it moderately and present a spectrum of ideas that will serve as a continual stimulation to nutritional research applied to medical problems.

OTHER than the measurement of urine volume and the amount of a specific nutrient under question in balance studies, the kidney and its functions have received remarkably little attention from nutrition investigators. This despite the fact that interrelationships have repeatedly been shown between dietary factors and renal excretion patterns, both of which may in turn be in interplay with endocrine factors. The kidney is exposed to an enormous blood flow from which it selectively extracts or reabsorbs materials for excretion or retention, thereby preserving the normality of the internal environment particularly with respect to water, ions and pH. Some of the pertinent papers of current interest are reviewed to emphasize these important relationships.

RENAL LESIONS OF ELECTROLYTE IMBALANCE

Structural changes in the kidney are associated with potassium and chloride deficiency as well as hypercalcemia. The effect of potassium deficiency is localized primarily in the collecting tubule and consists of the following changes: (1) hyperplasia of the tubular epithelial cells in the outer zone of the medulla, (2) a specific hyperplasia of the intercalated cells in the same area, and (3) the development of droplets in the cells in the papillary portion of the collecting system.[1] These changes are accompanied by a marked defect in ability to concentrate urine. Considerable, if not complete, reversibility of these lesions may follow potassium repletion. Of particular interest is the observation that a modest increase in phosphate intake, which produces no change in the kidney of normal animals, leads to the added lesions of necrosis and calcification of the terminal segments of the proximal convoluted tubule.

It has been found recently that extensive changes occur in the renal cortex of rats acutely depleted of chloride. This pathologic condition consists of damage and hyperplasia in the proximal convolutions which is followed by an excessive hyperplastic reaction of the renal epithelium. Chloride depletion also predisposes or exaggerates the structural alterations that accompany phosphate intake.[2]

The observation that potassium deficiency exaggerates the lesion of chloride deficiency in the proximal convoluted tubule in man may be related more to a deficit of chloride than of potassium.

Certainly potassium deficiency in human subjects is known to develop all too frequently in clinical situations associated with such factors as severe diarrhea, vomiting, prolonged gastric suction, chlorothiazide therapy and glucose administration in diabetic ketoacidosis without sufficient potassium accompanying the infusion. Particularly in children, potassium depletion may be catastrophic. These alterations in potassium metabolism must be guarded against by evaluating the serum levels of potassium and urinary losses and supplying appropriate amounts of potassium to restore normalcy.

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THE KIDNEY AND CALCIUM METABOLISM

Hypercalciuria may be associated with many diseases such as those involving dissolution of bone or related to excessive ingestion or absorption of calcium.[3] The latter may be of particular significance in populations or in subjects in whom calcium intakes are routinely high as the result of a large consumption of milk. Infusions of calcium decrease maximum urinary concentration in dehydrated subjects, and alteration in renal concentrating capacity is found in calcium nephropathy. This may be produced by the administration of either large doses of vitamin D or parathyroid hormone. There are marked similarities, both morphologic and functional, between the renal effects of potassium deficiency and calcium excess.

Ferris et al.[4] described a young boy in whom hypercalcemic nephropathy developed, apparently as a result of repeated vitamin D intoxications associated with the treatment of hypoparathyroidism. Associated with the nephrocalcinosis, impairment of renal tubular function was found with an inability of the kidney to conserve potassium, excrete acid or concentrate urine. Potassium deficiency as a result would, of course, be made worse on a limited potassium intake from food.

Metabolic acidosis as well as most acidifying therapy promote hypercalciuria which is of particular significance in persons with renal calculi. Also, increases in dietary protein result in an increased excretion of calcium in the urine. On the other hand, increasing phosphate in the diet reduces the urinary excretion of calcium, although in man calcium absorption is little changed by this procedure.

Although the kidney vigorously conserves sodium, and less completely potassium, when placed on dietary restriction of these ions, the renal conservation of calcium is much less rigid and urinary calcium losses may continue to be considerable even on low calcium intakes. Since fecal losses continue, negative calcium balance is readily noted. As the skeleton becomes depleted in calcium, however, the kidneys retain calcium more tenaciously. In patients with osteomalacia, who may have normal serum calcium levels and who may be ingesting as much as 1 gm. of calcium per day, the urine may be practically devoid of calcium. The addition of sodium phytate, which binds calcium in the gut, is often followed by a rapid reduction in the urinary excretion of calcium even though serum calcium levels remain unchanged.

Any effect which influences parathyroid function will reflect on the renal excretion of calcium in the urine since the parathyroid hormone aids in controlling the renal threshold for calcium. Hence, in hyperparathyroidism, the renal threshold for calcium may be elevated to prevent significant hypercalciuria even though the serum calcium is elevated above normal.

An intriguing concept has been proposed by Jackson and Dancaster[5] who suggested that the kidney is so important in calcium metabolism that the intestinal absorption of calcium may continually be governed by the level of calcium in the urine in normal people throughout life. "The absorptive calcium barrier is therefore controlled by the urinary output of calcium." The mechanism is not understood. These authors present data on abnormalities of calcium metabolism which suggest that hypercalciuria is produced first which then in some way acts as a stimulus to the increased absorption of calcium.

In sarcoidosis, the interesting situation may exist of increased calcium absorption, possibly secondary to increased sensitivity to vitamin D; hypercalciuria is present of a degree greater than can usually be explained by excessive calcium absorption; hypercalciuria is generally, but not always found. Of importance is the reversal of these factors by the administration of cortisone, which suggests the possibility that cortisone might be an antagonist to vitamin D at least in this situation.

Is it not of interest that under emotional stress, when corticosteroid production is naturally increased, spontaneous negative calcium balance may ensue?

In idiopathic hypercalciuria serum calcium is generally not elevated and there is usually no evidence of bone disease. Although there may be a renal tubular defect, accounting for excessive calcium excretion, this may be reduced when sodium phytate is fed to reduce

calcium absorption. Idiopathic hypercalciuria is not improved by cortisone, but may in fact be made more severe. The question is, does the increased urinary excretion of calcium lead to increased calcium absorption as a compensatory mechanism? If such a compensation does take place, or if dietary calcium is kept too low, a net negative calcium balance continues with eventual demineralization.

RENAL TUBULAR DEFECTS

Although primary renal tubular insufficiency of the chronic type is relatively rare, an increasing number of clinical syndromes related to renal tubular defects are described. Three of these, Fanconi's syndrome, Vitamin D resistant rickets and familial hypophosphatasia, have significant nutritional significance.

Fanconi's Syndrome

In this syndrome is found osteomalacia, renal glycosuria, aminoaciduria and phosphaturia, with an associated metabolic acidosis and hypokalemia.[6] The cause of this syndrome is obscure, but there exists a renal tubular reabsorptive defect, localized in the proximal tubule, for phosphate, glucose and amino acids. Hypophosphatemia and normal serum calcium with an elevated alkaline phosphatase level are the common laboratory findings. The hypophosphaturia leads to hypophosphatemia and ultimately to bone demineralization. Metabolic acidosis is common, and hypokalemia due to excessive urinary excretion of potassium can occur.

Therapy involves replacement of the losses of phosphorus and potassium, plus the addition of calcium if demineralization has developed. While the rickets and osteomalacia are resistant to the usual levels of vitamin D, improvement occurs when huge amounts of as much as 50,000 to 400,000 I.U. of vitamin D are given per day. Obviously, these doses require careful supervision to guard against hypercalciuria.

Vitamin D Resistant Rickets and Familial Hypophosphatasia

In these conditions, the most evident biochemical disturbance is hypophosphatemia. Serum calcium is usually normal, but the alkaline phosphatase level is elevated. There is reduced tubular reabsorption of phosphorus which is normally decreased by parathyroid hormone and increased by vitamin D. Hypophosphatemia in this disease has been found to follow a sex-linked dominant pattern.[7]

Treatment involves the administration of large doses of vitamin D, starting with 25,000 to 50,000 I.U. per day with gradual increases up to 150,000 to 250,000 I.U. per day. Obviously, these huge doses involve the risk of vitamin D intoxication and such patients must be observed closely. Although rickets may be controlled with this therapy, dwarfism remains a problem in these patients.

Renal Tubular Acidosis

The clinical and laboratory findings here are similar to those in the Fanconi syndrome with the additional findings of nephrolithiasis and nephrocalcinosis.[8]

Metabolic acidosis is a key feature of this problem along with an inability to form a sufficiently acid urine and the absence of glomerular insufficiency. One or more of the following factors may be involved: (1) inability to secrete hydrogen ion, (2) inability to excrete ammonia, and (3) bicarbonate wasting. Despite a metabolic acidosis, the urine is alkaline.

The associated nephrocalcinosis and nephrolithiasis has been attributed to the hypercalciuria. Urinary citrate, which normally chelates calcium ions, is low and may in part explain excessive calcium deposits. Hypokalemia, rickets and osteomalacia reflect excessive urinary losses.

Treatment involves the use of alkalis to combat the metabolic acidosis, adequate fluid intake to eliminate dehydration, and vitamin D in large doses plus calcium orally in the presence of osteomalacia and rickets.

RENAL CALCULI

The role of citrate as a chelating agent in the urine and the prevention of urinary calculi formation is emphasized by the studies of vitamin B_6 deficiency in rats.[9] Pyridoxine

deficiency was accompanied by primary renal deposits of calcium oxalate along with an increased excretion of oxalic acid, xanthurenic acid and a decreased excretion of citric acid. The addition of magnesium (400 mg. per 100 gm. of diet) markedly reduced oxalate deposition; at the same time urinary citrate returned to normal levels or above and xanthurenic acid excretion was lowered.

The pyridoxine requirement is normally considered to be in the range of 1.5 to 2.0 mg. per day. Certain patients, particularly infants, exhibit a vitamin B_6 dependency manifesting symptoms of irritability and convulsions. This condition responds favorably to pyridoxine therapy at levels of 5 to 10 mg. per day.

Pregnancy may also increase the pyridoxine requirement to the range of 10 mg. per day, as measured by increased xanthurenic acid excretion after tryptophan loading.[10]

GROWTH HORMONE AND CALCIUM METABOLISM

Hormones other than the parathyroid may influence mineral metabolism. For example, the administration of growth hormone, as well as observations on a patient with acromegaly, revealed effects of calcium and magnesium metabolism consisting of an increased absorption of both magnesium and calcium from the gut, an increased urinary excretion of both elements, a lowering of plasma magnesium and an elevation of plasma calcium.[11]

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