CHANGES IN PHOSPHORUS CLEARANCE DETERMINED BY THE ADMINISTRATION OF GLUCOSE IN DISEASES OF THE PARATHYROIDS AND IN OTHER PATHOLOGICAL CONDITIONS

By

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ABSTRACT

A reduction in tubular phosphorus reabsorption caused by the effect of competition induced by the intravenous injection of a glucose load, may provide information on the state of phosphorus reabsorption before the introduction of the glucose. The authors use the term \( C_p1 \) for the phosphorus clearance value in the basic condition and \( C_p2 \) to indicate clearance modification brought about by glucose. The ratio \( C_p2/C_p1 \) thus shows the increase over the basic clearance. For normal subjects (10 cases) the ratio varied between 1.7 and 3.7 (mean value 2.6); in simple renal calculus (10 cases), in osteoporosis (2 cases), in thyrotoxicosis (3 cases), and in prolonged heparin therapy (2 cases) the ratio was within the normal range; in acromegaly (4 cases) the values tended to be above normal. There was a characteristic increase in the value of the ratio only in the case of hypoparathyroidism (3 patients). The reduction in the ratio found in hyperparathyroidism (3 cases) cannot be considered as characteristic since a reduction was also observed on occasion in other diseases, namely Paget's disease (1 case out of 2) and osseous metastasis (2 cases out of 4).

Tubular reabsorption of phosphorus is reduced in hyperparathyroidism and increased in hypoparathyroidism: this functional behaviour of the renal tubules with regard to phosphates is linked to the activity of the parathyroid hormone. This hormone controls phosphorus metabolism and may be the cause of reduced phosphate reabsorption and thus of hyperphosphaturia.

A reduction of tubular phosphate reabsorption may also be found as a
consequence of the administration of substances which have a neutralizing effect on the enzymes responsible for the intratubular transport of phosphates. A similar reduction occurs if substances are administered which are able to compete with phosphorus for tubular reabsorption.

Particular attention has been paid to the study of glucose as an example of a substance in the latter group (Pitts & Alexander 1944; Levitan 1951). An increase in glycaemia, and a consequent increase in the tubular glucose load, are brought about by an increased reabsorption of glucose at the expense of phosphorus. When this condition is present the lowest phosphorus reabsorption value is reached at the same time as the maximum glucose reabsorption rate (Martini 1964 a, b).

For these reasons we thought that the best demonstration of the effect of glucose administration, as a means of reducing phosphorus reabsorption, would be in cases in which there was already an increase in phosphate reabsorption due e.g. to hypoparathyroidism. In hyperparathyroidism, however, the fact that phosphate reabsorption was already pathologically reduced would make it difficult to assess the effectiveness of glucose as a competitor.

We have already confirmed the validity of this theory by experiment and the results obtained have encouraged us to widen the field of our investigations (Martini & Piancino 1964; Martini et al. 1965). The present study, therefore, deals with variations in phosphate reabsorption caused by the intravenous administration of large quantities of glucose to patients with diseases in which changes in phosphorus and calcium metabolism are sometimes encountered. A comparison is made with the results obtained in normal subjects and in those with hyper- and hypoparathyroidism.

Apart from the physiopathological value of such research as a means of learning more about the mechanism of phosphate reabsorption, we feel that it could also be used as a starting point for further work in the field of differential diagnosis.

**MATERIAL AND METHODS**

The data on which this paper is based were obtained from 4 patients with osseous metastasis, 2 with osteoporosis, 3 with thyrotoxicosis, 4 with acromegaly, 2 with Paget's disease and 2 who were receiving prolonged heparin therapy.

The cases used for comparison consisted of the following (previously reported by us): 10 normal subjects, 10 cases of simple renal calculus, 3 cases of hypoparathyroidism and 3 of hyperparathyroidism (Martini & Piancino 1964; Martini et al. 1965).

In all cases the subjects had fasted for at least 12 hours. No special dietary regimen was followed on the days preceding the tests.

Urine-phosphorus excretion is given in terms of phosphorus clearance (Cp). The term Cp1 is used to indicate the mean value of 2 or 3 basic phosphorus clearances measured before the administration of glucose. The term Cp2 is used for each separate
phosphorus clearance value measured after the administration. The ratio \( \frac{C_{p2}}{C_{p1}} \), therefore, shows the increase in phosphorus excretion in terms of multiples of the basic \( Cp \).

The blood samples used for the measurement of plasma-phosphorus levels were drawn from the cubital vein at the mid-point of each phosphorus clearance test; urine samples for the measurement of the extent of phosphaturia and diuresis were obtained by means of a catheter which was left in situ for the whole period of the test.

Each clearance test began immediately after the conclusion of the one before it. The only exception to this procedure was made at the time of change-over from the basic to the post-glucose-administration tests. At this point a short pause of a few minutes was allowed. The test methods used may be summarised as follows:
- 2–3 basic phosphorus clearance tests.
- intravenous injection of 70–100 ml (according to body weight) of a 50% solution of glucose over a period of 5 min approx., followed by the maintenance of the hyperglycaemic level by means of intravenous drip of the same solution throughout the test, at the rate of about 70 drops per min.

The beginning of the post-glucose clearance test was taken from the time at which the intravenous injection was concluded: an interval of about 5 min was left between the basic and the post-glucose clearances.

The normal phosphorus clearance value was found to be between 4.1 and 17.0 ml/min (Vitelli et al. 1963): these figures are in agreement with those given in the literature by other investigators (Milne 1951; Kyle et al. 1958; Hodgkinson 1961).

For the evaluation of the phosphorus content of the blood and of the kidney we used the method of Fiske & Subbarow (1925).

**RESULTS**

Table 1 gives a summary of the results. Fig. 1 shows the behaviour of the \( \frac{C_{p2}}{C_{p1}} \) ratio in the present series of cases and also records the values obtained in normal subjects and in previously reported cases.

In addition Fig. 1 shows that the ratio \( \frac{C_{p2}}{C_{p1}} \) has an abnormal behaviour pattern in cases of hyper and hypoparathyroidism, in two cases of osseous metastasis and in one case of Paget's disease.

In Fig. 2 the abscissa shows the mean basic phosphorus clearance value for each individual case \( (C_{p1}) \) and the other co-ordinate, gives the mean value of the ratio \( \frac{C_{p2}}{C_{p1}} \) obtained in each case. The normal range was considered that between the highest and lowest observed mean normal values. For this reason, the range of values shown in Fig. 2 is narrower than in Fig. 1 in which the normal range was defined by the highest and lowest observed absolute values.

**DISCUSSION**

A short statement is necessary of the reasons for our choice of the methods of glucose administration which we have described.
Table 1.
Table of C_p2/C_p1 ratio values for the cases examined.

<table>
<thead>
<tr>
<th>Type of case</th>
<th>No. of subjects</th>
<th>C_p2/C_p1 variation range</th>
<th>C_p2/C_p1 mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Osseous metastasis</td>
<td>4</td>
<td>1.3–3.1</td>
<td>2.1</td>
</tr>
<tr>
<td>2) Osteoporosis</td>
<td>2</td>
<td>2.6–3.8</td>
<td>3.2</td>
</tr>
<tr>
<td>3) Thyrotoxicosis</td>
<td>3</td>
<td>2.2–3.3</td>
<td>2.7</td>
</tr>
<tr>
<td>4) Acromegaly</td>
<td>4</td>
<td>2.7–3.8</td>
<td>3.4</td>
</tr>
<tr>
<td>5) Paget's disease</td>
<td>2</td>
<td>1.6–2.9</td>
<td>2.1</td>
</tr>
<tr>
<td>6) Prolonged heparin therapy</td>
<td>2</td>
<td>2.7–3.8</td>
<td>3.2</td>
</tr>
<tr>
<td>7) Hyperparathyroidism</td>
<td>3</td>
<td>1.0–1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>8) Hypoparathyroidism</td>
<td>3</td>
<td>3.5–6.3</td>
<td>4.6</td>
</tr>
<tr>
<td>9) Renal calculus</td>
<td>10</td>
<td>1.7–3.5</td>
<td>2.6</td>
</tr>
<tr>
<td>10) Normal subjects</td>
<td>10</td>
<td>1.7–3.7</td>
<td>2.7</td>
</tr>
</tbody>
</table>

The data given under 7, 8, 9, and 10 have already partly been published elsewhere (see text).

Fig. 1.
Behaviour pattern of the ratio C_p2/C_p1 in various pathological situations, compared with normal values. (The range of normal variability refers to the values obtained from the 10 normal subjects).

We observed, during the course of a previous study, that the sudden administration of glucose followed by the maintenance of the hyperglycaemic level by means of intravenous drip of a hypertonic solution of glucose was sufficient to ensure that tubular glucose reabsorption reached saturation point (Vitelli et al. 1965). When the tubules are fully engaged in the reabsorption
Comparison between basic phosphorus clearance \((C_p_1 = \text{ml/min})\) and the ratio \(C_{p_2}/C_{p_1}\) in normal subjects and in various pathological situations.

of glucose \((T_mG)\), the reabsorption of phosphorus reaches the lowest level, because of competition between these two substances for intratubular transport.

We therefore considered that it was necessary to obtain complete tubular glucose saturation before measuring the effects of glucose on phosphorus excretion. In this way it was possible to standardize the results obtained and also to evaluate each finding against a unit base.

Glucose, on the other hand, reduces the blood-phosphorus content and, in view of the large quantity of glucose used in our tests, we might have been faced with a paradoxical decrease in urine-phosphate excretion due to the reduced quantity of phosphorus brought to the tubules by the low phosphorus content of the circulating blood. It was for this reason that the shortest possible time was allowed to elapse between the last basic clearance and the first post-glucose clearance.

In our experiments the use of this procedure in most cases, was sufficient to avoid the paradox of a decrease in urine-phosphate excretion. This phenomenon will, however, occur if the time used for the introduction of the glucose is greater than that allowed by us. It is in fact, by contrast with the hyperphosphaturia produced by glucose, only a constant feature, when the tubular phosphorus load level is below or only slightly above the threshold level for phosphorus. In order that this should be accomplished, the blood-phosphorus reducing action of the glucose must continue for a certain time.

For these reasons we consider that the ratio \(C_{p_2}/C_{p_1}\) can only be a valid expression of the increase of urine-phosphate excretion when the values for
Cp₂ are taken within a glucose perfusion which is not unduly prolonged: in our experiments this was not more than 45–60 min after injection of the glucose.

In this connection a few remarks may be made about the results themselves. Fig. 1 compares the ratio Cp₂/Cp₁ found for the subjects of the present study with those previously obtained in normal subjects and in patients suffering from hypo- and hyperparathyroidism. Although this ratio is clearly outside the normal range in patients with parathyroid dysfunctions, in 2 with osseous metastasis and in 1 with Paget’s disease, in all other cases it lies practically along the line given by the results obtained in the normal subjects.

The abnormal and opposite results given for the ratio in the case of hypo- and hyperparathyroidism are, of course, explicable on the well known basis of the differing tubular phosphate reabsorptions observed in these two conditions. It is of greater interest to examine the reasons for the modification of the ratio in the remaining cases.

The value of the ratio in acromegaly was, in most cases, at the higher limits of the normal range and this finding is probably attributable to the particular form of renal activity which is characteristic of the disease. Nephromegaly is in fact one aspect of a more or less general state of visceromegaly and is not solely an anatomical feature. It has been shown by modern clearance techniques that an increase in kidney volume is accompanied by an equivalent increase in function which may sometimes be considerable. Both the glomeruli and the tubules may be affected in this way but neither of these will display a greater increase of activity than the other (Corvilain & Abramow 1962; Gershberg & Gash 1956; Heller et al. 1954; Ikkos et al. 1956; White et al. 1949).

We have already shown that in cases of acromegaly, maximum tubular phosphorus absorption is increased (Cattaneo et al. 1964); results obtained in a later paper (Piancino et al. 1966) also tended to confirm the hypothesis that, in addition to the increase in the maximum reabsorption due to the phosphate load, acromegaly also leads to an increase in basic tubular phosphorus reabsorption. This hypothesis is now confirmed by the finding that the value of the ratio Cp₂/Cp₁ lies at the higher limits of the normal range or just above the normal value.

Similar considerations apply to the results obtained in the 3 cases of thyrotoxicosis. Various investigators (Anderson & Parsons 1964; Bijovet et al. 1964; Bijovet & Mayoor 1965; Parsons & Anderson 1964) have shown that this condition leads to an increase in maximum phosphorus reabsorption but our research would seem to indicate that this is not accompanied by a corresponding increase in the Cp₂/Cp₁ ratio, since this was found to lie within normal limits. We may assume that in the case of thyrotoxicosis there is a »potential« increase in the reabsorption of phosphorus which is evidenced by a stimulation.
of tubular activity with phosphate solutions, so as to obtain maximum reabsorption, but that in the absence of an artificial phosphate load, the basic reabsorption is normal.

The results obtained in the cases of osseous metastasis and Paget's disease are more difficult to interpret since the ratio was found to vary from case to case. We would like to point out, however, that these findings reflect the lack of agreement in the literature concerning phosphorus excretion (Courvoisier et al. 1959; Lichtwitz et al. 1957; Nagant de Deuxchaisnes & Krane 1964).

The fact that the Cp₂/Cp₁ ratio found for the other patients in the present study was normal seems to indicate that the mechanism of tubular phosphorus reabsorption in their cases is not different from that of normal subjects. This would also hold true for the patients receiving prolonged heparin therapy also if some authors have actually described bone lesions attributable to the treatment itself (Jaffe & Willis 1965; Griffith et al. 1965; Nichols et al. 1965) while others have found a lowering of the phosphorus excretion threshold in these patients (Bijovet et al. 1964).

Lastly, this test does not invalidate the significance of Kyle's test (Kyle et al. 1958) which deals with the basic clearance of phosphorus (Cp₁). The test which we carried out, not only gives results which are characteristic of those obtained in Kyle's test, but has also the advantage that it differentiates some subjects for whom the clearance test on its own would only give a very doubtful diagnostic interpretation.

The same may be said about the analysis of the results shown in Fig. 2. This is of particular interest in some cases of acromegaly and nephrolithiasis, where the basic Cp is at the upper limits of the normal or even slightly above, whereas the increase in phosphorus elimination induced by the administration of glucose is, by contrast, within the normal limits.

These observations, therefore, are of importance from the diagnostic point of view when they are added to the simple phosphorus clearance value, particularly in the case of parathyroid diseases. This becomes even more clear when it is remembered that Kyle himself has recently shown that the evaluation of the phosphorus clearance may sometimes lead to erroneous diagnostic interpretation when it is done in isolation (Kyle et al. 1962).

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