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ACQUIRED NON-FAMILIAL OSTEOMALACIA OF VITAMIN-D-RESISTANT TYPE

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Hypophosphatemia associated with vitamin D-resistant rickets has commanded increasing interest, yet despite the prominent clinical and metabolic features, the basic abnormality has not been defined. Winters and associates have written extensively on the familial aspects, and they also reviewed evidence for and against defective renal tubular function, secondary hyperparathyroidism and vitamin D refractoriness as possible causal factors.

As might be expected for patients with familial disease, both skeletal abnormalities and hypophosphatemia have been recognized shortly after birth. The designation "congenital" has been applied to the refractory rickets in such cases. In most, but not in all of these children, a familial basis has been established. In contrast, scattered case reports exist in which the earliest clinical expressions of osteomalacia appeared in adulthood, suggesting that latent familial and distinctly non-familial forms can occur. We are primarily concerned in this paper with the non-familial, non-congenital disorder, which hereafter is referred to as "acquired" refractory osteomalacia. Although similarities exist between this and the congenital type, certain differences can be recognized, particularly in the light of recent experiences with treatment. We will draw from information accumulated in the literature and from personal observations of two patients with presumably the acquired form, one of whom was previously reported in detail. Additional observations have confirmed our early impressions that high dietary phosphorus, achieved through the use of phosphate supplements, is of therapeutic value to at least certain patients with acquired, vitamin D-resistant osteomalacia.

CASE REPORTS

Case 1. (H.F.H. #96 24 45)

H. F., a 60 year old salesman, first experienced low back pain in January 1959. Several weeks later, he noted ankle and foot pain which increased with weight bearing. General weakness and fatigue were prominent symptoms, and the back pain, aggravated by coughing and sneezing, gradually progressed in intensity to the point that motion, such as turning in bed, was almost unbearable. His general health otherwise was good, and historical evidence was lacking for dietary deficiency, diarrhea and renal calculi. When first examined in August 1959, he was considered to have a herniated lumbar disc, despite lack of neurological signs. In the initial laboratory studies, hemoglobin was 14 grams per 100 ml. and white cell count was 6500 with a normal cellular differential. Specific gravity of 1.019, acid pH and negative tests for protein and reducing substances were noted for the urine which on microscopic study was normal. Serological test for syphilis was negative.

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Figure 1a
Pelvic x-ray film demonstrating bony demineralization and pseudo-fracture, right superior ramus.

Figure 1b
Progress film after eight months oral phosphate feeding. Increase in mineral content of bone near site of pseudo-fracture is apparent.

When later the symptoms progressed in severity and the original diagnosis seemed untenable, additional studies were performed. Fasting serum sugar was 100 mg.,
Figure 2

Photomicrographs of undecalcified iliac crest bone prepared by the method of Frost. Wide osteoid seams are demonstrated between the black bars.

carotene 125 mcg., creatinine 0.8 mg., calcium 10.3 mg., inorganic phosphorus* between 1.0 and 1.8 mg. and phospholipid phosphorus 10 mg. per 100 ml. Serum sodium was 137, potassium 3.8, chloride 96, and carbon dioxide 28.2 meq. per liter. Urinary calcium excretion was 87 mg. per 24 hours. Serum alkaline phosphatase

*Hereafter referred to as serum phosphorus
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was 10 and 12 Bodansky units, while acid phosphatase was 1.2 K. A. units. Tubular reabsorption of phosphate (TRP) was 78 per cent (normal 86-95). Chromatographic pattern of urinary amino acids was normal.** Roentgenograms of the small intestine were normal. A linear zone of demineralization (pseudofracture) in the right superior pubic ramus was noted in the pelvic roentgenograms (Fig. 1-a). Widened and increased numbers of osteoid seams typical of osteomalacia were present in sections of bone (Fig. 2) obtained from an iliac crest open biopsy.

The family history was negative for evidence of skeletal disease. Blood relatives were not available to test for evidence of familial hypophosphatemia.

SPECIAL STUDIES

1. Renal Tubular Response to I. V. Parathyroid Extract and to I. V. Calcium.

   (a) Parathyroid extract, 200 units intravenously, produced less phosphaturic effect in the patient than in the control subject, while basal phosphate excretion in the patient was three times that in the control (Fig. 3).

   (b) Calcium gluconate, 15 mg. per kg. body weight, was given intravenously over a four hour period. Urinary phosphate excretion decreased approximately 50 per cent while TRP increased to normal. At this point intravenous parathyroid hormone was given (same dose and lot number as used above). Phosphate excretion rate increased as TRP returned to the original low value (Fig. 4).


   One hundred ml. of the special phosphate solution* was given in single oral doses to the patient and control subject, both being in the fasting state. For both patients an increase was observed in serum phosphorus concentrations, comparable in rate and degree (Fig. 5). A similar result was obtained following the simultaneous ingestion of calcium lactate (Fig. 6).

   On the premise that the underlying defect was one of phosphorus depletion from hyperphosphaturia, treatment was begun with the special phosphate solution, 30 ml. orally six times daily. Within six weeks the patient reported complete relief of bone pain and tenderness as well as increased strength and sense of well-being. Treatment was continued, and eight months later laboratory studies were repeated. Serum calcium was 9.0 mg. and phosphorus, still depressed, averaged 1.8 mg. 100 ml. Urinary excretion of calcium was now only 7 to 20 mg. per 24 hours. Serum alkaline phosphatase levels continued increased at 9.9 Bodansky units, and tubular reabsorption of phosphate was even further reduced to 50 per cent. In pelvic x-ray films, a definite increase in mineral content was noted near the pseudofracture (Fig. 1-b).

   The iliac crest was again biopsied and the previously mentioned histologic evidence of osteomalacia was still present.

*196 gm. Na$_2$HPO$_4$ and 47.4 gm. NaH$_2$PO$_4$. H$_2$O in 4 liters aqueous solution

**Kindly performed by Dr. C. E. Dent of London, England
Figure 3
Effect of 200 units i.v. parathyroid extract (PTE) in patient H. F. and in control. The greater phosphaturic effect in the control (> 3-fold) as compared to the patient H. F. (< 1-fold) is evident.

Figure 4
Effects of i.v. calcium followed by parathyroid extract (PTE) in patient H.F. During calcium infusion urinary phosphate excretion decreased concomitant with increased tubular reabsorption of phosphate (TRP). Parathyroid extract then increased urinary phosphate excretion and reduced its tubular reabsorption to the low base line level.
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Case 2. (H.F.H. #60 83 72)

A. E., a 47 year old woman, was the subject of a previous report. The clinical history, physical and biochemical findings, and skeletal roentgenographic and histologic observations were qualitatively similar but more severe than those of the first case. Initial treatment in 1950 with vitamin D, 100,000 to 180,000 units, and 3.6 gm. calcium lactate daily had not resulted in any measurable improvement. The addition of oral phosphate supplements, totaling 2 gm. of phosphorus daily, was followed by prompt relief of bone pain, healing of pseudofractures and improved metabolic balances for calcium and phosphorus. This combined treatment was continued for one year with sustained clinical improvement. Treatment with oral phosphate supplement alone was then given for one year with continued healing of pseudofractures and freedom from pain. In July 1960, ten years after the initial observations, serum calcium was 9.0 and phosphorus 1.5 mg. per 100/ml. Tubular reabsorption of phosphate remained low at 76 per cent, and serum alkaline phosphatase was still elevated at 12 Bodansky units. Pseudofractures have remained healed, but a coarsened trabecular pattern, particularly in the lumbar vertebrae, suggests a continuing skeletal abnormality.

CASE COMMENTS

Evidence was lacking in both patients for the more common causes of osteomalacia such as dietary deficiencies, malabsorption and hypercalciuria. The late onset of symptoms and absence of skeletal abnormalities in blood relatives suggested for both patients that the metabolic disorder was not familial. Serum concentrations of phosphorus were normal in the two sons and sister of patient A. E. Similar determinations were not possible in family members of patient H. F. Pertinent biochemical data were the normal levels of serum calcium, marked hypophosphatemia, increased levels of serum alkaline phosphatase and low urinary calcium excretion. Phosphate reabsorption by the kidney was impaired, while evidence was lacking for other tubular defects. Radiologic findings were those of osteomalacia, in keeping with the prominent and increased numbers of osteoid seams noted in bone sections.

In both patients the reduced TRP and increased basal phosphate excretion, when compared to the control subject, suggested the possibility of excessive renal
phosphate loss. Parathyroid extract exhibited only minimal effect on phosphate excretion, suggesting that either the tubules were already under maximal hormonal influence or, irrespective of the level of tubular activity, the kidney was truly refractory to the hormone. That the tubular defect was not “fixed” or unresponsive was suggested by the reduced phosphate excretion and improved TRP which followed intravenously administered calcium. This new rate of reabsorption was then reversed by intravenously administered parathyroid hormone. However, a purely glomerular action by infused calcium and the subsequent hormone could not be excluded.

The rapid rise in serum phosphorus observed in both patients following the ingestion of oral phosphate excluded the possibility that an absorptive block for this mineral was the primary defect. Calcium ingested simultaneously did not interfere with phosphate absorption, and no difference in the latter was noted between patient
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A. E., receiving large amounts of vitamin D, and patient H. F. who was untreated. A significant reduction in urinary calcium occurred in both patients during phosphate therapy, and judged from the results of metabolic balance studies in patient A. E., calcium retention was materially enhanced. That this was clinically significant was clearly evident in the remineralization of the pseudofractures noted in serial roentgenograms for both patients.

The effects of phosphate feeding could be clearly assessed in patient H. F., who had not received previous vitamin D or other therapy. His favorable clinical course and improved skeletal status, judged by roentgenographic evidence, were similar to those of patient A. E. The latter, clinically and metabolically refractory to vitamin D, had made a striking improvement after phosphate supplements were added. As with patient H. F., however, persistent fasting hypophosphatemia and increased levels of serum alkaline phosphatase were indicative of a continuing biochemical defect. The question may be raised as to whether or not vitamin D contributed significantly or at all to her skeletal remission. Our opinion is that it did not and that augmenting dietary phosphorus was the decisive factor. The favorable effect of the latter in alleviating bone pain and improving skeletal mineralization in the two patients seems beyond question.

In respect to patient H. F., it cannot be said that he was truly vitamin D-resistant since this agent in conventional doses was not used in treatment. However, it is doubtful that the symptomatic response to vitamin D alone, even in large doses, would have been more effective than that which was observed with phosphorus. To further reverse the histological evidence of osteomalacia, prolonged treatment with phosphorus will undoubtedly be required. These high levels of total phosphorus intake, approximating three grams daily, have been well tolerated without evidence of impaired renal function. The latter is mentioned only because renal damage in rats has resulted from high phosphorus intake.

The over-all evidence led to a final diagnosis in both patients of acquired non-familial osteomalacia of vitamin D-resistant type. The favorable response to treatment with oral phosphate was considered strong evidence that the basic disorder was phosphate depletion, presumably through hyperphosphaturia.

DISCUSSION

In their review, Winters and co-workers found 65 reported cases of vitamin D-resistant rickets which they defined as a specific disorder, similar clinically, biochemically and radiologically to vitamin D deficiency rickets but resistant to this vitamin except in very large doses. In their judgment, the disease is almost always inherited and usually congenital. Considerably fewer reported patients appear to have had the acquired form of the disease. In the older literature, cases reported by Debray, Milkman and Leedham-Green may have been examples of acquired vitamin D-resistant osteomalacia, but the evidence is inconclusive. Other more recently reported cases are apparent examples of the acquired form. Bakwin’s case may also have been of this type despite the early age of onset. Swann and others have reported the interesting though unexplained association of neuro-
fibromatosis and acquired refractory osteomalacia. In their review of hereditary rickets and osteomalacia, Dent and Harris record information on four young adults who apparently have an acquired but slightly different form, since increased glycinuria and mild acidosis were present.

Features common to the congenital and acquired types of refractory osteomalacia are the persistent hypophosphatemia, increased renal clearance of phosphate, decreased intestinal absorption of calcium and failure to respond to conventional doses of vitamin D. On the other hand, there are clinical differences to be recognized.

Muscular weakness, more characteristic of the acquired form, is often so profound as to limit activity and, in some instances, muscle wasting and adynamia are present. The weakness is suggestive of that associated with hypokalemia, but this and areflexia have not been reported. We have noted that increased strength, an early sign of improvement following the institution of oral phosphate supplements, has occurred without concomitant increase in fasting levels of serum phosphorus. Meroney observed muscle weakness in a patient with hypophosphatemia to improve after supplementary phosphate feeding. That depleted body phosphorus might result in impaired muscle function is not surprising in view of the importance of high energy phosphate bonds to muscular contraction. Whether or not intracellular phosphorus is reduced during extracellular phosphorus depletion is not known.

In contrast, the hypophosphatemia in congenital refractory rickets is not usually associated with significant muscle weakness. The authors have under observation three children with the latter condition, and all have normal strength and stamina. That age is not a factor in this difference is suggested by the occurrence of muscle weakness and adynamia in infants with vitamin D-deficiency rickets and hypophosphatemia.

In patients with the acquired type of refractory osteomalacia, bone pain and tenderness often restrict physical activity. When prolonged, this immobilization may result in superimposed osteoporosis such as we believe occurred in patient A. E. of the present report. In contrast, patients with congenital refractory rickets are usually free of skeletal pain and tenderness. This we have observed in three patients, despite persistent hypophosphatemia and radiologic evidence of marked skeletal deformities.

Differences in the clinical course of the two types might suggest basically different diseases. However, since the contrast is between a childhood and adult illness, the phenomena of growth and sexual maturation must be considered as possible conditioning factors. The congenital form tends to abate clinically and radiologically during adolescence. Serum concentrations of alkaline phosphatase often decrease to normal, although hypophosphatemia may persist. On the other hand, the untreated acquired form of refractory osteomalacia is generally progressive, although Dent has observed an apparent remission in the case originally reported by McCance.

Winters and co-authors have cited the considerable clinical evidence that vitamin D in large amounts facilitates healing of congenital refractory rickets. How-
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However, such therapy is not always effective and hypercalcemia may result. For these reasons, other therapeutic measures such as increasing dietary phosphorus have been tried. Evidence suggests that this approach, achieved by the use of oral phosphate supplements, is more effective in refractory osteomalacia of the acquired type. For patients with the later disease, results similar to those we are reporting have been observed by Henneman and Jarowski. Meroney reported a positive calcium balance of 500 mg. per day in a patient with acquired refractory osteomalacia receiving a normal diet supplemented with four grams of phosphorus.

In contrast, neither radiologic evidence of bone healing nor improved mineral balances were noted in three children with congenital refractory rickets who received only phosphate supplements for a period of one year. Likewise, Frazer in a personal communication to Winters expressed a lack of confidence in such therapy for the congenital disorder. This apparent difference in response to phosphorus may be another distinguishing feature between the congenital and acquired forms. However, a plausible explanation for this refractoriness in children should not be overlooked. The normal phosphorus concentration in serum is substantially higher in children than in adults, and adequate mineralization in the former might occur only at the higher level. If true, even sizable amounts of dietary phosphorus may prove inadequate to "push" serum phosphorus concentrations in children to the higher level necessary for skeletal mineralization. Furthermore, the bone of children may have a greater competition with other somatic structures, such as muscle and liver, for available phosphorus.

In Figure 7 is schematically outlined the metabolic derangement for phosphorus in refractory osteomalacia of the acquired, non-familial type as it has been considered in the present report. For comparison, a similar schema is included for experimental osteomalacia in phosphorus-deprived rats, which is also resistant to the action of vitamin D. The central thesis for both is that phosphorus depletion alone, in the former from an apparent renal phosphate leak and in the latter from inadequate dietary supply, can result in osteomalacia. Suppressed calcium absorption is considered to be sequential to a hypophosphatemic block in skeletal mineralization. The parathyroids, if they have any role, would then serve to correct the hypocalcemic tendency which may occur early in the course of the disease. When phosphate is given in amounts adequate transiently to increase serum phosphorus levels in patients with acquired refractory osteomalacia, remineralization can temporarily proceed. The resulting utilization of serum calcium for mineralization then necessitates a secondary increase in calcium absorption. The above explanation is compatible with Harrison's thesis that intestinal absorption of calcium proceeds at a rate which is dependent to a large degree upon the rate of skeletal mineralization. If correct, this explanation would relegate vitamin D to a role of questionable significance in both the pathogenesis and treatment of acquired refractory osteomalacia.

SUMMARY

The metabolic defect of refractory osteomalacia has been discussed in the light of recent knowledge concerning its natural history and treatment. Although biochemically similar, the congenital and acquired forms appear to have differences in the clinical course and response to treatment. The case histories have been
presented of two patients with the acquired form in whom favorable treatment with high dietary phosphorus stand in contrast to the poor results observed in patients with the congenital disease. Since phosphorus repletion alone may be beneficial, the thesis that vitamin D refractoriness is the primary defect may not be applicable to all patients with this interesting disorder.

REFERENCES


