Phosphate Deficiency in Haemodialysed Patients

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Patients treated for long periods with antacids containing magnesium and aluminium hydroxide may sometimes develop clinical and radiological signs of osteomalacia (Lotz et al, 1964; Ludwig et al, 1967). Low concentrations of phosphate in blood and urine suggest that this bone disease is due to phosphate deficiency from excessive faecal losses (Lotz et al, 1964; Lotz et al, 1968). Furthermore, weakness, anorexia and debility may be clinical effects of depletion of intracellular organic phosphate compounds. In chronic renal failure the plasma phosphorus concentration tends to rise due to reduced glomerular filtration, increased protein catabolism and excessive bone resorption. The resultant elevation of the calcium phosphate product may lead to ectopic calcification, particularly around joints and in the walls of blood vessels. Another disadvantage of hyperphosphataemia is that it may be one of the factors which leads to secondary hyperparathyroidism (Bricker et al, 1969) although there is no evidence for a direct effect of phosphate upon parathyroid hormone secretion (Reiss et al, 1970; Sherwood et al, 1968). For these reasons phosphate binding agents are commonly used to reduce the intestinal absorption and plasma concentration of phosphorus. The intake is reduced further if the patient is given a low protein diet. However, the hyperphosphataemia of chronic renal failure is not due to overabsorption of dietary phosphate and the overall phosphate balance is known on occasion to be negative (Dent et al, 1961). 'Aludrox' or similar compounds may therefore control plasma levels at the expense of tissue depletion and rickets in an uraemic patient treated with this compound has been reversed after its withdrawal (Dent et al, 1961). Prolonged haemodialysis adds a further complication to those of renal failure, since it is another cause of obligatory phosphate loss. In problems of bone disease and ectopic calcification in haemodialysed patients more attention has been concentrated on calcium, parathyroid hormone and disorders of Vitamin D metabolism than on phosphorus.

Phosphate losses due to dialysis have been measured in a previous study
of factors modifying dialysate calcium requirements (Soyannwo et al, 1968). However, the likelihood that continued use of oral phosphate-binding agents and phosphate-free dialysate could lead to significant total body phosphate deficiency has not been seriously considered. No other investigators have measured simultaneous alimentary and dialysis balance in patients on a known phosphate intake. We present here the results of such a study which may provide a useful preliminary basis for more detailed investigation.

PATIENTS AND METHODS

The five patients all had chronic renal failure due either to chronic pyelo-nephritis or glomerulonephritis (Table I). They were dialysed for three ten-hour periods each week using the Kiln artificial kidney in a single pass system. Dialysate was delivered by a Lucas monitor and proportionating system from softened tap water proportioned 34 to 1 with concentrate. Patients were up and about; three were studied during the training period, whilst two were

Table I. Phosphate balance study. Summary of clinical data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Bone disease</th>
<th>Time on dialysis (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>JG</td>
<td>OF</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>DW</td>
<td>OF</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>DR</td>
<td>OF + OM</td>
<td>6</td>
<td>Anephric</td>
</tr>
<tr>
<td>AE</td>
<td>OP + OM</td>
<td>18</td>
<td>Intermittent Aludrox</td>
</tr>
<tr>
<td>ET</td>
<td>OF + OM</td>
<td>18</td>
<td>Continuous Aludrox Anephric</td>
</tr>
</tbody>
</table>

KEY: OF = Osteitis fibrosa. OM = Osteomalacia. OP = Osteroporosis

| W | Th | F | S | S | M | T | W | Th | F | S | S | M | T | W |
|---|----|---|---|---|---|---|---|----|---|---|---|---|---|---|---|
|   |    |   |   |   |   |   |   | RUN UP Ba + CONSTANT DIET | MARKER | 1 | 2 | MARKER | PERIOD 1 |
|   |    |   |   |   |   |   |   | DIET CONTINUED UNTIL MARKER | RECOVERED | 3 | 4 |   | PERIOD 2 |

Figure 1. Scheme for balance studies on patients DW, AE, JG and ET. The two 4-day alimentary balance periods include two periods of haemodialysis treatment in each
admitted from home. ET had symptoms of bone disease and all five had histo-
logical abnormalities on bone biopsy. Balance data from DW were obtained
both before and after regular dialysis treatment had been started. A constant
diet was provided throughout the studies and contained approximately 70 g of
protein and 500 mg of calcium in each case. Three patients were on a low
sodium intake. Carmine external and barium internal markers were used
according to conventional methods (Dick, 1967). The scheme for alimentary
and dialysis balance in the first four patients is shown in Figure 1. Each
4-day balance period included two 10-hour dialyses. The fifth patient was
studied for two 5-day periods, the first including two, and the last, three
dialyses.

The loss of phosphate during haemodialysis was measured in the dialy-
sate effluent. This was collected continuously throughout the 10-hour period
in five 2-hour portions of approximately 60 litres each and the total volume
determined from the weight and specific gravity of the fluid. Aliquots were
taken from each portion after mixing and stored frozen until they were ana-
lysed. The dialysate entering the Kil was found to contain small amounts
of phosphate, perhaps due to contamination of the lines. Aliquots of input
fluid were therefore sampled from the overflow line of the header in the
monitor tank and total phosphate input calculated. In the study on patient
DR the total volume of effluent was not collected but an accurately determined
fraction of the whole was analysed using a proportioning pump adjusted to
give a reversed flow and to discard a major fraction of the effluent.

Diet samples and stools were homogenised, ashed at 600°C and redis-
solved in acid. Urine was collected in two day pools. Phosphate concentra-
tion was measured by the method of Gomorri (1942).

RESULTS

The results of a representative balance study and the data on all five patients
are summarised in Tables II and III respectively. The overall balance has
been calculated from the difference between input in diet and the small quan-
tity of phosphate in the dialysate, and output in stool, urine and effluent over
the course of four days.

In the first four patients the overall phosphate balance was negative with
one exception. This is the second balance period on patient AE. Both dialy-
ses in this period were complicated by frequent and long periods of trouble
with dialysate conductivity with intermittent automatic bypass of the Kil
board. The low effluent phosphate recovery might therefore be accounted
for by bad dialysis on these occasions.

The fifth patient, DR, was studied over the course of 10 days. The
results (Table II, Figure 2) show that during the first 5-day balance period
when he was dialysed twice overall phosphate balance was positive. In the
Table II. Results of a representative balance study (JG)

<table>
<thead>
<tr>
<th></th>
<th>132</th>
<th>121</th>
<th>129</th>
<th>65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis input mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis output mg</td>
<td>1,281</td>
<td>1,107</td>
<td>1,124</td>
<td>1,170</td>
</tr>
<tr>
<td>Dialysis balance mg</td>
<td>-1,150</td>
<td>-986</td>
<td>-995</td>
<td>-1,105</td>
</tr>
<tr>
<td>Plasma mg/100 ml Pre</td>
<td>6.8</td>
<td>6.3</td>
<td>5.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Post</td>
<td>3.8</td>
<td>3.5</td>
<td>3.4</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Diet mg/4 days          | 3560 | 3676 |
Faeces mg/4 days        | 1660 | 2024 |
Urine mg/4 days         | 170  | 218  |
Alimentary balance      | 1730 | 1434 |
Total balance (mg)      | -406 | -666 |

Table III. Results of phosphate balance studies on five haemodialysed patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Period</th>
<th>Dialysis balance</th>
<th>Alimentary balance</th>
<th>Overall balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>JG</td>
<td>1</td>
<td>-2136</td>
<td>+1730</td>
<td>-406</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-2100</td>
<td>+1434</td>
<td>-666</td>
</tr>
<tr>
<td>ET</td>
<td>1</td>
<td>-808</td>
<td>-1900</td>
<td>-2708</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-1042</td>
<td>+541</td>
<td>-501</td>
</tr>
<tr>
<td>DW</td>
<td>1</td>
<td>-1860</td>
<td>+1542</td>
<td>-318</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-1611</td>
<td>+1601</td>
<td>-10</td>
</tr>
<tr>
<td>AE</td>
<td>1</td>
<td>-2033</td>
<td>+1524</td>
<td>-509</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-734</td>
<td>+1168</td>
<td>434</td>
</tr>
<tr>
<td>DR</td>
<td>1</td>
<td>-1778</td>
<td>+1821</td>
<td>+43</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-2843</td>
<td>+2107</td>
<td>-736</td>
</tr>
</tbody>
</table>

second 5-day period when there were three dialyses he was in overall negative balance.

Patient DW was studied on two occasions before and after dialysis treatment had begun (Figure 3). The results indicate that the proportion of dietary phosphate absorbed in the pre-dialysis studies was approximately the same (40%). After one month of routine haemodialysis treatment the net intestinal absorption of phosphate had increased (60%).
Figure 2. Phosphate balance on patient DR. Dietary intake is plotted below the zero line, and output upwards from the bottom of the intake line. Shaded area represents net dialysis phosphate losses.

Figure 3. Phosphate balances on patients DW plotted as in Figure 2. In two pre-dialysis studies urine phosphorus represented by shaded area, and in dialysis study, by cross-hatched area. Dialysis losses represented by shaded area as in Figure 2. In pre-dialysis balances, approximately 40% of the dietary phosphorus intake absorbed. In dialysis balance 60% of intake absorbed.
DISCUSSION

Previous workers have shown an increase in gut absorption of phosphate in dialysed compared with non-dialysed patients (Verberckmoes et al., 1969) and our results on patient DW would agree with this finding. However, it has been said that such an increase in absorption excludes phosphate deficiency as a significant factor in the cause of the bone disease of patients undergoing chronic haemodialysis. Such a view is not justified unless simultaneous dialysis losses are measured.

In our first four patients phosphate balance was negative in seven of the eight periods and the positive balance in the eighth period may have been caused by unusual technical problems. The prime importance of dialysis losses in determining overall balance is clear and is particularly illustrated in the study on the fifth patient DR. Here the 5-day alimentary balance periods contained consecutively two and three dialyses. Phosphate balance was positive in the first and negative in the second period. If, for the sake of argument, the dialysis balance routine was divided into consecutive 5-day units a cycle of 35 days duration would elapse before the balance began again on the same day of the week. The 15 dialysis periods in the 35-day cycle would include 6 two dialysis units and one three dialysis unit. The total negative phosphate balance would therefore amount to about 500 mg. Quantities of this order are small compared with approximate estimates of total body phosphate (Documenta Geigy, 6th Edition), but symptoms thought to be due to phosphate deficiency, including bone pain, have developed after experimental depletion maintained over the course of only a few weeks.

Plasma phosphate concentrations did not correlate with the balance data and may not reflect total body phosphate with accuracy. Only one of our patients (ET) had had Aludrox (aluminium hydroxide) and had a normal plasma phosphate concentration. This was apparently achieved at the expense of a gross overall negative phosphate balance, and she was also the only patient in this group to have symptoms of bone disease.

The inherent inaccuracies of balance study techniques and the particular difficulties introduced by haemodialysis dictate that our data should be interpreted with caution. However, net loss of phosphate was consistent and we suggest that the cumulative effects of such degrees of negative balance over many months could be of serious importance in the development of bone disease and perhaps of more generalised ill-health in dialysed patients. Phosphate deficiency could lead to osteomalacia as it may do in individuals who have a specific defect in the renal tubular reabsorption of phosphate. Alternatively, the action on the bone of already elevated concentrations of parathyroid hormone in the blood might be augmented by lowering plasma phosphate. Studies on foetal bone in culture have shown this increased responsiveness in hypophosphataemic media (Raisz, 1970). Furthermore calcium kinetic
data obtained from patients with normal renal function treated with phosphate binders have been said to show increased bone resorption which is consistent with the negative external calcium balance (Lotz et al, 1964). In patients with chronic renal failure the effects of Aludrox upon $^{47}$Ca turnover have been variable and the results are difficult to interpret (Friis & Weeke, 1970). However, in some cases kinetic changes have related to deterioration in the radiological signs during the period of treatment.

**SUMMARY**

Osteomalacia may be due specifically to phosphate deficiency in patients who have taken excessive quantities of antacid or who have a defect in renal tubular conservation of phosphate. We have measured simultaneous alimentary and dialysis phosphate balance in five patients treated on a chronic intermittent haemodialysis programme.

Our results suggest that, under standard dialysis conditions, phosphate depletion may occur which depends on frequency of dialysis treatment and is increased by use of oral phosphate binders. Pre-dialysis plasma phosphate levels were normal or elevated despite overall negative phosphate balance.

Results on one patient studied before and after the start of haemodialysis treatment suggested that relatively more of the dietary phosphate may be absorbed after treatment. Nevertheless this may not entirely correct for losses due to use of phosphate free dialysate and oral phosphate binders. Phosphate depletion may therefore contribute to the cause of bone disease in haemodialysed patients.

**ACKNOWLEDGMENTS**

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OPEN DISCUSSION

A Fournier (Paris): I quite agree with Dr Bishop as regards the question of using phosphate binding agents, but I am not so sure that the use of these agents may cause osteomalacic bone disease provided positive calcium balance is assured by using an appropriate calcium concentration in the dialysate. In the experience of the Mayo Clinic, in spite of the extensive use of Aludrox to keep phosphate in the normal range, we controlled and improved bone disease by using a dialysate calcium concentration of 8 mg/100 ml.

Bishop: In fact I was suggesting that this may be a contributory cause of bone disease. There are many possible causes of bone disease in dialysed patients: it’s a complex subject. Can you be sure in your particular measurements that in fact the calcium was going into bone and not into areas of ectopic calcification?

Fournier: Yes, because calcinosis didn’t increase and furthermore gamma ray densitometry of the bone showed increased density. The results of the bone biopsies support this view.

Bishop: There was improvement in the biopsy?

Fournier: Improvement of the biopsy, yes.

D N S Kerr (Newcastle): Dr Bishop, when looking at phosphate balance in the dialysed patient, one has a problem of which comes first, the chicken or the egg. If the patient is losing phosphate from his bones because of some obligatory process, his plasma phosphate will rise and he will go into negative phosphate balance whatever you do to his external balance. It seems to me that you could only prove your thesis by increasing phosphate intake and showing that this will put the patient back into positive balance: have you tried this?

Bishop: No, we haven’t yet, but I gather that there are people in the audi-
ence who have in fact increased the phosphate input in the dialysate but we haven't tried this, so I can't answer your question.

M H MAXWELL (Los Angeles): This is hard to reconcile with the reports of Michael Kaye in Canada, who, as you know, reports the lowest incidence of bone disease in the literature in chronic dialysis while the basis of his therapy is aluminium hydroxide binding of phosphate and control of the calcium concentration of the dialysate.

I am wondering if the danger, at any given state of activity of the parathyroid glands, and at any given metabolic state, of metastatic calcification particularly in the blood vessels and in the joint spaces, is greater, if the phosphate is permitted to increase with an increase in the calcium phosphate product, than the possible danger of osteomalacia from phosphate depletion?

BISHOP: First of all, I don't believe we have heard any very recent reports of how Kaye's patients have done. The most recent published report is some years old now and I don't believe that at that stage Kaye was in fact biopsying all his patients. In fact in Oxford we have a very low incidence of symptomatic bone disease, although a high incidence of histological bone disease, and we biopsy these people frequently. Secondly, I agree that increasing the phosphate input would give rise to the danger of ectopic calcification and I wouldn't suggest that increasing the input was pushed to this level. I am merely suggesting that we should perhaps use intermittent Aludrox when it is required to bring down the plasma phosphorus concentration to avoid this danger of ectopic calcification, but the patient shouldn't be allowed to continue to take it in the long term once this has been achieved.