VITAMIN D RESISTANCE IN OSTEOMALACIA AFTER URETEROSIGMOIDOSTOMY

WAYNE PERRY, M.B., LEONARD N. ALLEN, F.R.C.S., TREVOR C. B. STAMP, M.D. AND PETER G. WALKER, M.D.

OSTEOMALACIA after ureterocolic anastomosis has been recognized for 25 years.[1] Its cause is uncertain, but both renal damage and acidosis may contribute.[2-4] A requirement for vitamin D is variable: although vitamin D "resistance" has been documented[3] other workers have suggested that only correction of acidosis, with little or no added vitamin D, is necessary.[5]

25-Hydroxycholecalciferol is several times more potent than the parent vitamin in the treatment of various forms of rickets[6,7] and is effective in renal osteodystrophy.[8-10] The reason for its superior potency has been somewhat clarified by recent comparison of relative plasma 25-hydroxyvitamin D levels produced in different subjects.[11] The analogue 1α-hydroxycholecalciferol[12] closely resembles 1,25-dihydroxycholecalciferol, the active hormonal form of the vitamin that is synthesized only in kidney, and is even more potent than 25-hydroxycholecalciferol.[13,15] There are no reports of the use of these metabolites in the treatment of osteomalacia after ureterocolic anastomosis, nor has the relative efficacy of all three compounds been compared in any one patient with osteomalacia of renal origin.

In the patient described below, the degree of "vitamin D resistance" was measured by the level of circulating 25-hydroxyvitamin D required to overcome it. Our findings thus explain the superior potency of 25-hydroxycholecalciferol over vitamin D that was found and also indicate that vitamin D resistance in this condition was of renal rather than end-organ origin.

METHODS

We performed metabolic balances in the classic manner,[16] using barium sulfate as an internal marker and carmine markers to separate successive four-day fecal-collection periods. Dietary calcium was based on the patient's calculated previous long-term intake. In contrast to other metabolic studies in patients with ureterocolic anastomosis the combination of a permanent colostomy and rectosigmoid bladder allowed complete separation of urine and feces. Plasma 25-hydroxyvitamin D was measured by the protein-binding method of Haddad and Chyu,[17] which recognizes equally the 25-hydroxy derivatives of vitamin D_2 and vitamin D_3.[18] 25-Hydroxycholecalciferol was supplied by the UpJohn Company and 1α-hydroxycholecalciferol by Leo Laboratories.

CASE REPORT

In 1965 a 58-year-old woman underwent total cystectomy and ureterocolostomy, followed by radiotherapy, for anaplastic bladder carcinoma. Recurrent loin pain and pyrexia, and persistent hyperchloremic acidosis subsequently developed, and she was treated with intermittent antibiotics and sodium bicarbonate, 6 g daily. In 1969 a permanent colostomy with ureteric transplantation to the rectosigmoid was performed, and infective symptoms subsequently were better controlled. Nevertheless, acidosis persisted, and plasma calcium between 1970 and 1972 ranged from 5.0 to 6.0 mg per deciliter. In 1972 progressive muscle weakness and increasing bone pain developed. Sodium bicarbonate was increased, but she took medication irregularly and acidosis and hypocalcemia persisted.

On admission to the hospital in February, 1975, she had dry, inelastic skin and was unable either to rise from a chair or to walk because of bone pain and muscle weakness. Dietary history showed an inadequate vitamin D intake of less than 50 IU daily. The hemoglobin was 8.4 g, plasma calcium 6.1 mg (albumin 3.5 g), and phosphorus 4.9 mg per deciliter, alkaline phosphatase 19 King–Armstrong Units, and the sodium 142, potassium 3.0, chloride 118, and total carbon dioxide 6 meq per liter; blood urea was 102 mg per deciliter. The pH was 7.30. Plasma 25-hydroxyvitamin D was low at 5 ng per milliliter, but serum parathyroid hormone (kindly assayed by Dr. J. L. H. O'Riordan) was normal, 0.3 ng per milliliter (antiserum 199 [Bu 211-32] — normal range, 0.15 to 1.0[19]). Urine was infected on culture, there was no aminoaciduria, and 24-hour urine calcium excretion was 68 mg. X-ray examination showed pseudofractures in the pubic rami and both femoral necks, together with increased density in the thoracolumbar spine. An intravenous pyelogram showed moderate bilateral hydronephrosis. Iliac-crest biopsy showed gross osteomalacia without hyperparathyroidism; quantitation by Dr. P. D. Byers demonstrated the total area occupied by bone to be 17.6 percent (normal range, 4.9 to 30.0), by osteoid 39.4 per cent (normal, 0 to 14.3) and by bone plus osteoid 57.0 per cent (normal, 4.9 to 30.0); the proportion of trabecular surface covered by osteoid was 99.1 per cent (normal, 0 to 30.0), with resorption of 0.0 per cent (normal, 4 to 20.0) (normal ranges were derived from the literature[20]).

In the expectation that the disease was due to a combination of acidosis and vitamin D deficiency the patient was treated first with vitamin D_2, 45 μg (1800 IU) per day, and sodium bicarbonate was increased to 12 g daily. After rehydration the plasma urea fell to 49 mg per deciliter (with a creatinine clearance of 28 ml per minute). Plasma total carbon dioxide rose to 23 meq per liter in four days and, apart from minor fluctuations, remained normal thereafter; plasma phosphorus fell to 3.6 mg per deciliter and remained normal throughout. Other changes are shown in Figure 1. To our surprise, at the end of 28 days she was unimproved symptomatically despite attaining high normal plasma 25-hydroxyvitamin D (26 ng per milliliter), nor had plasma alkaline phosphatase changed in response to vitamin D and alkali. A slightly lower dose of 25-hydroxycholecalciferol, 40 μg daily, was substituted, and she was transferred to the Metabolic Ward. Within eight days bone pain had disappeared, and she could easily rise unaided from a sitting position. Plasma calcium rapidly returned to normal, alkaline phosphatase showed a gain consistent with healing for the first time, and there was a rapid further fivefold increase in plasma 25-hydroxyvitamin D (Figure 1). Metabolic balance studies showed strongly positive calcium balance of 1000 mg per day with appropriate phosphorus retention of 589 mg per day not shown in Figure 1. Healing continued during brief treatment with 1α-hydroxycholecalciferol and vitamin D_2, 250 μg daily, was then substituted on discharge when she was free of pain and walking well. However, this treatment proved inferior to the previous, much smaller dose, of 25-hydroxycholecalciferol-D since five months later, muscle weakness was again developing, her activity was declining, and plasma calcium had fallen to 7.8 mg per deciliter; plasma 25-hydroxyvitamin D had fallen to 73 to 77 ng per milliliter (mean in 15 patients receiving 250 μg daily, 64[11]). Plasma urea and creatinine had not risen, nor had acidosis returned. Vitamin D_2 was therefore increased to 500 μg daily, and she again recovered (Fig. 1). After three months, vitamin D_2 was stopped and 1α-hydroxycholecalciferol was substituted, at first with 2 μg daily for three months and later with 1 μg daily for seven months. Finally, unwitting withdrawal of 1α-hydroxycholecalciferol for eight days precipitated hypocalcemic tetany (without change in her adequate colostomy habit), which was reversed by the same dose within one week (Fig. 1). She remained active and well in August, 1977.

From the Metabolic Ward, Royal National Orthopaedic Hospital, Stanmore, Middlesex, and the Edgware General Hospital, Edgware (address reprint requests to Dr. Stamp at the Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, Middlesex, HA7 4LP, England).

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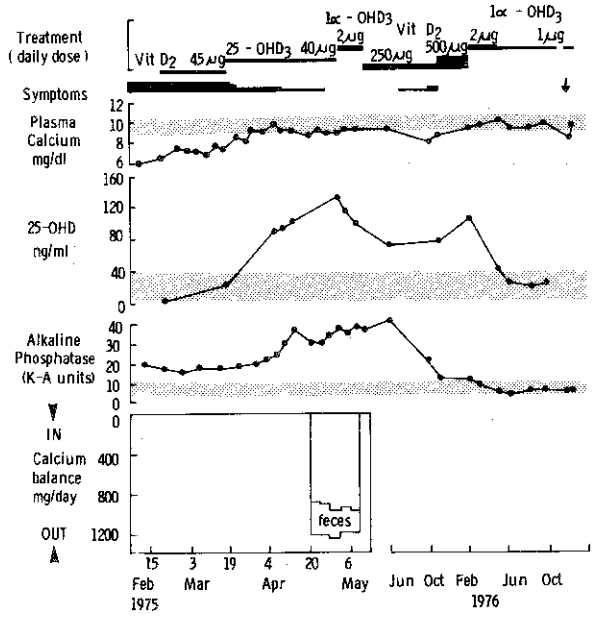

Figure 1. Clinical, Biochemical and Metabolic Balance Data. Stippled areas represent normal ranges within our laboratory; for 25-hydroxyvitamin D (25-OHD) this range is approximate (since the normal seasonal variation is not represented[25]). Note the negligible improvement during treatment with vitamin D_2, 45 μg daily over one month; the relation throughout between clinical state, treatment and circulating 25-OHD (note altered time scale after May, 1975), and the extreme positive calcium balance produced by 25-hydroxycholecalciferol (25-OHD_3) despite our patient's age. Urine calcium was less than 40 mg daily throughout and could not be represented. The arrow represents hypocalcemic symptoms of short (eight days') duration when 1α-hydroxycholecalciferol (1α-OHD_3) was stopped.

Discussion

The osteomalacia associated with hyperchloremic acidosis from ureterocolic anastomosis has been cured with bicarbonate alone,[2] so that some authorities have recommended vitamin D either in a small dose or not at all.[5] Other studies using metabolic balance (but without separation of urine and feces) have shown that "vitamin-D-resistant" rickets may indeed occur.[3] In our patient the surprising absence both of clinical response and of change in alkaline phosphatase four weeks after rapid correction of both severe acidosis and marginal vitamin D deficiency strongly suggested that neither was a noteworthy factor in the original production of her disease. Moreover, her estimated dietary calcium intake, on which her metabolic balance study was based, appeared adequate. Having clearly demonstrated resistance to treatment by excluding these factors, we then attempted to investigate the nature of this resistance. The subsequent efficacy of a small dose of 1α-hydroxycholecalciferol, 1 μg daily, showed that it was renal in origin. The reason for this resistance has been better understood since the demonstration that 1,25-dihydroxycholecalciferol is synthesized only in renal tubules,[21-23] and their damage in any form of chronic renal disease may therefore inhibit synthesis of that vitamin and produce "vitamin-D-resistant" renal rickets (or osteomalacia). Studies of renal osteodystrophy do not often differentiate the relative importance of glomerular and tubular damage in determining the type of resulting bone disease. Our patient had only moderate impairment of glomerular function; yet she had very severe osteomalacia, which was resistant to treatment with vitamin D in the physiologic dose range, presumably owing to the preponderant renal tubular damage produced by this unusual form of hydronephrosis from chronic infective ureteric reflux. We cannot exclude her earlier radiotherapy as a contributory factor. On this basis the osteomalacia that follows ureterosigmoidostomy may be more likely than not to show "resistance" to vitamin D, contrary to some earlier views.[5] Our patient's long-term sensitivity to 1α-hydroxycholecalciferol, 1 μg daily, together with the rapid relapse when she later stopped it briefly, indicates moreover that her "vitamin-D-resistant" disease was due to deficiency of renal vitamin D-1α-hydroxylase.

25-Hydroxycholecalciferol has been calculated on clinical grounds (but without measurement of plasma 25-hydroxyvitamin D) to be several times more potent than the parent vitamins (vitamin D_2 or D_3) in the treatment of X-linked hypophosphatemic rickets and anticonvulsant osteomalacia.[7] 25-Hydroxycholecalciferol was also markedly superior to vitamin D_2 in our patient, and the present study indicates the probable reason, which has hitherto been poorly understood. Plasma 25-hydroxyvitamin D rose to 26 ng per milliliter during one month's treatment with vitamin D_2, 45 μg daily, but when 25-hydroxycholecalciferol itself was substituted (in slightly lower dosage of 40 μg daily), levels rose to 130 ng per milliliter in the same interval. We should have expected little further rise in our patient's plasma 25-hydroxyvitamin D if either treatment had been continued to clear steady-state levels.[11] The subsequent clinical inadequacy of vitamin D_2 in a dose of 250 μg daily (appropriate circulating 25-hydroxyvitamin D levels confirming compliance with treatment[11]) further confirmed that her vitamin-D-resistant osteomalacia was independent of her original acidosis and that 25-hydroxycholecalciferol was well over six times more potent on a weight basis in our patient. This clinical superiority of 25-hydroxycholecalciferol over vitamin D_2 on a molar basis was clearly related to the higher plasma 25-hydroxyvitamin D that it produced. A similar relation between dosage and plasma 25-hydroxyvitamin D levels has recently been found in a large study among different subjects.[11]

The circulating level of plasma 25-hydroxyvitamin D required to control any form of rickets or osteomalacia, when treated with either vitamin D or 25-hydroxycholecalciferol thus appears to be a good index

of "resistance" to the vitamin; in our patient this requirement lay above 77 and below 104 ng per milliliter. Whether a partial blockade in 1,25-hydroxycholecalciferol synthesis due to renal tubular damage is overcome by sufficiently high substrate levels, or whether 25-hydroxyvitamin D itself at adequate concentration exerts a direct effect on target organs in man is not certain. A direct effect of 25-hydroxyvitamin D is not unlikely in view of the response to vitamin D or to 25-hydroxycholecalciferol that occurs in nephrectomized patients.[9,24]

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References

1. Pines KL, Mudge GH: Renal tubular acidosis with osteomalacia: report of 3 cases. Am J Med 11:302-311, 1951
2. Tobler R, Prader A, Bühlmann A, et al: Rachitis als Folge der Ureterosigmoidostomie. Helv Paediatr Acta 12:215-240, 1957
3. Harrison AR: Clinical and metabolic observations on osteomalacia following ureterosigmoidostomy. Br J Urol 30:445-462, 1958
4. Leite CA, Frame B, Frost HM, et al: Osteomalacia following ureterosigmoidostomy: with observations on bone morphology and remodeling rate. Clin Orthop 49:103-108, 1966
5. Fourman P, Royer P: Calcium Metabolism and the Bone. Second edition. Oxford, Blackwell, 1968, p 443
6. Balsan S, Garabedian M: 25-hydroxycholecalciferol: a comparative study in deficiency rickets and different types of resistant rickets. J Clin Invest 51:749-759, 1972
7. Stamp TCB, Round JM, Rowe DJF, et al: Plasma levels and therapeutic effect of 25-hydroxycholecalciferol in epileptic patients taking anticonvulsant drugs. Br Med J 4:9-12, 1972
8. Balsan S, Witmer G: Treatment of renal osteodystrophy with 25-hydroxycholecalciferol, Second International Symposium of Paediatric Nephrology, Laboratory Sandoz, Rueil-Malmaison, France, 1971, p 108
9. Rutherford WE, Blondin J, Hruska K, et al: Effect of 25-hydroxycholecalciferol on calcium absorption in chronic renal disease. Kidney Int 8:320-324, 1975
10. Teitelbaum SL, Bone JM, Stein PN, et al: Calcifediol in chronic renal insufficiency: skeletal response. JAMA 235:164-167, 1976
11. Stamp TCB, Haddad JG, Twigg CA: Comparison of oral 25-hydroxycholecalciferol, vitamin D, and ultraviolet light as determinants of circulating 25-hydroxyvitamin D. Lancet 1:1341-1343, 1977
12. Holick MF, Semmler EJ, Schnoes HK, et al: 1α,-hydroxy derivative of vitamin D_3: a highly potent analog of 1α,25-dihydroxyvitamin D_3. Science 180:190-191, 1973
13. Haussler MR, Zerewekh JE, Hesse RH, et al: Biological activity of 1α-hydroxycalciferol, a synthetic analog of the hormonal form of vitamin D_3. Proc Natl Acad Sci USA 70:2248-2252, 1973
14. Chalmers TM, Davie MW, Hunter JO, et al: 1-alpha-hydroxycholecalciferol as a substitute for the kidney hormone 1,25-dihydroxycholecalciferol in chronic renal failure. Lancet 2:696-699, 1973
15. Pierides AM, Ellis HA, Simpson W, et al: Variable response to long-term 1α-hydroxycholecalciferol in haemodialysis osteodystrophy. Lancet 1:1092-1095, 1976
16. Albright F, Reifenstein EC: The Parathyroid Glands and Metabolic Bone Disease. Baltimore, Williams & Wilkins, 1948
17. Haddad JF Jr, Chyu KJ: Competitive protein-binding radioassay for 25-hydroxycholecalciferol. J Clin Endocrinol Metab 33:992-995, 1975
18. Haddad JG Jr, Hillman L, Rojanasathit S; Human serum binding capacity and affinity for 25-hydroxyergocalciferol and 25-hydroxycholecalciferol. J Clin Endocrinol Metab 43:86-91, 1976
19. Addison GM, Hales CN, Woodhead JS, et al: Immunoradiometric assay of parathyroid hormone. J Endocrinol 49:521-530, 1971
20. Byers PD: The diagnostic value of bone biopsies, Metabolic Bone Disease. Edited by LV Avioli, SM Krane. New York, Academic Press, 1977, pp 183-236
21. Fraser DR, Kodicek E: Unique biosynthesis by kidney of a biologically active vitamin D metabolite. Nature 228:764-766, 1970
22. Shain SA: In vitro metabolism of 25-hydroxycholecalciferol by chick intestinal and renal cell preparations: identification of a metabolic product as 1,25-dihydroxycholecalciferol and delineation of its metabolic fate in intestinal cells. J Biol Chem 247:4393-4403, 1972
23. Rasmussen H, Wong M, Bikle D, et al: Hormonal control of the renal conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. J Clin Invest 51:2502-2504, 1972
24. Stanbury SW: Azotaemic renal osteo dystrophy. Clin Endocrinol Metab 1:267-304, 1972
25. Stamp TCB, Round JM: Seasonal changes in human plasma levels of 25-hydroxyvitamin D. Nature 247:563-565, 1974