Decreased Bone Turnover after Nephrectomy. Possible Mediation by Endogenous Calcitonin

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Summary

Several biochemical, radiological and histological indices of bone turnover were studied in 27 patients before and after bilateral nephrectomy. Plasma alkaline phosphatase derived from bone fell abruptly after surgery in patients in whom initial activity of AP was increased. This fall in AP was associated with histological evidence of decreased bone turnover, an increase in plasma immunoreactive calcitonin, but no change in plasma immunoreactive parathyroid hormone. It is concluded that in patients with chronic renal failure treated by haemodialysis, low levels of endogenous calcitonin may contribute to increased bone turnover. The reversal of these abnormalities of bone which occur after nephrectomy may be due to increased levels of calcitonin.

Introduction

The kidney appears to be the sole site of 1α-hydroxylation of vitamin D₃ in animals (Midgnett et al, 1973) and synthesis of 1α,25 dihydroxycholecalciferol (1α,25(OH)₂D₃) becomes undetectable in end stage renal disease in man (Mawer et al, 1971, 1973). If diminished production of 1α,25(OH)₂D₃ were a major factor in the aetiology of renal bone disease then all patients with end stage renal disease might be expected to have overt bone disease requiring hormonal replacement therapy. This is not so, which suggests either that 1α-hydroxymetabolites of vitamin D₃ are produced in sufficient quantities in some patients, or that failure to produce these is not necessarily followed by bone disease.

Studies on patients having bilateral nephrectomies provides one method of
distinguishing between these two possibilities since nephrectomy should remove any residual source of 1α,25(OH)₂D₃. Though nephrectomy may result in decreased intestinal absorption of calcium (Oetinger et al, 1974), there is no evidence that nephrectomy has any effect on skeletal metabolism. Indeed Bordier et al (1973) have reported only minimal changes in histology of bone after nephrectomy. The present study suggests that bilateral nephrectomy is followed by a rapid though transient decrease in bone turnover which may be mediated by changes in the metabolism of calcitonin.

PATIENTS AND METHODS

Twenty-seven patients who underwent bilateral nephrectomy before renal transplantation were studied. All patients were established on chronic intermittent haemodialysis (15–24h/wk; Kiil Multipoint) and the duration and frequency of treatment, dialysate calcium (1.53 mmol/l), and dose of phosphate-binding agent [Alucap (Riker Laboratories); generally 1 capsule/7.5 kg body weight/day] were kept constant. No patient had received barbiturates, anticonvulsants, vitamin D, its metabolites or analogues.

Plasma calcium, inorganic phosphate, bicarbonate and alkaline phosphatase (AP) were measured on the Vickers autoanalyser. Plasma immunoreactive parathyroid hormone (iPTH) and calcitonin (iCT) were measured by radioimmunoassay. The assay for iPTH, based on that of Berson et al (1963) used a guinea pig antiserum (Wellcome Laboratories AS 211/32) characterised as having mainly N-terminal specificity (Woo & Singer, 1974; Franchimont & Heynen, 1976), though with possible C-terminal specificity also (antiserum 199 of Barling et al, 1975). The assay used for plasma iCT (Heynen & Franchimont, 1974; Franchimont & Heynen, 1976) detects both the large and small forms of CT (Heynen et al, 1975) found in chronic renal failure.

Transiliac bone biopsies (6 mm Bordier trephine) were fixed in 10% formalin buffered with veronal and longitudinal undecalcified 10μm sections stained for quantitative histological examination.

RESULTS

Activity of plasma alkaline phosphatase (AP) fell rapidly after nephrectomy in the 10 patients in whom the initial AP was above the upper limits of normal (> 120 iu/l). The rate of fall appeared to be a first order process with a calculated half-time of disappearance of 0.8 to 5.6 days (Figure 1). In contrast plasma AP in patients whose initial activity was normal (≤ 120 iu/l) showed no change or small increases, but polyacrylamide gel electrophoresis from 10 patients showed a decrease in AP iso-enzyme from bone irrespective of the initial plasma AP. A new steady state value of AP was seen in all patients 2 months after nephrectomy (Figure 2). Comparable studies were done in a control group of 17
Figure 1. The fall in plasma alkaline phosphatase (AP) after bilateral nephrectomy. Plasma AP is shown on a logarithmic scale plotted against time on a linear scale. The top curve joins observed values and the lower line the observed values less the final (asymptomatic) value.

Figure 2. Plasma alkaline phosphatase (AP) before and 2 months after bilateral nephrectomy in patients with increased (left) and normal (right) pre-operative activities of AP.
dialysed but non-nephrectomised patients undergoing arterial shunt surgery. These control patients had a similar period of bed rest and immobilisation after surgery as did the patients after nephrectomy, but they showed no change in plasma AP.

Histological measurements from paired bone biopsies were taken before and from 0.5 to 12 months after nephrectomy in 11 patients. The operation was associated with a decrease in resorbing surfaces, active osteoblastic surfaces, in the calcification front, and in bone fibrosis when measurements taken within 4 months of nephrectomy were compared with preoperative values (Figure 3).

![Figure 3. The difference in histological measurements from iliac bone biopsies taken before and after nephrectomy. Changes in the resorbing surface (% total trabecular surface), active osteoblastic surface (% osteoid surface), and calcification front (% osteoid surface; toluidine blue) are plotted against the time interval after nephrectomy that the second bone biopsy was taken. Bone fibrosis (semi-quantitative) is shown as lines connecting values observed before and after nephrectomy. Thereafter the differences between pre- and post-operative biopsies decreased and where increases in bone turnover (osteoblastic and resorbing activity) were found plasma AP also rose.

In each of the 3 patients in whom subperiosteal erosions were detected before operation, radiographic healing occurred within the first 5 months after nephrectomy.

Pre-dialysis plasma levels of calcium and bicarbonate measured in 15 patients before and 2 months after nephrectomy did not change significantly, but plasma levels (mean ± SEM) of inorganic phosphate fell from 1.72 ± 0.11 to 1.43 ± 0.08 mmol/l (P < 0.001), despite no apparent change in diet or dose of phosphate-binding agent. Measurements of iPTH and iCT in 7 patients before and
Figure 4. Mean plasma levels of iPTH and iCT (± SEM) before and at intervals after nephrectomy. The numbers refer to the number of observations at each time.

5–9 days after nephrectomy showed no change in iPTH but plasma iCT increased markedly (P < 0.02 – Figure 4). Though subsequent levels of iCT (unpaired data) were still increased they did not differ significantly from pre-operative values.

DISCUSSION

In this study plasma AP fell rapidly after bilateral nephrectomy in those patients in whom the initial activity of AP was increased. Such changes were not observed in patients after arterial shunt surgery who shared a similar convalescence, suggesting that the fall in AP was specific for nephrectomy. The half-life of disappearance of bone AP is probably shorter than AP from other sources and in our patients the half-time equalled the estimated half-time of bone AP (Walton et al, 1975). These data and the iso-enzyme studies support the view that the fall in plasma AP was due to changes in release of the skeletal enzyme which may, moreover, cease altogether at the time of nephrectomy.

The histological findings also suggest that nephrectomy resulted in an immediate decrease in the rate of bone turnover. These changes seem unlikely to be due to random fluctuations in bone turnover or to changes in the sampling site of the biopsy in view of the correlation of plasma AP with the histological and radiographic findings. There was no evidence that nephrectomy was associated
with the development of osteomalacia, suggesting that, if the kidney is the sole site of production of 1α,25(OH)₂D₃, this metabolite does not have a great influence on bone turnover or mineralisation in these patients. Similar conclusions were made by Bordier et al (1973) in their study of the effects of nephrectomy, though they did not show decreases in bone turnover. However, only four paired biopsies were studied, so that time-dependent changes were unlikely to be seen.

It is tempting to suppose that the changes in skeletal turnover after nephrectomy were mediated by the increases seen in plasma iCT. Though interpretation of the results of radioimmunoassay is difficult, due to the uncertain biological nature of the immunoreactive fragments, we have found good correlations of both plasma iPTH and iCT in dialysed patients with histological and indirect estimates of bone turnover (Heynen et al, 1976), suggesting that these assays are measuring fragments of biological relevance.

Low levels of endogenous CT may be one reason for increased bone turnover in patients with chronic renal failure. A rise in plasma CT may be responsible for the decreases seen in bone turnover which occur after bilateral nephrectomy.

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Open Discussion

SWENSON (Palo Alto, California) A number of antihypertensive drugs are associated with elevations in alkaline phosphatase. These drugs may have been discontinued or decreased in dose following surgery. Would you comment on that?

KANIS There is accumulating, though largely unpublished evidence, that hypotensive agents may affect skeletal metabolism. However, in the study presented today we excluded patients in whom there were changes in drug treatment.

VISKOPER (Ashkelon, Israel) Did you see a different pattern of PTH/CT ratio in those uraemic patients with osteosclerosis?

KANIS Our experience of osteosclerosis resembles that of Newcastle, in that we find osteosclerosis associated with osteomalacia. Plasma levels of calcitonin and PTH are no different in our osteomalacic patients than in patients without osteomalacia. We therefore find low levels of PTH and high levels of calcitonin in patients with osteosclerosis.

FOURNIER (Amiens) I want first to say that I am very interested in your study because I have previously studied the effect of binephrectomy on bone histology. I am interested to see that you find a decrease in osteoblastic activity, because when we studied the effect of phosphate-binders on bone histology we found a difference in the behaviour of the bone according to the presence or absence of the kidneys. The patients without kidneys did not increase their osteoblastic activity when their plasma phosphate decreased and this led to an increase of inactive resorption surface, whereas the patients who still had their kidneys increased their osteoblastic surface and their inactive resorption surface did not change. I am glad to see that you did not see any significant change of the calcification front on the biopsies taken after 3 months because this confirms the findings we have already published with P Bordier and J Eastwood.

KANIS In both your studies the times at which the second biopsies were taken would have precluded any chance of seeing this effect.

FOURNIER How do you explain why calcitonin increases, whereas you have no change in PTH after the nephrectomy, since you may assume that the role of the remaining kidneys is probably the same for both PTH and calcitonin degradation?

KANIS Melick and Martin have shown that in the end-stage kidney the half-life of parathyroid hormone is not further increased by binephrectomy. This fits with
our observation that there is no change in the level of PTH. This suggests that, if calcitonin is degraded by the same mechanism as PTH in the end-stage kidney, the changes that we have observed are due to alterations in secretion.

BONE (Liverpool) You have suggested that patients with high PTH and low CT show signs of osteitis fibrosa. Did these patients show radiological signs of hyperparathyroidism such as extensive subperiosteal erosions? Does extraskeletal calcification correlate with hormone measurements?

KANIS Firstly, we have defined increased bone turnover in terms of alkaline phosphatase, marrow fibrosis, osteoblastic activity, and sub-periosteal erosions. Whichever index we have used, our conclusions do not differ. Finally, we do not often see soft-tissue calcification. As far as metastatic calcification is concerned, there is no relationship between its presence and plasma levels of PTH or CT.