SHORT COMMUNICATION

Dissociation between calcium and phosphate absorption in nephrotic syndrome

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Summary

1. Intestinal calcium and phosphate absorption have been measured in nine patients with nephrotic syndrome and normal renal function, by a combined radioisotope technique which allows simultaneous measurement of both quantities. The values obtained were compared with those obtained in 20 normal controls.

2. Calcium absorption in the nephrotic group was significantly lower than in the control group ($P<0.01$), but phosphate absorption in the nephrotic group did not differ from controls.

3. This dissociation between calcium and phosphate absorption provides further evidence for independent mechanisms governing the two absorption processes.

Key words: calcium absorption, nephrotic syndrome, phosphate absorption.

Introduction

Abnormalities of calcium metabolism have been described in patients with nephrotic syndrome and normal renal function. Abnormal calcium absorption has been demonstrated in balance studies [1-3] and by a radioisotope technique [4] but other workers have found normal radiocalcium absorption [5]. Phosphate absorption has only rarely been studied in this situation, but the data available from balance studies [3, 6] have not shown any abnormality. There are no reports of studies of radiophosphorus absorption in such patients. We have studied patients with nephrotic syndrome and normal renal function, using a radioisotope technique which enables the simultaneous assessment of intestinal calcium and phosphate absorption in order to assess the relationship between these two factors in this condition.

Patients and methods

Nine patients with nephrotic syndrome and good renal function were studied. The age range was 16-63 years (mean 35 years). Creatinine clearance ranged from 78 to 148 ml/min (mean 100 ± 7.3 ml/min, normal 75-150). Urinary protein excretion ranged from 4.6 to 36 g/24 h (mean 12.4 ± 2.0, normal <0.05 g/24 h). Plasma albumin ranged from 19 to 36 g/l (mean 29.7 ± 1.9, normal range 35-50 g/l). Plasma calcium ranged from 1.86 to 2.40 mmol/l (mean 2.15 ± 0.05, normal range 2.20-2.63 mmol/l). Plasma phosphate ranged from 0.63 to 1.70 mmol/l (mean 1.11 ± 0.11, normal range 0.80-1.40 mmol/l). Two patients had minimal change nephropathy, two had membranous nephropathy, two had focal segmental glomerular sclerosis and three had recurrent nephrotic syndrome after renal transplantation. These three patients were receiving baseline immunosuppressive therapy (prednisolone 12.5 mg daily and azathioprine 50-100 mg daily). None of the patients was receiving any other therapy apart from diuretics.

A combined radiocalcium and radiophosphate absorption test was performed in each patient. All tests were started at 09.00 hours after a 10-12 h fast. The absorption tests consisted of the administration of oral doses of 5 μCi of $^{45}$Ca with 20 mg of calcium carrier and 5 μCi of $^{32}$P with 50 mg of phosphate carrier dissolved in 250 ml of dilute orange squash. Plasma samples were collected at 0, 15, 30, 60, 90 and 120 min and the activities of
Radioisotopes 45Ca and 32P assessed by liquid scintillation counting [7]. The fractional rates of absorption (α) for calcium (αCa) and phosphate (αPO4) were then calculated as previously described [7, 8] and the 60 min plasma concentrations corrected for extracellular fluid volume (FCA and FP) were also obtained.

The values obtained were compared with those found in a group of 20 normal controls, by the Wilcoxon rank sum test. Correlations between the various indices of calcium and phosphate absorption and other variables were performed by the Spearman rank correlation coefficient (rs).

Results

The fractional rates of absorption for calcium and phosphate (αCa and αPO4) and the corrected 60 min plasma radioactivities of 45Ca and 32P (FCA and FP) for individual patients and in 20 normal controls are shown in Fig. 1. Both αCa and FCA for the nephrotic patients were significantly lower than the corresponding values in normal controls (P<0.01 in both cases), but the nephrotic patients did not differ significantly from controls with respect to αPO4 and FP (Fig. 1). There were significant correlations between αCa and FCA (rs = 0.917, P<0.01) and αPO4 and FP (rs = 0.863, P<0.01). The only indices of calcium absorption and phosphate absorption to correlate were αCa and FP (rs = 0.717, P<0.05). There were no correlations between any of the indices of calcium or phosphate absorption and creatinine clearance or serum albumin.

Discussion

Estimates of calcium and phosphate absorption based on plasma values after oral administration of radioisotopes with low doses of carrier substances only measure selected aspects of the absorption of those substances from the upper gastrointestinal tract. Hence conclusions from the data obtained by such methods cannot necessarily be extrapolated to absorption processes which may occur elsewhere in the gut or to what may be seen during a metabolic balance study. Nevertheless, such estimates of absorption have been shown to correlate with estimates obtained by other methods. Both αCa and FCA have been shown to correlate well with values for net calcium absorption obtained from balance studies [8] and from the double-isotope method [9]. Both αP and FP have been shown to correlate well with values obtained from a double-isotope method [10].

We found a dissociation between the intestinal absorption of calcium and phosphate in patients with nephrotic syndrome and normal renal function. The finding of radio calcium malabsorption confirms the observations of Goldstein et al. [4] and conflicts with those of Mountokalakis et al. [5]. The differences between these studies may be accounted for by differences in calcium intake. In this study calcium intake was assessed as 800-1000 mg daily, a value similar to that of

![Graphs](image-url)
controls. It is thus unlikely that the differences in calcium absorption seen here could be explained on the basis of adaptation. Calcium malabsorption was also found in previous balance studies [1-3]. Our finding of normal phosphate absorption also corroborates previous balance data [3, 6].

Abnormalities of vitamin D metabolism have been described in nephrotic syndrome in the presence of normal renal function. Low serum levels of 25-hydroxyvitamin D (25-OHD) have been attributed to abnormal urinary losses of the protein-bound fraction of this metabolite [4, 11, 12]. Low serum levels of 1,25-dihydroxyvitamin D₃ [1,25-(OH)₂D₃] and 24,25-dihydroxyvitamin D₃ [24,25-(OH)₂D₃] have been described [4], which are inadequately explained solely on the basis of low circulating 25-OHD levels. Abnormal urinary losses of 1,25-(OH)₂D₃ and decreased renal production of this metabolite are possible alternative explanations. Whatever the reason for these abnormalities of vitamin D metabolism, they provide the likely explanation for the calcium malabsorption which occurs and also probably underlie the findings of secondary hyperparathyroidism and osteomalacia which have been reported [13]. It is noteworthy that the calcium malabsorption demonstrated in these patients by balance techniques failed to respond to pharmacological doses of vitamin D [3], which suggests that there may indeed be some impairment of the renal production of active vitamin D metabolites in this situation, as occurs in renal failure.

A dissociation between calcium and phosphate absorption has also been noted in other situations. In chronic renal failure normal phosphate absorption appears to be maintained until a much later stage in the progression of chronic renal failure than does normal calcium absorption [14]. In addition, phosphate malabsorption occurs in some patients after renal transplantation in the presence of normal renal function and normal calcium absorption [14]. There are also reports of differential responses to vitamin D and its analogues and metabolites [15-17]. These observations, together with the dissociation found in this study, suggest that there are separate systems controlling calcium and phosphate absorption.

In this study, normal phosphate absorption has been demonstrated in a situation in which low circulating levels of 25-OHD, 1,25-(OH)₂D₃ and 24,25-(OH)₂D₃ are likely to be present, as has been previously reported [4]. This suggests that intestinal absorption of phosphate can be maintained by vitamin D-independent processes. In experimental animals two separate pathways for phosphate absorption can be demonstrated: an active process, sensitive to 1,25-(OH)₂D₃, which may operate only in special cases such as phosphate deprivation, and a passive process which may operate under normal conditions [18]. This study provides some clinical evidence for a similar system of phosphate absorption in man.

References


