The Department of Medicine, University of California
School of Medicine, San Francisco, California, U. S. A.

PARATHYROID HORMONE
AND PHOSPHATE HOMEOSTASIS IN MAN

By

Allan Halden, E. Eisenberg and
Gilbert S. Gordan

ABSTRACT

To determine whether parathyroid hormone is required for renal response to phosphorus loading, the effects of ingestion of 3100 mg of phosphorus daily for 3 days were compared in 5 treated hypoparathyroid patients and 5 normal control subjects of comparable age and sex.

In both normal and hypoparathyroid subjects the response to phosphorus loading was characterized by an increase in urinary excretion of phosphorus without a concomitant increase in the rate of glomerular filtration of phosphorus. Some mechanism other than changes in rates of parathyroid hormone secretion probably accounts for renal responses to changes in phosphorus intake. The timing of urine and serum collections with regard to food intake and the total amount of phosphorus in the diet were found to affect the assessment of renal handling of phosphorus. The finding that a 3-day period of oral phosphorus loading did not increase the serum phosphorus level in the hypoparathyroid patients suggests that phosphorus restriction is not always necessary in the treatment of hypoparathyroidism. The addition of one more condition to the list of those that may affect the percentage of renal tubular resorption of phosphorus in no way decreases the usefulness of this determination in the diagnosis of hyperparathyroidism.

The important role of the parathyroid glands in calcium homeostasis has been known for over three decades. Parathyroid hormone also affects renal clearance of phosphorus and has therefore been assigned a central role in phosphorus homeostasis. Crawford et al. (1950) have suggested that the phosphaturia resulting from high phosphorus intake is mediated by increased secretion of parathyroid hormone. Copp & Davidson (1961), however, in studies on isolated dog thyroid-parathyroid glands, could detect no response to increased levels of phosphorus in the perfusing medium.
In the present study the relationship of the parathyroid gland to phosphorus homeostasis in man was investigated by comparing the content of phosphorus in the serum and urine of normal subjects and of treated hypoparathyroid patients before and after high phosphorus diets.

MATERIAL AND METHODS

The subjects were 4 women and 1 man with long-standing, permanent postthyroidectomy hypoparathyroidism who were otherwise healthy. All had been treated for prolonged periods with vitamin D and had normal serum calcium and phosphorus levels. Five normal subjects of comparable age and sex served as controls. Both experimental and control subjects were asked to eliminate all dairy products from their diet for 3 days. After 6 p.m. on the third day they took no food. Urine was collected by voluntary voiding from 8 p.m. to 8 a.m. and then for two 2-hour periods (8 to 10 a.m. and 10 to 12 noon). Blood samples were taken at 8, 9 and 11 a.m. The subjects drank one pint of water every hour from 8 a.m. to 12 noon.

After the collection of control samples the subjects were given 3100 mg of phosphorus daily for 3 days, half of which was provided in the diet. The other half was supplied in the form of an aqueous solution containing 775 mg of NaH₂PO₄ and 775 mg of Na₂HPO₄, which was given in 3 equally divided doses with meals. At the end of the third day blood and urine specimens were again collected as described.

The levels of calcium in serum and urine were determined with a modified Beckman flame photometer by the method of Loken et al. (1963). Phosphorus levels in serum and urine were determined by the method of Taussky & Shorr (1953). Serum creatinine was determined by the method of Loken (1954), with the use of Lloyd’s reagent to adsorb true serum creatinine. The phosphorus filtration rate was calculated by multiplying the creatinine clearance rate by the serum concentration of inorganic phosphorus; no correction was made for protein binding of phosphorus (Loken et al. 1960; Walser 1960). The calcium filtration rate was calculated as the product of creatinine clearance and serum nonprotein-bound calcium (Loken et al. 1960).

RESULTS

The results of studies in the 5 normal subjects are shown in Table 1. When their oral intake of phosphorus was raised, the rate of phosphorus excretion in the urine increased from 371 μg/minute to 672 μg/minute during the 2-hour morning clearance periods. This phosphaturic response was not associated with detectable changes in the serum phosphorus level or in the glomerular filtration rate. The increased rate of excretion resulted from decreased reabsorption of phosphorus by the tubules, both in absolute amount transported and in percentage tubular reabsorption (% T. R. P.). The 10% decrease in % T. R. P. resulted in a twofold increase in the rate of phosphorus clearance. Before phosphorus loading the rates of phosphorus filtration and reabsorption calculated from determinations on the 12-hour overnight urine specimen did not differ significantly from the morning values. After the period of high-
Table 1.
Effect of oral phosphorus loading on serum levels and renal handling of phosphorus and calcium in normal subjects.

<table>
<thead>
<tr>
<th></th>
<th>Phosphorus</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum mg/100 ml</td>
<td>Filtered µg/min</td>
</tr>
<tr>
<td><strong>2-hour morning collection periods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before phosphate loading</td>
<td>3.50 ± 0.19</td>
<td>3402 ± 294</td>
</tr>
<tr>
<td>After phosphate loading</td>
<td>3.50 ± 0.08</td>
<td>3398 ± 98</td>
</tr>
<tr>
<td><strong>P value†</strong></td>
<td>0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**12-hour nocturnal collection period**

<table>
<thead>
<tr>
<th></th>
<th>Phosphorus</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum mg/100 ml</td>
<td>Filtered µg/min</td>
</tr>
<tr>
<td>Before phosphate loading</td>
<td>3.65 ± 0.19</td>
<td>4642 ± 822</td>
</tr>
<tr>
<td>After phosphate loading</td>
<td>3.76 ± 0.18</td>
<td>3584 ± 268</td>
</tr>
<tr>
<td><strong>P value†</strong></td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

C = renal clearance; TR = renal tubular resorption.
* Mean of results obtained on two 2-hour specimens since values did not differ significantly.
† Significance level noted only if P < 0.05.
Table 2.
Effect of oral phosphorus loading on serum levels and renal handling of phosphorus and calcium in hypoparathyroid patients.

<table>
<thead>
<tr>
<th></th>
<th>Phosphorus</th>
<th>Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum mg/100 ml</td>
<td>Filtered µg/min</td>
</tr>
<tr>
<td>Before phosphate loading</td>
<td>3.59 ± 0.15</td>
<td>2925 ± 401</td>
</tr>
<tr>
<td>After phosphate loading</td>
<td>3.40 ± 0.26</td>
<td>2926 ± 434</td>
</tr>
<tr>
<td>P value†</td>
<td>0.02</td>
<td>0.02</td>
</tr>
</tbody>
</table>

2-hour morning collection periods*

12-hour nocturnal collection period

C = renal clearance; TR = renal tubular resorption.
* Mean of results obtained on two 2-hour specimens since values did not differ significantly.
† Significance level noted only if P < 0.05.
phosphorus intake, the rate of phosphorus excretion was greater during the 12-hour nocturnal period than during the morning periods. Increased intake of phosphorus by the normal subjects did not affect the concentration of calcium in the serum. Urinary excretion of calcium showed a 10% decrease during the morning collection periods and a 30% decrease during the 12-hour collection period, but the changes were not statistically significant because of the wide variation in urinary calcium levels among the subjects.

The results of studies in the 5 patients with hypoparathyroidism are shown in Table 2. In these patients the response to increased oral intake of phosphorus was similar to that in the normal subjects. During the 2-hour morning clearance periods the rate of phosphorus excretion in the urine increased without a detectable change in the serum phosphorus level or in the glomerular filtration rate. The 8% fall in the tubular reabsorption rate resulted in a 74% increase in phosphorus clearance. The data derived from determinations on the 12-hour overnight urine collections showed a similar response to increased phosphorus intake. It should be noted that the rate of phosphorus excretion in the hypoparathyroid patients was more than twice as great during the 12-hour overnight period as during the 2-hour periods. This was true both before and after phosphorus loading. After phosphorus loading the rate of calcium excretion during the night fell significantly. A similar trend was seen in the 2-hour morning periods, but as with the normal subjects the difference was not statistically significant.

**DISCUSSION**

Because tubular resorption of phosphorus goes up with phosphorus restriction and down with phosphorus repletion (Chambers et al. 1956; Crawford et al. 1950; Gordan et al. 1962), it has been suggested that the parathyroid gland is responsible for phosphorus homeostasis (Crawford et al. 1950). The present study shows that the renal response to increased intake of phosphate can occur in the absence of functioning parathyroid glands. Since the magnitude of the changes in % T. R. P. was the same in the normal subjects and in the hypoparathyroid patients, it is probable that no alteration in parathyroid gland activity occurred, even in the normal subjects. Unless these acute changes in % T. R. P. can be correlated with other effects of high or low levels of parathyroid hormone (such as hypocalcaemia or hypercalcaemia) or with parathyroid hormone levels, other mechanisms must be considered. For example, (1) the renal tubular cells themselves may be responsive to very small changes in serum phosphorus levels, (2) phosphorus may be held at various sites (perhaps bone or muscle) when intake is high, and then may be slowly excreted until the excess is depleted, (3) tubular resorption of phosphorus may be subject to another type of hormonal control that is sensitive to small changes in
serum phosphorus. No available evidence supports any of these possibilities. The pharmacologic doses of vitamin D required by hypoparathyroid patients seem to allow the kidney to adjust to phosphate intake. Parathyroid hormone, or a normal level of serum calcium, may act in a similar permissive manner. Fairhurst (1963) recently reported similar changes in tubular resorption with phosphorus loading in hypoparathyroid patients and concluded that the % T. R. P. had no value as an aid in diagnosing hyperparathyroidism. His interpretation seems unwarranted for it is clear that an abnormal rise or fall in the levels of parathyroid hormone does induce consistent changes in tubular resorption of phosphorus (Gordon et al. 1962). As is well recognized, other pathologic states may affect this tubular function, and the finding of one more condition associated with decrease in % T. R. P. does not vitiate its usefulness in the diagnosis of hyperparathyroidism. Lack of specificity is common to most physical and biochemical signs in medicine. A specific constellation of nonspecific signs usually leads the physician to a correct diagnosis.

Observations in this laboratory suggest that the renal tubules begin to respond to changes in oral phosphorus intake within 12 hours, but that a maximal response is not achieved in this time. These observations are supported by the finding that tubular resorption of phosphorus is lower during the initial 12 hours of phosphorus restriction (overnight fast) than it is during the subsequent 4 hours, even though preceded by high intake of phosphorus. The change in tubular function induced by phosphorus loading is still apparent in the morning periods, since the % T. R. P. at that time is lower than it is in the morning period before phosphorus loading. Thus, the results obtained on the 12-hour overnight urine specimen reveal more clearly the changes in renal tubular handling of phosphorus induced by dietary variation. Standard clearance determinations done on urine collected for brief periods after an overnight fast of 14–16 hours tend to minimize the effects of dietary variation. Slight changes in details of timing and of total phosphorus intake may result in quite different values for tubular resorption of phosphorus, and as suggested previously (Eisenberg 1962) these factors may account for some of the controversy regarding the usefulness of % T. R. P. in the diagnosis of hyperparathyroidism.

Of interest is the fact that the hypoparathyroid patients were able to tolerate large amounts of phosphorus in the diet without changes in the levels of calcium and phosphorus in the blood. It may be that the usually advised phosphorus restriction is not necessary when a maintenance dose of vitamin D has been established.
ACKNOWLEDGEMENTS

We wish to thank Dr. Hans F. Loken and Miss Joan Manning for their valuable technical assistance and Dr. Harold Upjohn, The Upjohn Company, Kalamazoo, Michigan, for generous supplies of vitamin D₂ (Calciferol).

REFERENCES


Eisenberg E.: Recent Progr. Hormone Res. 18 (1962) 333.


Received on November 8th, 1963.