Editorial Comment

PTH, FGF-23 and early CKD*

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Introduction

Patients with early CKD (GFR > 30 ml/min per 1.73 m²) do not usually have changes in the serum calcium and phosphate concentration. PTH may be minimally increased and more recent publications have shown that the phosphaturic hormone, FGF-23, is clearly increased. Thus in early CKD, serum levels of phosphate and calcium are maintained within normal levels because hormonal changes compensate for the decrease in GFR. The aim of the study by Isakova et al. [1] was to analyze postprandial changes in serum calcium and phosphate which may serve as an intermittent stimulus for PTH and FGF-23 production. The study included 21 healthy volunteers and 13 CKD patients with a mean GFR of 41 ± 8 ml/min per m² and normal serum levels of calcium, phosphate and PTH. In the fasting state, CKD patients had significantly higher levels of FGF-23, a higher fractional excretion of phosphate (FEPO4) and a lower fractional excretion of calcium (FECa). After standardized meals, urinary phosphate excretion increased only in healthy volunteers despite unchanged FGF-23 levels and minimal changes in serum phosphate values. Although the postprandial urinary excretion of calcium increased in both groups, a significant reduction in serum calcium with a concomitant, but delayed increase in PTH was observed only in CKD patients. Thus, in this study, FGF-23 did not change in response to a meal (phosphate load). The authors also concluded that a postprandial decrease in serum calcium with enhanced calcium excretion may represent an early mechanism in the development of hyperparathyroidism.

Comments

The initial events responsible for the development of 2° HPT are the accumulation of phosphate, decreased vitamin D production and the need for more PTH to maintain a normal serum calcium concentration. Although deranged mineral metabolism occurs in early stages of CKD, fasting serum levels of calcium, phosphate and calcitriol are frequently normal. These results have been attributed to increased PTH secretion that promotes phosphate excretion, reduces urinary excretion of calcium and stimulates renal production of calcitriol. Thus, it has been generally accepted that a moderate elevation in PTH was responsible during PTH elevation, as is seen in the 2° HPT of vitamin D deficiency, suggests the possibility that even a normal serum phosphate value could contribute to the development of 2° HPT [2]. Recent studies have shown that FGF-23 is an important factor for enhanced urine phosphate excretion in early-to-moderate CKD.

In the study by Isakova et al. [1], CKD patients had normal fasting serum levels of calcium and phosphate. Changes present included reduced calcitriol values, an increased FEPO4 and a decreased FECa. Since PTH was normal, the increased FGF-23 levels may explain the increased FEPO4 in the fasting state. Therefore, if we accept that in the fasting state, mineral metabolism is altered in early CKD, an important lesson to be learned is that an increased PTH may not be the only cause of the increased FEPO4, and thus, PTH may not be the earliest marker of phosphate overload. However, one must be cautious in attributing to FGF-23 the entire control of phosphate in renal failure. With the test meal, FEPO4 increased only in the controls and FGF-23 did not change in either group. In a study, in healthy humans consuming increasing amounts of dietary phosphate, FGF-23 levels decreased despite large increases in the FEPO4 [3]. Moreover, in a recent study in rats, instillation of phosphate directly into the small intestine resulted in a rapid increase in phosphate excretion that was independent of changes in FGF-23, other phosphatonin and renal denervation [4]. Thus, factors besides FGF-23 appear to be important for postprandial phosphate excretion.
Although the authors are to be commended for performing a complex clinical study addressing important clinical questions, we feel that the design of the study could have been improved. First, as was done in the classic studies by Portale et al. in the 1980s [5,6], the participants could have been on a fixed phosphate diet for several days before the test meal. Second, testing of a high phosphate diet (750 or 1000 mg) would have been instructive. Although 1500 mg of phosphate approximates the usual daily intake, the ingestion of phosphate is asymmetric because of differences in meal size and content. Third, because changes in serum calcium were an important feature, measurement of ionized calcium would have been helpful. Finally, it was not explained why dietary calcium content was different between the 500 mg (389 mg calcium) and 250 mg phosphate (272 mg calcium) diets. Such a difference makes a direct comparison of the effect of dietary phosphate on serum calcium and calcium excretion difficult.

Another important observation by the authors is that in both controls and CKD patients, there was a postprandial increase in urinary calcium excretion on both phosphate diets. In only the CKD patients, the increase in calcium excretion was accompanied by significantly reduced serum calcium and increased PTH levels. The decrease in serum calcium in the CKD patients was 0.2–0.3 mg/dl and was first observed at 60 min after the test meal. However, the increase in PTH did not occur until 180 min for the 500 mg phosphate diet and 150 min for the 250 mg phosphate diet. It is possible that the initial decrease in serum calcium could have been in part or entirely due to a dilutional effect of water loading with 1–2 litres ingested during the meal and more during the collection period. In CKD patients, the diminished capacity to excrete a water load would result in a greater dilutional effect. Measurement of ionized calcium is important to answer why PTH did not respond immediately to the decrease in serum calcium. Also, an alkaline tide is generally seen after eating and alkalaeemia has been associated with PTH suppression probably through its effect on the calcium-sensing receptor [7,8]. Perhaps CKD patients with their propensity toward acidosis had less alkalaeemia than normal controls.

The authors conclude that the postprandial calciuria together with the hypocalcaemia is inappropriate in the CKD patient and may represent a previously unreported mechanism of 2nd HPT in CKD patients. While the hypothesis is attractive, it deserves scrutiny. Previous studies have shown that when the GFR falls below 80 ml/min, urinary calcium excretion falls and is generally <60 mg/day. In the study by Isakova et al., we are given the FECa, but not the total amount of calcium excreted. Thus, if the total 24-h calcium excretion in CKD patients is 60 mg and such patients eat three meals per day and FECa increases by threefold after meals, then at most CKD patients would excrete 20 mg during the 4 h after each meal or 60 mg for three meals. Moreover, such a calculation maximizes postprandial calcium excretion because it does not even consider calcium excretion during the 12 h not associated with eating. Thus, if a patient ingested 389 mg of calcium on diet 1, the patient would only need to absorb 5% of the ingested calcium to match urinary calcium losses. For diet 2, 272 mg of calcium, the percent absorption would need to be 7% to match urinary calcium excretion. In summary, it would have been helpful to know the total calcium excreted during the 4-h collection period. It would also seem unlikely that postprandial urinary calcium losses are a major contributing factor to the development of 2nd HPT. If the postprandial decrease in serum calcium is confirmed by ionized calcium measurement, the reason for it could be greater bone or soft tissue deposition of calcium in the CKD patients. The fact that postprandial serum phosphate decreased while phosphate excretion did not change would also seem to support the possibility of enhanced bone or even soft tissue deposition.

Abnormal mineral metabolism is an early complication of CKD that may be a risk factor for cardiovascular events [9,10]. An increase in serum phosphate even within the normal range has been associated with increased cardiovascular events [11] and also is associated with a progressive decrease in renal function [12,13]. Vitamin D insufficiency/deficiency is another key factor in the pathogenesis of 2nd HPT. The current evidence indicates that both phosphate accumulation and vitamin D insufficiency/deficiency have to be treated not only to prevent hyperparathyroidism, but also to prevent mortality and delay the progression to end-stage renal disease. One message of the study by Isakova et al. is that abnormal mineral metabolism is present in early CKD even when PTH is not significantly increased. A strategy to reduce phosphate overload in early CKD by dietary phosphate restriction or phosphate binders may need to be implemented even before the PTH is increased.

Conflict of interest statement. None declared.

References


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