Clinical Evaluation Of Renal Tubular Phosphorus Reabsorption Test

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CLINICAL EVALUATION OF RENAL TUBULAR PHOSPHORUS REABSORPTION TEST

BOY FRAME, M.D.* AND RAYMOND MELLINGER, M.D.**

The diagnosis of hyperparathyroidism continues to be difficult in many borderline cases. Even in far advanced stages of the disease the usual indices of serum calcium, serum inorganic phosphorus and urinary calcium values may be misleading. Since the problem exists, there has been increasing emphasis placed on the urinary excretion of phosphorus as a measure of hyperparathyroidism. The total urinary phosphorus excreted per twenty-four hours is in itself variable and considered of little diagnostic significance.¹ However, various authors have utilized the ratio of reabsorbed to filtered phosphorus and the measurement of per cent tubular reabsorption of phosphorus in the diagnosis of hyperparathyroidism.²,³ Considerable clinical experience has now been gained with these new techniques.⁴

In the past year we have had the opportunity to evaluate the per cent tubular reabsorption of phosphorus (TRP) in 104 patients (Figure 1) while searching for cases of possible hyperparathyroidism. Most of the patients, as might be expected, were studied because of kidney stones or bony demineralization, but patients with other types of metabolic bone disease and renal tubular defects were also included in the study.

The purpose of this report is to add to the total clinical experience of the TRP test and to evaluate its diagnostic usefulness.

METHODS

The control subjects comprised healthy doctors, nurses, and persons undergoing annual routine physical examinations. Patients in the study were taking a diet containing average amounts of calcium and phosphorus and were fasted from midnight on the day of the test. Adequate water intake was given to insure a good urinary flow. Starting at 10 a.m. a four-hour collection of urine was obtained and at 12 noon a blood sample was drawn. Inorganic phosphorus and creatinine determinations were performed on both the blood and urine. From these values the endogenous creatinine clearance was determined and considered to be equal to the glomerular filtration rate. With the knowledge of the serum and urinary phosphorus values the per cent tubular reabsorption of phosphorus was then calculated using the formula:

\[ TRP = 1 - \frac{\text{phosphate clearance}}{\text{creatinine clearance}} \]

Patients with serum creatinine over 1.3 mg. per cent were not used in the study since the creatinine clearance reflects the glomerular filtration rate only through normal ranges of serum creatinine. Repeat studies in an attempt to eliminate error were carried out on many of the patients. When two or more studies were performed on any one patient the final value used was an average.

*Division of General Medicine.
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### Renal Tubular Phosphorus Reabsorption Test

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*Not due to Hyperparathyroidism

Figure 1
Comparative values for Phosphorus Reabsorption Test.

#### RESULTS

1. Normal Subjects.

   The TRP in 20 control subjects ranged from 86.9 to 95.1 per cent with a mean of 90.9 per cent. These figures compare favorably with the normal values obtained by others.35

2. Hyperparathyroidism.

   Six patients with surgically proven primary hyperparathyroidism had phosphorus reabsorption tests. The values were reduced in all six instances ranging from 51 to 82 per cent. One patient with surgically proven hyperparathyroidism who had a normal TRP, is excluded because phosphorus had been restricted in the diet pre-
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ceding the test. Phosphorus deprivation is known to elevate the TRP in both normal and hyperparathyroid patients. There was a prompt return to normal after removal of a parathyroid adenoma in five of the patients tested. In the sixth patient despite good initial response after the operation there has been some evidence of progressive renal impairment eight months later as reflected by a rising serum creatinine of 2.8 mg. per cent. This has invalidated progress measurement of the TRP.

Two patients with presumed secondary hyperparathyroidism due to steatorrhea of sprue had reduced TRP of 70.2 and 83.3 per cent respectively. Both of these patients had biochemical and x-ray evidence of osteomalacia.

3. Renal Lithiasis.

Thirty-eight patients with renal lithiasis thought not due to hyperparathyroidism had phosphorus reabsorption tests. The values ranged from 70.2 to 97.1 per cent with a mean value of 89.5 per cent. In only two of these patients however was the value depressed to the degree usually seen in hyperparathyroidism. In one of the patients with renal stones and a depressed TRP to 70.7 per cent there was hypophosphatemia of 2.2 mg. per cent and hypercalciuria. Normal parathyroid glands were identified at operation. In the other patient who has renal lithiasis and a low TRP of 78.6 per cent, parathyroid exploration has not been carried out because the values for serum calcium, phosphorus and urinary calcium are normal. To our knowledge a depressed TRP has not been proved in any instance to be the only biochemical abnormality present in hyperparathyroidism and is not in itself sufficient evidence for parathyroid exploration.

4. Osteoporosis.

Seventeen patients with post-menopausal or senile osteoporosis had phosphorus reabsorption tests. The values ranged from 85 to 95.1 per cent with a mean of 90.9 per cent. The diagnosis of osteoporosis was made on the basis of obvious demineralization of the spine by x-ray in conjunction with a normal serum calcium and inorganic phosphorus. The urinary calcium was either normal or moderately increased.

5. Phosphate Diabetes (Vitamin D — Resistant Osteomalacia).

Two patients with phosphate diabetes had phosphorus reabsorption tests. This disease is considered to be a unifactorial defect in renal tubular reabsorption of phosphorus leading to negative phosphorus balance and osteomalacia. The value was distinctly reduced in both patients to 65 and 80 per cent respectively. The TRP remains depressed in this condition even after forced phosphorus loading has led to healing of the osteomalacia.

6. Hyperthyroidism.

Ten patients with hyperthyroidism had phosphorus reabsorption tests. Previous experimental work in dogs has shown that triiodothyronine reduces the tubular reabsorption of phosphorus. Clinical hyperthyroidism is occasionally associated with hypercalcemia as well as hypercalciuria without associated parathyroid hyperfunction. It therefore seemed worthwhile to evaluate the test in hyperthyroidism. The values
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were within normal range in all the tested patients except one. This patient, who had a repeatedly low TRP of 70 per cent, was the only one of the group with associated hypercalcemia to 14 mg. per cent as well as marked hypercalciuria. With the remission of the hyperthyroid state after treatment with I\(_{131}\), the hypercalcemia, hypercalciuria, and TRP all returned to normal range.

7. Miscellaneous.

Single or small groups of patients with a variety of diagnoses were included for one reason or another in the present study. Cases of bilateral aseptic necrosis of the hips, psychogenic polydipsia, and mono-ostotic fibrous dysplasia of bone all had normal TRP. One patient with wide-spread lymphosarcoma of bone had normal serum calcium, phosphorus and creatinine, but a reduced TRP to 78 per cent on one occasion and 82 on another. Four patients with myxedema were tested. Two of these had a normal TRP; but in the other two it was reduced to 79.1 and 81 per cent for which there was no ready explanation.

A remarkable reduction in the TRP to 50 percent was repeatedly found in a 5 year old girl with Metaphyseal Dysostosis.\(^9\) This disease is characterized by a most unusual disorganization of metaphyseal ossification and in addition there is evidence in the few reported cases that hypercalcemia and hypophosphatemia may be present. The x-rays suggested a congenital bone defect, but the chemical changes were characteristic of hyperparathyroidism. Surgical exploration was performed and normal parathyroid glands identified. The striking changes in the serum calcium and phosphorus and the markedly depressed tubular reabsorption of phosphorus were unexplained.

DISCUSSION

There is now sufficient accumulated data to indicate that the measurement of the per cent tubular reabsorption of phosphorus may be of aid in the diagnosis of hyperparathyroidism and certain renal tubular defects. Its final assessment in the evaluation of these conditions, however, awaits further clinical experience with the test. In the opinion of Hills and Burr a normal TRP rules out hyperparathyroidism.\(^7\) Reynolds et al, however, have reported the TRP to be within normal range in some patients with the disease.\(^10\)

The danger of progressive renal failure in hyperparathyroidism, even after its surgical correction, makes the earliest possible diagnosis of paramount importance. The TRP will be a significant additional diagnostic aid if it can be shown to be depressed in hyperparathyroidism before hypercalcemia, hypophosphatemia, and hypercalciuria are present. To our knowledge this has not occurred in any proved case. In our experience the diagnosis of hyperparathyroidism has been well established by diagnostic changes in the serum calcium and phosphorus with the TRP giving only confirmatory evidence. When hyperparathyroidism has progressed to renal failure with elevation of serum creatinine the TRP, like the value for the serum inorganic phosphorus, will be unreliable and misleading. It is probable that the TRP will be useful primarily as supportive diagnostic evidence in hyperparathyroidism. A significantly depressed TRP in the face of borderline charges in serum calcium
and phosphorus or in the urinary calcium, may be sufficient evidence to proceed with parathyroid exploration.

The TRP may be of value in ruling out hyperparathyroidism in cases of renal lithiasis due to other causes. Recently the occurrence of idiopathic hypercalciuria as a factor in the etiology of kidney stones has been more completely described. This condition is characterized by a normal serum calcium level, a low serum phosphorus and an increased urinary calcium excretion. Normal TRP in patients with the above findings is strong supportive evidence that hyperparathyroidism is not causing the lithiasis and unnecessary surgical exploration can be avoided. Of the thirty-eight patients with kidney stones in the present series, eight are considered to have idiopathic hypercalciuria. In seven of these eight patients the TRP was within normal range or only minimally depressed and parathyroid exploration was deferred. The eighth patient, a 48 year old male, had been previously diagnosed at the Massachusetts General Hospital by Dr. Fuller Albright as having idiopathic hypercalciuria. Dr. Oliver Cope carried out parathyroid exploration and found four parathyroid glands grossly and microscopically normal. The patient continued to pass kidney stones and was subsequently seen at the Henry Ford Hospital. Serum calcium was 10.5 and phosphorus 2.2 mg. per cent. Twenty-four hour urine calcium collected while the patient was taking a 150 mg. calcium diet was 211 milligrams. Repeated TRP was depressed to 70 per cent. On the basis of the previous operative findings of four normal parathyroid glands, further surgical exploration of the neck or mediastinum has been deferred, at least for the time. The case illustrates that the TRP in idiopathic hypercalciuria may be significantly depressed either due to renal tubular damage or secondary hyperparathyroidism. It would seem, however, that in most patients with this condition the TRP will be within normal range.

Since most patients with osteoporosis have normal serum calcium and phosphorus, this disorder is readily differentiated from hyperparathyroidism with bone involvement. However, when osteoporosis is rapidly progressive, especially in children, the serum calcium may be elevated. Hypercalciuria occurs frequently in both conditions and is not always a helpful point of differentiation. Depressed serum phosphorus favors hyperparathyroidism, but this important finding may be absent. A normal TRP under these circumstances is substantial evidence against the diagnosis of hyperparathyroidism.

The TRP may be a significant aid in diagnosing renal tubular insufficiency as it occurs in the Fanconi syndrome or in phosphate diabetes. In both of these conditions the renal mechanism for reabsorbing phosphorus is defective owing to an intrinsic alteration in the renal tubule. In the Fanconi syndrome this renal tubular defect for reabsorption of phosphorus is accompanied by similar defects for the reabsorption of glucose and amino-acids. Phosphate diabetes represents the single defect of impaired phosphorus reabsorption.

A depression of TRP alone does not separate an intrinsic renal tubular defect in phosphorus reabsorption from the effect of excess parathyroid hormone. Appreciation of this fact will help avoid errors in diagnosis. As with any other laboratory test, the TRP is of value only when interpreted in light of the other clinical findings.
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It should be used only as supportive evidence in the diagnosis of hyperparathyroidism or renal tubular insufficiencies, and final decisions should not be made on basis of the TRP alone.

SUMMARY

1. The results of the per cent tubular reabsorption of phosphorus (TRP) has been evaluated in 104 patients. These have included normal controls and patients with hyperparathyroidism, renal lithiasis, osteoporosis, and intrinsic renal tubular insufficiencies.

2. The TRP may be of acid in the diagnosis of hyperparathyroidism and renal tubular defects, but should be used only as supportive evidence and in light of the total clinical picture.

The authors appreciate the help of Miss MacIntosh, Head Nurse, General Medical Clinic, for her aid in carrying out the phosphorus reabsorption tests.

REFERENCES


