PART XII

RENAL OSTEODYSTROPHY

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CESSATION OF BONE LOSS IN CHRONIC RENAL FAILURE BY 1-ALPHA-HYDROXYVITAMIN D₃: A CONTROLLED TRIAL

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Summary

The study was undertaken in patients with chronic renal failure (CRF patients) in order to evaluate 1) the degree and course of skeletal demineralisation and 2) the effect on the bone mineral content (BMC) of long-term treatment with 1α-hydroxyvitamin D₃ (1α(OH)D₃). BMC was measured on the radius by ²⁴¹Am-photonabsorptiometry and the results were corrected for age, sex and bone width. In a cross-sectional study BMC was measured in 191 normal subjects and in 88 renal patients. In a controlled longitudinal trial 22 CRF patients were treated for 25.6 months with 1α(OH)D₃, while 22 CRF patients did not receive vitamin D supplements. In CRF patients an accelerated bone loss (~ 3%/year) and a significantly reduced BMC (mean 87.2% of normal) was found. In the 1α(OH)D₃ treated patients BMC increased on an average 0.9%/year. This was significantly different from the continued bone loss recorded in the non-treated control patients. The data indicate that 1) CRF patients develop reduced bone mass because of accelerated bone loss; 2) cessation of this bone loss may be achieved by long-term treatment with 1α(OH)D₃.

Introduction

Renal osteodystrophy has attracted increasing attention in recent years. This is primarily due to important discoveries in vitamin D metabolism [1]. In 1968 it was demonstrated that vitamin D from the diet is hydroxylated at carbon atom 25 in the liver to form 25(OH)D₃, the major circulating metabolite of vitamin D. In 1970 it was discovered that a very potent metabolite of 25(OH)D₃, 1,25(OH)₂D₃, is produced exclusively in the kidneys. The current opinion is that 1,25(OH)₂D₃ is the metabolically active form of vitamin D and that the kidney can be considered to be an endocrine organ, which synthesises and secretes this calcitropic steroid hormone. Insufficient capacity to biosynthesise 1,25(OH)₂D₃ is proposed as a significant pathogenetic factor in the development of renal osteodystrophy.
A convenient analogue of 1.25(OH)₂D₃, 1α-hydroxyvitamin D₃ (1α(OH)D₃), was synthesised in 1973 [2] and it is now generally accepted that 1α(OH)D₃ is of therapeutic value in the treatment of renal osteodystrophy [3]. However, the effect of 1α(OH)D₃ on the bone mass has still to be evaluated.

Valid measurement of bone mass in chronic renal failure can be performed by gamma-ray densitometry [4] and neutron activation analysis [5]. The first method, by which the bone mineral content (BMC) of a small segment of an appendicular bone is measured, provides at present the most favourable combination of high precision and relatively simple equipment. Furthermore, it has been demonstrated that results from densitometric measurements on the radius are representative of the total amount of calcium present in the body [5].

In the present paper results of a continuing long-term study by bone densitometry on osteopenia in chronic renal failure are assessed. The study was undertaken in order to evaluate 1) the degree and course of skeletal demineralisation, and 2) the effect on the bone mineral content of long-term treatment with 1α(OH)D₃.

Material and Methods

In the cross-sectional part of the study 88 patients (46 females and 42 males) with a mean age of 45.6 years (range 20–68) and a creatinine clearance of less than 30 ml/min were investigated. Forty-seven of these uraemic patients (22 females and 25 males) received maintenance dialysis treatment with a dialysis fluid containing 1.5 mmol calcium per litre. Forty-one non-dialysis patients (23 females and 18 males) had chronic renal failure. Their mean creatinine clearance was 11.4 ml/min (range 3–29). All dialysis patients and 25 of the non-dialysis patients received an oral phosphate binder. The mean duration of uraemia (creatinine clearance < 30 ml/min) was 6.1 years in all the 88 patients (range 0.3–25), 6.7 years in dialysis patients and 5.3 years in non-dialysis patients. To establish the normal range of radial BMC, 191 normal subjects (111 females and 80 males) with a mean age of 40.5 years (range 20–69) were investigated.

In the longitudinal part of the study 44 patients (22 1α(OH)D₃ treated patients and 22 control patients) with chronic renal failure were investigated. As shown in

| TABLE I. Changes in Bone Mineral Content (BMC) in 22 Uraemic Patients Receiving 1α(OH)D₃ Therapy and in 22 Uraemic Control Patients not Receiving Vitamin D Supplemets |
|---|---|---|---|---|
| No. of | Sex | Mean | Duration | BMC (mean ± SD) | BMC change |
| patients | | age | of study | (g/cm²) | (g/cm²) | (%) |
| | | (yrs) | (mths) | Initial | Final | |
| 1α(OH)D₃ group | 12 | F | 45.7 | 26.2 | 0.938±0.180 | 0.953±0.204 | + 1.61 |
| | 10 | M | 42.7 | 24.9 | 1.273±0.227 | 1.301±0.239 | + 2.18 |
| | 22 | F+M | 44.3 | 25.6 | 1.090±0.201 | 1.110±0.220 | + 1.87 |
| Control group | 10 | F | 45.3 | 24.2 | 0.921±0.191 | 0.855±0.178 | − 7.12 |
| | 12 | M | 46.2 | 25.1 | 1.324±0.147 | 1.271±0.169 | − 4.02 |
| | 22 | F+M | 45.8 | 24.7 | 1.141±0.167 | 1.079±0.173 | − 5.43 |
Table I, the two groups were comparable as regards age, sex and duration of study. Duration of uraemia was 6.1 years in the 1α(OH)D$_3$ treated group and 5.7 years in the control group. The treatment group comprised 6 dialysis and 16 non-dialysis patients (mean GFR 9.9 ml/min, range 2–20) and the control group comprised 13 dialysis and 9 non-dialysis patients (mean GFR 8.4 ml/min, range 4–12). All patients in the longitudinal part of the study received an oral phosphate binder throughout the trial. Patients in the treatment group received an oral dose (0.25–2.0 μg/day) of 1α(OH)D$_3$ (Leo Pharmaceutical Products) for an average of 25.6 months and patients in the control group were studied over 24.7 months.

**Investigations**

The bone mass measurements were performed by a modification of the original gamma radiation attenuation method [4]. A gamma-ray densitometer with a 100 mCi $^{241}$Am as radiation source was used. BMC (g/cm) and BMC/bone width (BMC/W; g/cm$^2$) were calculated by a computer programme. The measurements were performed on the radius 6 cm from the distal end of the bone. The BMC was measured on the right forearm if the patient was not left-handed. In dialysis patients with arterio-venous fistulas or shunts on one arm the measurements were performed on the other forearm. The in vivo day-to-day variation of the measurements has been calculated to be 4.1%. The BMC (g/cm) was used for comparisons in the individual, whereas the BMC/W (g/cm$^2$), taking into account the individual variations in size of the bone, was used for comparisons between individuals.

In all patients in the longitudinal study and in 51 of the patients in the cross sectional study the following investigations were performed: serum Ca$^{++}$ [6], phosphate, alkaline phosphatase, i-PTH [7]; skeletal X-ray and $^{99m}$TcTechnetium-polyporphosphate bone scintigraphy [8].

**Results**

**Cross Sectional Study**

The BMC/W values (g/cm$^2$) of 191 normal adults and 88 patients with chronic renal failure are plotted as a function of age in Figure 1. The patients with chronic renal failure exhibited significantly (p < 0.005) reduced BMC/W. The mean BMC/W was on an average reduced to 87.2% of normal and in 22% of the patients the BMC/W was more than 2.5 SD below normal mean.

Reduction of BMC/W was greater in uraemic females than in uraemic males (p < 0.05). When renal diagnoses were considered, patients with polycystic kidney disease demonstrated almost normal bone mass. The duration of renal failure was inversely correlated (r = -0.37, p < 0.01) with BMC/W, whereas BMC/W values were not significantly different whether the patients received dialysis or not or whether the patients had previously been kidney transplanted or not.

Scintigraphic bone changes of renal osteodystrophy were present in 76% of
Figure 1. The bone mineral content/width (BMC/W; g/cm$^2$) of cortical radius in 191 normal adults (shaded area = mean ± SD) and in 88 patients with chronic renal failure ($\bullet$ = mean ± SD). Upper panel: females. Lower panel: males

the patients, radiographic signs of this bone disorder were present in 24% and 10% had bone pain. The BMC/W values were significantly lower ($p < 0.025$) in patients with bone pain and in patients with generalised scintigraphic bone changes ($p < 0.005$), while radiographic signs of renal osteodystrophy were not correlated with the BMC/W values.

Elevated levels of i-PTH were present in 83% of the cases, elevated serum alkaline phosphatase was present in 40% and 52% had decreased Ca$^{++}$. The BMC/W values were significantly lower in uraemic patients with elevated serum alkaline phosphatase and hypocalcaemia ($p < 0.005$), while the i-PTH levels were not correlated with BMC/W.

**Longitudinal Study**

BMC changes over 2 years in 22 uraemic patients receiving 1α(OH)D$_3$ treatment and in 22 uraemic control patients are shown in Figure 2. Fifteen patients in the treatment group increased their BMC during the trial and in 4 patients the increase was significant; the mean increase (1.8%) (Table I) was, however, not significant. Conversely, in the control group 17 patients showed a continuing reduction (mean 5.43%, $p < 0.05$) of BMC during the trial. The difference between the BMC changes in the two groups was highly significant ($p < 0.005$).
Figure 2. Changes of bone mineral content over 2 years (% of basal value) in 22 uraemic patients receiving 1α(OH)D₃ therapy (left) and in 22 uraemic control patients not receiving vitamin D supplements (right). The mean changes are indicated by the thicker lines.

In the treatment group a significant reduction of alkaline phosphatase and i-PTH was found, but despite the fact that a reduction of i-PTH took place in all 1α(OH)D₃ treated patients, i-PTH remained increased in 50% of the patients and in 2 of these patients alkaline phosphatase declined but did not become normal during the trial. The BMC continued to fall in 4 of the patients with persisting increase of i-PTH.

In the control group the reduction of BMC was correlated (p < 0.05) with the initial levels of serum alkaline phosphatase and i-PTH and with the degree of hypocalcaemia.

Discussion

The present investigation demonstrates that osteopenia is an important and frequent component of renal osteodystrophy. The demineralisation of the appendicular skeleton seems to take place at a rate of approximately 3% per year, being most intensive in patients with severe hypocalcaemia and elevated serum alkaline phosphatase and i-PTH. Initiation of dialysis treatment with a dialysis fluid containing 1.5 mmol Ca/L does not seem to reduce progression of the bone loss. Generalised scintigraphic bone changes and bone pain are
predominantly present in patients with severe osteopenia, while radiographic bone changes do not properly reflect the degree of demineralisation. In patients with polycystic kidney disease bone changes are found less frequently than in other renal patients [9]. It was discovered correspondingly that these patients had almost normal BMC. This may indicate that some capacity for 1α-hydroxylation of vitamin D is preserved in the polycystic kidneys.

In the 1α(OH)D₃ treated patients as a group, the BMC did not increase significantly during therapy, but it was striking that the BMC changes were significantly different from the continued bone loss seen in non-treated uraemic patients. This finding indicates that cessation of skeletal demineralisation in patients with chronic renal failure may be achieved with 1α(OH)D₃ treatment. However, significant improvement of mineralisation of the skeleton in uraemic patients may, in accordance with our previous study [10], only be attainable in a minority of CRF patients.

References

2. Holick, MF, Semmler, EJ, Schnoes, HK and DeLuca, HF (1973) Science, 180, 190

Open Discussion

BAILEY (Christchurch) I wonder if you have any information on changes in renal function which occurred in those uraemic patients treated with the 1-alpha. Last week in Toronto at the International Conference on bone measurement, Dr Christianson from Scandinavia reported some data to show that there was a deterioration in renal function in those patients treated with 1-alpha compared with the controls. He was not sure but I suspect it was due to the hypercalcaemia. Have you any comments on that?

MADSEN I agree with you. There have been some reports of more rapid deterioration of renal function during 1-alpha and 1,25 treatment of these patients. As far as I know the trial you refer to is the first trial I have heard about and I think we should remember that we are dealing with patients who all have progressively deteriorating renal function and the groups in such a study need to be very large. Finally I would emphasise that the effect of calcium may give some explanation for those small differences which I have seen. In our study the decrease in the creatinine clearance in the patients was exactly the same in the two groups of patients.
KANIS (Oxford) I wonder whether I could make two comments? The first is that although I agree with your conclusion that the efficiency of 1-alpha hydroxylating capacity may not be the sole factor in the pathogenesis of renal bone disease, even before dialysis treatment, I think that the argument that replacement or treatment with 1-alpha does not reverse the defect is a dangerous one, because the administration of 1-alpha does not reproduce physiological conditions since it is rapidly absorbed and has a very short half-life. From the evidence of failure to reverse defects with 1-alpha, I do not think this is a particularly good argument. I was very pleased to see your results on bone mineral content and they confirm observations that I believe other people are also beginning to make. Again, it may be dangerous to assume that you are in fact treating osteoporosis. I know that isn’t what you claim, but it might be dangerous to assume that. In fact you may be just re-mineralising osteoid that is present because of the uraemic process, and in fact you are not altering total matrix area at all.

MADSEN Well we have not done bone biopsy studies on those patients so I cannot argue with what you say about that, but I would like to agree with you in that I think we are dealing with a multifactorial disease.

FOURNIER (Amiens) You said that you had bone loss of about three per cent, especially in the patients with elevated alkaline phosphatase. When your patients had normal alkaline phosphatase what was the degree of this bone loss, and would it be sufficient to justify 1-alpha treatment systematically to prevent bone loss?

MADSEN To answer the first part of your question, about the alkaline phosphatase, we did not notice any difference in the rate of change in the bone mineral content when the alkaline phosphatase had returned to normal. Whether we would recommend treatment, sort of prophylactically, I would not say absolutely ‘yes’ to that question. I think that some haemodialysis patients who are under very strict control in centres may benefit from treatment, and it will not be very hazardous to those patients without any significant improvement due to the very strict control. As regards children and adolescents I think it has been proven that in renal rickets the drug is beneficial to almost all patients.

LINDERGARD (Lund) I wonder if your patients were also controlled for the length of time on dialysis. We see a loss of mineral mass before dialysis and then regularly an increase in the first year of dialysis, and then they stay pretty well at the same level.

MADSEN I can only speculate on why we don’t find the same thing. I think we are a little alone in this respect. Further studies are necessary to finally settle this problem.