Refractory Rickets And Osteomalacia

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REFRACTORY RICKETS AND OSTEOMALACIA

BOY FRAME** AND GORDON MANSON**

The purpose of this presentation is to review some preliminary studies in patients with refractory rickets and osteomalacia. The patients include 4 congenital and 2 acquired cases of the disease. They are refractory to average doses of vitamin-D and have increased renal tubular rejection of filtered phosphate load, resulting in hypophosphatemia. Steatorrhea has been ruled out, as well as other causes of rickets and osteomalacia.

REFRACTORY RICKETS AND OSTEOMALACIA

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>AGE</th>
<th>SEX</th>
<th>SERUM CALCIUM (Mg. %)</th>
<th>SERUM PHOSPHORUS (Mg. %)</th>
<th>SERUM ALK. PTASE (Bod. u.)</th>
<th>% TRP</th>
<th>Mg. OF CALCIUM 24 Hr. Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. K.</td>
<td>8</td>
<td>M</td>
<td>9.4</td>
<td>2.1</td>
<td>14.6</td>
<td>75.6</td>
<td>12</td>
</tr>
<tr>
<td>I. K.</td>
<td>12</td>
<td>M</td>
<td>9.9</td>
<td>2</td>
<td>15.2</td>
<td>77.2</td>
<td>7</td>
</tr>
<tr>
<td>D. K.</td>
<td>35</td>
<td>F</td>
<td>10.4</td>
<td>2.4</td>
<td>2.6</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>A. S.</td>
<td>8</td>
<td>F</td>
<td>10.3</td>
<td>2.5</td>
<td>12.5</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>A. E.</td>
<td>46</td>
<td>F</td>
<td>9.5</td>
<td>2.2</td>
<td>5.2</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>H. F.</td>
<td>60</td>
<td>M</td>
<td>9.8</td>
<td>1.0</td>
<td>10.1</td>
<td>79</td>
<td>14</td>
</tr>
</tbody>
</table>

Figure 1

Chemical Data on Six Patients.

Figure 1 records the pertinent chemical data on these six patients. Note the normal serum calcium levels in association with hypophosphatemia. The alkaline phosphatase is increased in all subjects with the exception of one adult patient with a congenital form of the disease. Although we have no information on this point, data from other sources indicates that the elevated alkaline phosphatase of congenital refractory rickets returns to normal after adolescence.1 The per cent tubular reabsorption of phosphorus was depressed below normal (86-91%) in all patients tested except in the patient with the normal alkaline phosphatase. The 24 hour urine calcium was decreased in the five instances in which it was tested, after the patients had been on a 150 mg. calcium diet for three days. There are important clinical differences between patients with congenital and those with acquired forms of the disease; however, available evidence points to similar biochemical abnormalities.2,3,4

In Figure 2 are listed some of the factors to be evaluated in the pathogenesis of refractory rickets and osteomalacia. In the past most workers have considered that the absorption of calcium and phosphorus across the intestinal mucosa is impaired because of resistance to the action of vitamin-D. It will be demonstrated that the absorption of phosphorus at least in the condition is adequate in the absence of

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excessive amounts of this vitamin. The role of the parathyroid glands in refractory rickets and osteomalacia is not clear, although secondary hyperparathyroidism is thought to be present. Many studies point to an increased renal phosphate clearance.\(^5\)\(^,\)\(^6\) However, whether this is due to a primary renal tubular defect or secondary to dysfunction of some distant organ, such as the parathyroid glands, has not been clarified. Recent evidence has demonstrated a tubular secretory mechanism for phosphorus and may be a clue to the pathogenesis.\(^7\) The skeletal demineralization in the disease, as far as is known, comes about as a result of inadequate phosphorus balance. Once proper concentrations of serum inorganic phosphorus are maintained, the skeleton is then calcified. A binding role by organic acids and chelating agents for phosphorus has been postulated as playing an etiologic role, but no proof for this has been forthcoming.

Figure 3 demonstrates that patients with refractory rickets, although beginning at a lower initial level, are able to elevate the serum inorganic phosphorus after an oral phosphate load to the same degree as a control. Patient (A. E.) was taking 100,000 units of vitamin-D daily at the time of the test. However, the fact that two patients (A. S. and H. F.) were not taking vitamin-D at the time of the study proves that this vitamin is not necessary for the transfer of phosphorus across the intestinal mucosa in the disease.

Figure 4 shows that absorbed oral phosphate in refractory rickets is followed by a prompt and prolonged increase in the urinary phosphorus excretion, during which time the serum concentration returns toward the low base line level. The evidence implies that in this disease the kidney is unable to conserve sufficient absorbed phosphorus to maintain normal serum concentrations.
Rickets and Osteomalacia

Serum Phosphorus Response to Oral Phosphate Load

Figure 3

Serum & Urine Phosphorus Response to Oral Phosphate Load

Figure 4
It has been postulated that intestinal calcium, which fails to be absorbed in refractory rickets, may interfere with intestinal absorption of phosphorus. That this is not true is shown in Figure 5. Here it is seen that the administration of one gram of calcium, as calcium lactate with an oral phosphate load, does not interfere with the prompt intestinal absorption of phosphorus.

Evidence that the renal tubules in refractory rickets and osteomalacia exert a maximal rejection of filtered phosphorus is demonstrated in Figure 6. Whereas, a control patient exhibited more than a threefold increase in urinary phosphate excretion after 200 units of intravenous parathyroid extract, two patients (A. E. and H. F.) were essentially refractory to the same dose of extract. These two patients were already excreting, in the control period, over three times the amount of phosphorus as the control subject.

Further information regarding the nature of the renal phosphate leak in refractory rickets and osteomalacia is needed to clarify pathogenesis. If the phosphate leak in the condition could be reduced or shut off, the evidence would favor the defect causing the leak as functional rather than of a fixed organic nature.

Evidence does indicate that the renal tubular defect which accounts for the excessive phosphaturia can be altered and reduced (Figure 7). Intravenous calcium, in a dose of 15 mg./kilo., given over a six hour period reduced urinary phosphorus excretion and increased the per cent tubular reabsorption of phosphorus. This is similar to the response in a normal individual to intravenous calcium loading and may be secondary to reduced parathyroid influence on the renal tubules. Similar evidence that intravenous calcium loading in refractory rickets will reduce urinary phosphorus has been obtained by Fraser of Toronto. The unchanging serum phosphorus level during the intravenous calcium infusion may be due to extracellular shift of phosphorus from cellular depots.
Rickets and Osteomalacia

**Effect of Parathyroid Extract**

![Figure 6](image)

**Effect of I.V. Calcium**

![Figure 7](image)
In summary, vitamin-D resistance does not alone explain the etiology of refractory rickets and osteomalacia. Excessive vitamin-D is not necessary for intestinal absorption of phosphorus, and lack of the vitamin does not explain the urinary phosphate leak. In addition, available evidence presented elsewhere suggests that refractory osteomalacia, at least in the adult, can be healed by phosphate feeding alone and without additional vitamin-D. If further observations confirm that calcium storage will occur in the disease when phosphate stores are repleted and without the presence of excessive vitamin-D, there will be even less necessity to postulate a pathogenetic role for this vitamin.

Mounting evidence continues to confirm the presence of a reduced renal tubular reabsorption of phosphorus in refractory rickets and osteomalacia. Reduction in urinary phosphorus excretion, as well as an increase in per cent tubular reabsorption of phosphorus after intravenous calcium load, suggests that the tubular defect is functional in nature rather than one of a fixed organic lesion. Whether this derangement is primary in the renal tubule or secondary to the influence of a distant organ, such as the parathyroids, remains to be determined by further study. Indeed, if secondary hyperparathyroidism is present in the disease, the cause for its initiation and continuing action is not known.

REFERENCES