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Jack W. Coburn

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Jack W. Coburn, MD*

Ed. Note - This overview was originally presented at the International Symposium on Clinical Disorders of Bone and Mineral Metabolism, May 9-13, 1983. The following list indicates the presentations given in this session at the Symposium and the contents of the corresponding chapter in the Proceedings of the Symposium published by Excerpta Medica. The numbers in parentheses refer to pages in this volume. Complete information about the contents of the Proceedings can be found at the back of this issue.

Uremic osteodystrophy: Classification, cause and treatment. D. Sherrard, S. Ott, N. Maloney, D. Andress, and J. Coburn (254)

Use of 1,25(OH)$_2$D$_3$ in the treatment of renal osteodystrophy in patients with moderate renal failure. S.G. Massry, H. Gruber, A.S. Rizvi, D. Sherman, D.A. Goldstein, and J.M. Letteri (260)

Use of active vitamin D sterols in end-stage renal failure. J.W. Coburn, D.J. Sherrard, S.A. Ott, N.C. DiDomenico, G.F. Bryce, A.S. Brickman, L.W. Bassett, E.G.C. Wong, R.B. Miller, C.M. Bennett, R.H. Gold, O.N. Miller, S.A. Shupien, and P.C. Chang (263)

Suppression of secondary hyperparathyroidism by 1,25(OH)$_2$D$_3$. E. Slatopolsky, C. Weerts, B. Thielan, T. Galceran and K. Martin (267)

The management of aluminium related osteomalacia in renal failure. P. Ackrill, J. Ball, and J.P. Day (273)

This discussion of mineral metabolism and bone disease in renal failure focused on recent developments; more complete discussion of these problems can be found in the literature (1,2). This review summarizes views on the pathogenesis and management of the bone diseases encountered in renal failure, with emphasis on the concept that more than one process acts to distort mineral metabolism.

Sherrard and colleagues (pp. 254 ff.) summarized a 15-year evaluation of patients with end-stage renal disease (ESRD), including clinical findings, histomorphometric study of bone, and results of staining bone sections for aluminum. After nearly ten years of experience administering active vitamin D sterols, the indications for their use and the effects to be expected remain in doubt. Massry and colleagues (pp. 260 ff.) presented results of a controlled study using calcitriol (1,25(OH)$_2$-vitamin D$_3$) in treatment of patients with moderate renal failure. My review (pp. 263 ff.) summarized our data on the use of calcitriol to treat or prevent bone disease in dialysis patients. Slatopolsky and colleagues (pp. 267 ff.) presented other new and somewhat different results with parenteral calcitriol.

Growing evidence indicates that the accumulation of aluminum in bone can cause osteomalacia in patients with end-stage uremia. Ackrill and co-workers (pp. 273 ff.) described methods for chelating and removing aluminum from the body.

Pathogenesis of secondary hyperparathyroidism

Secondary hyperparathyroidism, which is nearly universal in patients with renal insufficiency, originates early in the course of progressive kidney disease, presumably in response to transient hypocalcemia. The most probable causes for hypocalcemia are 1) phosphate retention

*The Medical and Research Services, VA Wadsworth Medical Center, and the Department of Medicine, UCLA School of Medicine, Los Angeles.
Address reprint requests to Dr. Coburn, VA Wadsworth Medical Center, Wilshire & Sawtelle Blvds, Los Angeles, CA 90073.

secondary to a reduced renal capacity to excrete phosphate and 2) reduction in the renal generation of the hormone, $1,25(OH)_2$-vitamin D_3. Skeletal responsiveness to the calcemic action of parathyroid hormone (PTH) is reduced, probably in consequence of the phosphate retention and reduced generation of calcitriol.

The elegant studies of Slatopolsky, et al (3,4) have shown that restricting dietary phosphate in proportion to the magnitude of fall in the glomerular filtration rate (GFR) can largely prevent secondary hyperparathyroidism in dogs with experimental renal failure. These investigators postulated that serum phosphorus increases transiently as GFR falls early in the course of renal failure. The increments in serum phosphorus would lower blood calcium and thereby increase PTH secretion, which in turn would decrease tubular reabsorption of PO_4 and cause phosphaturia. Serum phosphorus and calcium levels would return to normal, but only at the expense of a higher PTH level. This process would continue as renal failure progressed to the limit of inhibition of tubular PO_4 reabsorption, i.e., GFR below 25-30 ml/min. Thereafter, persistent hyperphosphatemia would occur. The problem with this proposed theory is that serum phosphorus levels are actually normal or even low in patients with modest renal insufficiency. However, in advanced renal failure, with marked hyperphosphatemia, there is no question that hypocalcemia and elevated serum immunoactive PTH (iPTH) levels are directly related to the serum phosphorus concentrations (5).

Other data suggest that altered vitamin D metabolism contributes to the altered calcium and phosphorus homeostasis in uremia. Reduced generation of calcitriol with a consequent reduction in intestinal calcium absorption could contribute to developing secondary hyperparathyroidism, by causing hypocalcemia. Some studies (6) have shown that serum calcitriol levels are normal in patients with modest renal failure (GFR above 40 ml/min); however, children with moderate renal failure have subnormal serum $1,25(OH)_2D$ concentrations (1). Through an effector mechanism not yet apparent, phosphate retention in renal failure affects reduced calcitriol synthesis, increased PTH secretion, and secondary hyperparathyroidism. Thus, it is not possible to separate the effects of "PO_4 retention" from alterations in "vitamin D metabolism" (8) in the pathogenesis of the secondary hyperparathyroidism of renal failure because PO_4 retention may inhibit the generation of $1,25(OH)_2D$ (8); see Fig. 1.

As reported by Brown (9), abnormalities of parathyroid cell function have been identified in uremic patients with secondary hyperparathyroidism. Both hyperplasia with increased cell number and alterations of cell function occur. The latter is identified by a rightward shift of the "set point", defined as the ambient calcium level in the incubation media which affects half-maximal suppression of PTH release by the isolated parathyroid cells. This abnormality has been found in cells from 70-80% of parathyroid glands taken from patients with secondary hyperparathyroidism due to ESRD (9), but factors responsible for this shift in set point are unknown. In dialysis patients, the observation that elevated serum iPTH levels often are not reduced until the serum calcium exceeds normal concentrations is compatible with the concept of a rightward shift of the set point for PTH secretion (10).

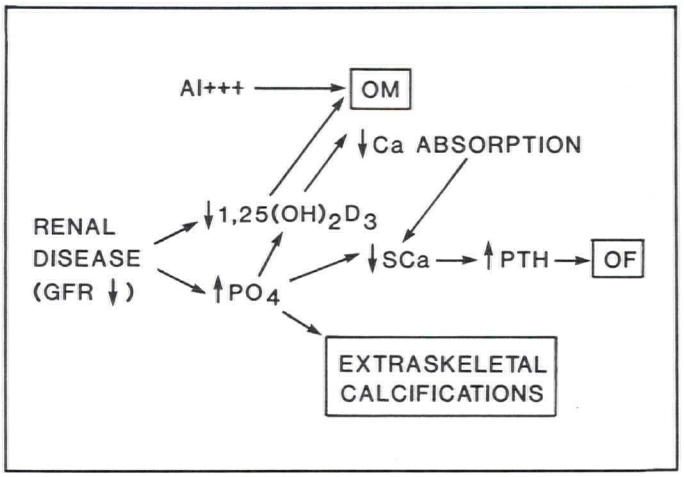

Fig. 1

Scheme showing the proposed pathogenesis of secondary hyperparathyroidism and osteomalacia in renal failure. Abbreviations: GFR, glomerular filtration rate; OM, ostemalacia, OF, osteitis fibrosa; and SCa, serum calcium.

Because serum iPTH levels are often used in the evaluation of patients with ESRD, it is important to understand that renal failure exerts a major effect on the results of such assays which employ antisera that recognize the mid- or carboxyl-terminus of the PTH molecule. Because glomerular filtration normally clears these PTH fragments from plasma, they can accumulate in substantial amounts in the plasma of uremic patients (11). For most immunoassays, data are not available to indicate the "normal" level of iPTH in renal failure. Immunoassay laboratories often include results from *all* dialysis patients with secondary hyperparathyroidism in a nomogram displaying the relation between serum iPTH and serum calcium concentrations. In dialysis patients, such nomograms have little value in detecting the presence of secondary hyperparathyroidism. Before serum iPTH assays can be used intelligently in formulating treatment for patients with renal failure, data must indicate the relationship between serum iPTH levels and a target organ response such as histomorphometric changes in bone.

Pathogenesis of osteomalacia in end-stage renal failure

Several factors can contribute to the development of osteomalacia in patients with renal failure. These include marked PO_4 depletion and hypophosphatemia, coexistent nutritional deficiency of vitamin D, and the use of anticonvulsant drugs. The calcitriol deficiency that is present in renal failure may also make uremic patients more prone to develop osteomalacia. However, the most common factor associated with vitamin D-refractory osteomalacia in renal patients is the accumulation of aluminum in bone.

The data supporting aluminum as a pathogenetic factor are overwhelming:

1) Aluminum, whether from the dialysate or absorbed from the intestine, is retained in the absence of kidney function.

2) A strong association exists between the aluminum content of water used to prepare dialysate and the incidence of osteomalacia in dialysis patients.

3) Aluminum accumulates along the calcification front of bone, and little or no tetracycline uptake occurs at sites where there is aluminum accumulation.

4) Aluminum injections can cause osteomalacia in animals.

5) Inadvertent infusions of aluminum, as has occurred in certain parenteral nutrition solutions, can cause osteomalacia in humans.

6) Treatment with the chelating agent, desferrioxamine, which can remove aluminum, has been reported anecdotally to produce improvement in dialysis osteomalacia.

The magnitude of the problem of bone disease associated with aluminum accumulation is unknown. It is possible that some other retained substance could also cause low-turnover osteomalacia in patients who have lost renal excretory capacity. If so, renal patients who do not have aluminum accumulation may be found to have refractory osteomalacia.

Management of calcium metabolism in renal failure

In secondary hyperparathyroidism, it is important to prevent hyperphosphatemia and maintain serum calcium levels within an acceptable range. The goals of clinical practice are listed in Table I. The first is to prevent hyperphosphatemia both by reducing dietary PO_4 and by using PO_4-binding antacids. Control of hyperphosphatemia can prevent or reverse the extraskeletal calcifications that were common during the early period after dialysis was first introduced. Phosphate restriction can aid also in controlling secondary hyperparathyroidism.

TABLE I

Principles of Management of Mineral Metabolism in ESRD

1. Control Serum P (4.0-5.5 mg/dl)
   - Restrict diet PO_4 (<1 g/d)
   - PO_4-binding gels
2. Adequate Ca Intake (#1 1st)
   - Dialysate Calcium (3.0-3.5 mEq/L)
3. Vitamin D Sterols (#1 1st)
   - Rx of secondary hyperparathyroidism
   - Hypocalcemia
   - Prevent bone disease*
   - Children with ESRD
   - Forms: Sterol with 1α-OH group is preferred
4. Miscellaneous
   - Water purification to remove aluminum, flourine; control magnesium, calcium
   - Normalize blood pH
   - Normalize serum magnesium
   - Avoid unneeded anticonvulsants
   - Chelate aluminum*
5. Parathyroidectomy indicated for:
   - Overt secondary hyperparathyroidism
   - Failure of 1, 2, and 3
   - Calciphylaxis

*Place in management is not established.

Once serum phosphorus is controlled, methods should be used to raise the serum calcium to normal. These include adjusting dialysate calcium levels to 3.3-3.7 mEq/L to prevent calcium loss, as well as adding calcium supplements to the diet. The active vitamin D sterols [calcitriol, dihydrotachysterol, 1-alpha-(OH)-vitamin D_3, and calcifediol (25-OH-D_3)] may also be used to maintain the serum calcium concentration. Other papers in this Symposium dealt more fully with the clinical effects of the active vitamin D sterols. Finally, parathyroidectomy is the treatment of choice for certain patients with overt secondary hyperparathyroidism. However, the presence of vitamin D-refractory osteomalacia, which is often accompanied by hypercalcemia (12), must be excluded, for this syndrome either fails to improve or may worsen after parathyroidectomy (12,13).

Prevention and treatment of osteomalacia

Ackrill and associates (pp. 270 ff.) emphasized that patients undergoing hemodialysis must receive appropriate water treatment. The occasional development of vitamin D refractory osteomalacia in uremic patients who have never undergone dialysis indicates that ingested aluminum-containing compounds may be the source of aluminum. When aluminum-associated osteomalacia develops, rigid dietary phosphate restriction and reduction in the dose of PO_4-binders is indicated. The use of calcium-carbonate to reduce PO_4 absorption has been employed by Moriniere, et al (14), and the use of desferrioxamine was discussed by Ackrill.

Other procedures which are employed without critical proof of efficacy in the treatment of secondary hyperparathyroidism include correction of acidosis, prevention of hypermagnesemia, and avoidance of fluoride in the dialysate. The loss of vitamin D sterols either into the urine of patients with the nephrotic syndrome or into peritoneal dialysate during treatment with continuous ambulatory peritoneal dialysis may increase the vitamin D requirements. We lack valid data on the efficacy of replacement treatment under these conditions.

Table II lists some unanswered questions and problems related to bone and mineral metabolism in patients with renal failure. Some of these questions were answered in this Symposium; others are awaiting further study.

TABLE II

Some Unanswered Questions About Renal Osteodystrophy

1. Pathogenesis
   - How does PO_4-retention act?
   - What is mechanism for the "set point" shift?
   - How important is PTH as a "uremic toxin?"
   - What is role of acidosis?
2. Types of bone diseases
   - What is significance of these?
3. Prevention
   - When to restrict diet PO_4
   - When to add calcitriol?
4. In managing established ESRD, Use of D sterols:
   - When to use?
   - Which to use?
   - Do their effects differ?
   - How do they act?
   - When to add calcium supplements?
   - When to do parathyroidectomy?
5. With "Dialysis Osteomalacia,"
   - Are there causes other than aluminum?
   - How can aluminum be removed?
   - How is aluminum absorbed?
   - Does aluminum removal help?
   - Do high PTH levels help?
   - What are safe and effective PO_4-binders lacking aluminum?

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