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Hypercalcemia and Hypophosphatemia in Ponies following Bilateral Nephrectomy (41180)

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Abstract. A clinical syndrome has been recognized previously in horses, characterized by hypercalcemia, hypophosphatemia and renal failure. The accumulated evidence suggested that hypercalcemia was a secondary effect of renal failure rather than the primary cause of renal disease. To test this hypothesis, the metabolic response following bilateral nephrectomy was investigated in five ponies. In contrast to the response observed in other mammalian species, nephrectomy in ponies resulted in significant hypercalcemia and hypophosphatemia. Forty-eight hours following nephrectomy, serum calcium had increased from a mean control value of 12.2 ± 0.4 to 17.6 ± 0.7 mg/dl and serum inorganic phosphorus had decreased from a control value of 3.2 ± 0.5 to 1.5 ± 0.3 mg/dl. These changes persisted until the time of death (mean survival time 7.2 ± 3.2 days) and suggest that the equine kidney plays a unique role in calcium homeostasis.

The disturbances in metabolism of calcium and phosphorus which accompany chronic renal failure are well recognized in man and several domestic animal species. Progressive loss of functional nephrons results in decreased renal clearance of phosphorus and an increase in serum inorganic phosphorus concentration (1). Intestinal absorption of calcium is also decreased (2) in part because of defective synthesis by the diseased kidney of 1,25-dihydroxycholecalciferol, the active, polar metabolite of vitamin D_3 (3, 4). Hyperphosphatemia and decreased absorption of calcium ultimately cause reduction in the concentration of ionized serum calcium. The secondary renal hyperparathyroidism which accompanies these disturbances results in increased bone resorption and osteodystrophy. Typically, advanced renal failure is characterized by hyperphosphatemia and by a total serum calcium concentration which is either normal or moderately low (5, 6).

In horses, a clinical syndrome has been reported in which chronic renal failure was associated with marked hypercalcemia and hypophosphatemia (Williams–Smith syndrome) (7, 8). No evidence of primary hyperparathyroidism or pseudohyperparathyroidism was found in these cases and it was concluded that hypercalcemia was the result rather than the cause of renal failure. To test this hypothesis, the serum calcium concentration of Shetland ponies was measured before and after bilateral nephrectomy. Unlike the response reported in other mammalian species, bilateral nephrectomy resulted in prompt, marked, and persistent hypercalcemia in ponies which demonstrated that the equine kidney has an unusual role in maintenance of serum calcium concentration.

Materials and Methods. The five Shetland ponies used in these studies were purchased from local sources for experimental use. The group ranged in age from 2 to 7 years and included four males and one female. For 1 month or more following purchase, the ponies were fed a diet consisting of either unsupplemented native pasture grasses or alfalfa and mixed grass hays plus a commercial grain–mineral supplement. One week prior to initial surgery and thereafter, the diet consisted exclusively of alfalfa hay and tap water provided *ad libitum*.

Nephrectomies were performed under halothane general anesthesia using aseptic surgical technique. An extraabdominal, paracostal surgical approach requiring resection of one or two ribs was used for all

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nephrectomies. Bilateral nephrectomy was completed in two stages with the second kidney removed 4 to 6 weeks following the first.

Serum sodium and potassium concentrations were determined by flame photometry, and serum chloride by electrometric titration. Automated chemical methods were used for analyses of serum calcium and inorganic phosphorus. Serum magnesium was determined colorimetrically as a titan yellow complex in an alkalinized, protein-free filtrate. Blood urea nitrogen (BUN) was determined using a urease procedure and serum creatinine by a modification of the Jaffe reaction with alkaline picrate. An automated freezing point depression method was used for serum osmolality. Results are given as mean values ± SEM. The statistical significance of differences between means was determined using the two-tailed, Student's *t* test.

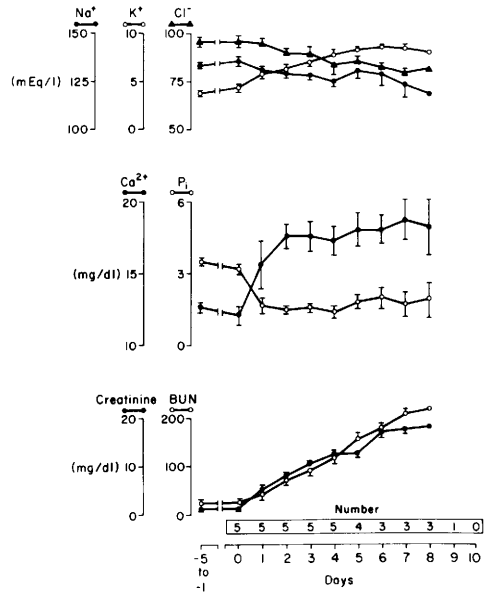

FIG. 1. Changes in serum electrolytes, BUN, and creatinine following bilateral nephrectomy in Shetland ponies. (Mean concentrations are plotted ± SEM.)

Results. All ponies recovered satisfactorily following initial unilateral nephrectomy. There were no significant postoperative changes in BUN, serum creatinine, or in serum electrolytes including calcium and phosphorus. The intake of alfalfa hay and water during the 4- to 6-week period between nephrectomies was normal and body weight was maintained. Following the second nephrectomy, there was satisfactory recovery from anesthesia and for a period of 24–36 hr the ponies appeared essentially normal. Thereafter, however, progressive anorexia and lethargy developed and there was a remarkable reduction in voluntary water intake. The ponies died or were humanely destroyed *in extremis* with a mean survival time of 7 days (range of 4–10 days) following removal of the second kidney.

As anticipated, BUN and creatinine concentrations increased rapidly following bilateral nephrectomy (Fig. 1). During the first 7 days the mean increase in BUN was 26 mg/dl/24 hr and in creatinine 2.3 mg/dl/24 hr. Serum sodium and chloride concentrations decreased gradually during the postnephrectomy period and after the fifth day, mean concentrations of both were significantly below normal control values ($P < 0.01$). Serum osmolality, however, increased significantly from a mean control value of 278 ± 2 to 341 ± 26 mOsm/liter on the fifth day following nephrectomy ($P < 0.01$). The increases in serum potassium concentration from 4.3 ± 0.3 to 8.3 ± 0.6 meq/liter and in serum magnesium from 1.1 ± 0.1 to 4.3 ± 0.3 mg/dl during the same 5-day period also were statistically significant ($P < 0.01$).

Serum calcium increased following bilateral nephrectomy from a mean control value of 12.2 ± 0.4 to 15.6 mg/dl 24 hr postoperatively ($P < 0.005$). At 48 hr, the mean serum calcium was 17.6 ± 0.7 mg/dl and remained elevated throughout the remainder of the study period (Fig. 1). Serum inorganic phosphorus was related reciprocally to serum calcium, decreasing from a control value of 3.2 ± 0.5 to 1.5 ± 0.3 mg/dl 48 hr following nephrectomy and remained low thereafter. The parathyroid glands were examined at postmortem and appeared grossly to be normal in size. Histologically the appearance also was considered to be essentially normal with no evidence of increased secretory activity.

Discussion. The mammalian kidney has several important functions in the control of

calcium metabolism. One of these is regulation of the serum calcium concentration by modification of tubular resorption of calcium filtered by the glomerulus (9). As the dietary intake of calcium is increased, urinary calcium excretion tends to increase but in most species the relationship is not linear (10–12). On very high calcium intakes, the percentage of dietary calcium excreted in the urine is decreased, in part, because of adjustments in fractional intestinal absorption (13). The pony and horse differ quantitatively from this general pattern (14–16). Although fractional absorption of calcium decreases as intake is increased (14), total calcium absorption continues to increase and a rise in serum calcium concentration is prevented by large increases in urinary excretion. In horses receiving a diet containing 2% calcium, urinary calcium excretion may be as high as 20 to 30 g/24 hr (18). Calcium carbonate crystalluria appears to be a physiological process in the horse and accounts for the frequently cloudy appearance of normal equine urine. The relationship of dietary intake to urinary excretion in horses appears similar to that observed in certain human subjects with hypercalciuria (17, 18).

The biochemical alterations of ponies following bilateral nephrectomy were similar to those reported in other species with the notable exception of the prompt and persistent hypercalcemia and hypophosphatemia. The actual cause of hypercalcemia in ponies is not known but in a species which normally excretes large amounts of calcium in the urine, loss of renal excretory capacity might be expected to predispose to hypercalcemia. Bilateral nephrectomy in hamsters has been shown to prolong hypercalcemia following administration of large doses of calcium chloride (19) and to augment the hypercalcemic response following injection of parathormone (20). A decreased calciuric response is also believed to cause the hypercalcemia which occurs following administration of vitamin D_3 to partially nephrectomized rats (21) and of 1,25-dihydroxycholecalciferol to human patients with chronic renal failure (22). In ponies, elimination of urinary calcium excretion may be particularly important in the development of hypercalcemia immediately following nephrectomy when dietary intake is maintained.

Increases in serum calcium concentration have been reported previously following bilateral nephrectomy. In both the rat (23–25) and the dog (26), however, the elevation in serum calcium was transient lasting less than 24 and 48 hr, respectively, and the magnitude of elevation was slight compared to that observed in ponies. Parathyroidectomy completely prevented this response in the dog (27) and rat (23) and parathyroid hormone has not been eliminated as a factor in the pathogenesis of hypercalcemia in nephrectomized ponies. No morphologic evidence of increased secretory activity was found by light microscopic examination of parathyroid glands. The kidney, however, appears to have an important role in removal of parathyroid hormone (28, 29) and a decreased rate of degradation has been demonstrated following nephrectomy (30, 31). Decreased removal could result in increased circulating parathyroid hormone activity in the absence of increased hormone secretion.

While hypercalcemia is an unusual sequela of renal insufficiency in most species of animals (5, 31), it is common in the horse. Although some horses with renal failure develop hypocalcemia (33), most become hypercalcemic (33, 34). The frequent development of hypercalcemia in spontaneous renal disease and its uniform occurrence following bilateral nephrectomy suggest that, in the horse, hypercalcemia should be considered a characteristic response in advanced renal failure.

Although much remains to be learned, it seems clear that what is known regarding the pathogenesis of disturbances in calcium and phosphorus metabolism associated with renal failure is most species must be modified for the horse because in the equine species, the kidney appears to have a special role in the regulation of the serum calcium concentration.

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