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Anabolic effect of human parathyroid hormone fragment on trabecular bone in involutional osteoporosis: a multicentre trial

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Summary and conclusions

After baseline studies, 21 patients with osteoporosis were treated with human parathyroid hormone fragment (PTH 1-34) given as once-daily subcutaneous injections for 6-24 months. The dose used did not cause hypercalcaemia even in the first few hours after injection. Calcium and phosphate balances improved in some patients, but there was no significant improvement in the group values. There were, however, substantial increases in iliac trabecular bone volume: the mean increase, confirmed by repeat blind measurements, was 70% above mean baseline volume. The new bone was histologically normal. Those patients who had the

largest increases in ⁴⁵Ca-kinetic and histomorphometric indices of new bone formation showed the greatest increases in trabecular bone volume, suggesting that treatment with human parathyroid hormone fragment caused a dissociation between formation and resorption rates that was confined to trabecular bone.

Since vertebrae are four-fifths composed of trabecular bone, this hormone fragment may prove useful in treating patients with the crush fracture syndrome.

Introduction

The rate of renewal of the skeleton in most patients with osteoporosis is about 5% yearly.^{1,2} Thus any treatment aimed at rapidly reversing a typical³ 20% relative deficit in bone mass must increase the rate of formation of new bone. We have reported that giving low doses of synthetic human parathyroid hormone fragment (PTH 1-34) daily for six months roughly doubles the bone formation rate.^{4,5} We report here further results from our multicentre study.

Patients and methods

Sixteen women aged 49 to 78 years (mean 63) and five men aged 52 to 61 years (mean 56) were studied. Each gave informed consent to participation in the trial in the manner approved by his or her local hospital ethical committee. All but one had at least one severe vertebral crush fracture (the mean number being five: the remaining patient had a history of fractures of long bones (table). No patient had received fluoride treatment or a prolonged course of glucocorticoid treatment. The only known precipitating cause for osteoporosis apart from a lack of oestrogen was thyrotoxicosis. This had occurred in one patient and had been successfully treated 35 years before the trial. At the time of acceptance into the study no patient had received pharmacological doses of any vitamin D preparation within two years, although one patient in Boston (case 21) was treated with vitamin D₃ 50 mg (2000 IU) daily for two years before entering the trial, and all the British patients (cases 1-8) were given vitamin D₃ 12.5 mg (500 IU) daily from three months before their baseline values were determined. These doses were maintained throughout the study.

The following indices were normal in all patients: liver function tests, age-corrected and size-corrected glomerular filtration rates, plasma calcium and phosphate concentrations, alkaline phosphatase

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activity, thyroxine and cortisol concentrations, 24-hour urinary calcium and hydroxyproline excretions, faecal fat excretion, and blood count. Three women (cases 21, 24, and 41) were given oestrogen replacement treatment for at least 10 months before entering the study and throughout it. The remaining 14 women were post-menopausal. One of the men (case 43) was given a course of testosterone preparations of the same dose throughout the study.

The degree of incapacity that each patient experienced was assessed before treatment and at the end of treatment on the following scale: 5—bedridden; 4—confined to bed, chair, or wheelchair; 3—ambulatory but lying down more than 12 hours daily; 2—ordinary activities limited by pain; 1—only strenuous activities limited by pain; 0—no activities limited by pain.

KINETICS

The schedule of preliminary investigations, the analytical methods, and the treatment protocol have been described.^{4,6} Before treatment started each patient was admitted for a full 18-day study of calcium, phosphorus, and magnesium balance on a constant diet. In all but four cases this was performed with a continuously administered chromium sesquioxide faecal marker to improve precision. A radio-calcium kinetic study was performed simultaneously to determine the accretion rate of calcium, which is an index of new bone formation.⁷ The bone resorption rate was calculated as the difference between the accretion rate and the calcium balance. Shortly before or immediately after the balance study an 8-mm transiliac trephine biopsy of the iliac crest was performed, usually after double tetracycline labelling.⁸ The biopsy samples were all reviewed by one of us (PJM), and for the sake of consistency the histological results reported here are those obtained in his laboratory alone.

HISTOMORPHOMETRY

Fourteen non-consecutive undecalcified sections were used from each biopsy specimen, of which four were unstained (20 µm) and used for measurement of the tetracycline labels, and 10 were stained (8 µm)—four by the method of Goldner,⁹ four by solochrome cyanine R,¹⁰ and two by toluidine blue. To estimate trabecular bone mass trabecular bone volume was measured as the percentage of the total space between the inner and outer cortices occupied by trabecular bone (including osteoid).^{8,11} Trabecular osteoid volume (VO) was measured as the percentage of trabecular bone volume occupied by osteoid. Bone resorption was estimated both by measuring surfaces showing evidence of osteoclastic resorption as a percentage of total trabecular bone surfaces and by counting osteoclasts (number seen/mm² in the total area between subcortical envelopes). Bone forming activity was estimated from the proportion of trabecular surface covered by osteoid (SO) and by the calcification rate, which was determined by measuring the mean distances between the two

tetracycline labels.⁸ The thickness index of osteoid seams¹² was computed as the ratio: (VO/SO) × 100.

The 10 earliest biopsy samples were taken after inadequate tetracycline labelling and processed in another laboratory in an embedding medium which made subsequent osteoclast counting difficult. The other cause of loss of data was fragmentation of some of the samples. Biopsy samples that were fragmented or that had lost their inner cortical plate and more than one-quarter of their trabeculae were not accepted for the measurement of trabecular bone volume.

TREATMENT

After the initial assessment each patient began treatment with human parathyroid hormone fragment. The initial daily dose of 100 µg was given as a single subcutaneous injection.⁴ In the intravenous chick hypercalcaemia assay¹³ each 100 µg dose of peptide from the first three batches had about the same activity as 500 U of bovine parathyroid hormone (PTH 1-84). The fourth batch, however, proved one and a half times as potent, and three patients in Boston and one in London who had started treatment with it had their doses reduced (cases 8, 21, 22, and 25). The weight of peptide needed to maintain a constant dose in subsequent batches was determined by bioassay using an early batch set aside as a standard and shown to be stable by accelerated degradation tests. This weight had fallen to 50 µg daily by the end of the trial.

In 19 patients all the studies outlined above were repeated six months after the start of treatment, second biopsies being performed on the other iliac crest when treatment was stopped. The other two patients continued treatment for longer: one (case 22) was studied after six months on 740 U/day and again six months later on a reduced dose of 500 U/day; the other (case 21) was studied after 18 months on 740 U/day and again six months later after reduction of the dose to 400 U/day in the 19th month.

Cortical bone densitometry was performed using ¹²⁵I-absorptiometry at the junction of the proximal two-thirds of the radius with the distal third in 14 cases,¹⁴ and using ²⁴¹Am-absorptiometry at the junction of the proximal four-fifths of the femur with the distal fifth in cases 1-8.¹⁵

Results

CLINICAL FINDINGS

No side effects of treatment were noted except transient redness and itching at the injection site in one patient. No qualitative or quantitative changes occurred in any of the formed elements of the blood in association with treatment.

As assessed clinically and by repeat radiography of the dorsal and lumbar spine only one patient suffered a further vertebral fracture during the six-month treatment period. She had earlier reported pain apparently related to this fracture during her baseline study.

Clinical and laboratory findings and results of bone biopsy before and (unless otherwise stated) six months after treatment with human parathyroid hormone fragment in 21 patients with osteoporosis. Dashes indicate results unsatisfactory or not obtained

Case No	Age and sex	No of vertebral fractures		No of peripheral fractures		Accretion rate (mmol ⁴⁵ Ca/24 h)		Calcium balance (mmol/24 h)		Urinary calcium (mmol/24 h)		Urinary hydroxyproline (mmol/24 h)		Alkaline phosphatase (% upper normal limit)		Trabecular bone volume (%)		Trabecular bone volume (%) (Quantimet method)		Surface osteoid (%)		Resorption surfaces (%)		Incapacity index	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	68 F	3	3	1	1	5.8	15.4	-1.6	+1.4	3.0	4.0	274	280	56	74	8.5	9.8	8.3	10.3	26.1	35.8	3.0	1.8	1	1
2	73 F	9	9	0	0	3.7	11.8	-3.0	+1.6	2.3	3.7	201	156	78	106	13.5	18.6	14.0	19.2	32.6	32.1	3.8	2.2	2	1
3	71 F	6	6	0	0	5.9	13.0	+1.2	+4.2	6.8	6.0	254	265	58	70	10.9	—	—	—	—	—	—	—	5.3	1
4	67 F	5	5	3	3	9.9	11.1	+2.6	+2.1	2.5	2.5	142	241	91	88	—	—	—	—	—	—	—	—	—	2
5	74 F	11	11	2	2	7.4	11.1	-0.7	+5.9	3.4	2.8	172	204	85	92	—	10.3	—	—	—	28.9	6.7	3.6	2	
6	77 F	4	5	0	0	5.5	18.5	+0.6	+0.7	4.3	6.0	196	207	89	80	9.2	15.4	8.9	16.9	19.7	36.0	1.6	5.5	2	
7	56 M	4	4	0	0	7.5	20.8	+1.6	+0.4	4.3	7.6	288	313	79	98	—	18.1	—	—	—	28.5	—	9.1	2	
8	53 F	8	8	0	0	10.2	28.5	-1.2	-0.6	4.7	9.2	218	565	104	158	10.6	39.1	9.3	36.6	14.9	45.5	2.9	9.2	1	
21	50 F	0	0	3	3	5.2	11.3	-0.8	-2.1	4.0	3.3	84	116	58	68	8.5†	33.7	8.7	29.9	55.8†	39.2	10.9†	4.4	2	
22	70 F	2	2	0	0	2.2	15.3	-4.1	-8.4	4.2	4.5	151	235	55	107	10.1	16.4	12.7	14.2	14.7	41.8	3.3	5.4	2	
24	58 F	5	5	0	0	4.8	3.1	-4.1	-2.8	5.3	4.7	133	139	102	71	—	8.7	—	—	15.3	29.1	—	2.2	1	
25	57 M	13	13	1	1	5.4	7.1	-5.6	-6.3	6.9	7.0	228	298	55	48	—	10.9	—	—	—	32.5	—	6.8	0	
26	64 F	8	8	1	1	7.0	4.9	-3.4	-1.7	5.0	3.0	165	127	92	89	11.2	11.1	14.1	9.4	23.3	23.8	7.4	6.1	1	
41	52 F	1	1	0	0	0	3.4	+4.1	+1.7	9.9	10.1	129	147	47	44	—	—	—	—	—	—	—	—	—	1
42	52 M	5	5	0	1	4.7	19.2	-1.3	-0.3	12.1	15.5	260	425	66	81	—	—	—	—	—	—	—	—	2	1
43	61 M	1	1	2	2	10.0	19.0	+1.2	+2.6	10.5	10.1	233	347	97	121	—	6.7	—	—	49.1	—	4.8	—	0	0
44	53 M	1	1	0	0	6.0	7.9	+2.3	-0.6	11.6	15.3	258	292	59	55	4.7	6.7	5.1	5.3	31.6	36.2	1.4	4.2	2	1
45	69 F	9	9	0	0	5.3	12.8	-2.5	-5.1	4.9	5.7	199	371	66	68	—	—	—	—	—	—	—	—	2	2
61	51 F	4	4	0	0	13.3	23.8	-4.7	-4.5	6.3	6.7	272	198	92	106	8.9	12.2	7.6	15.9	34.8	28.4	5.5	11.3	1	0
62	49 F	12	12	5	5	1.5	3.6	+1.3	-2.3	4.9	5.6	213	129	73	56	5.2	—	6.0	—	15.1	41.8	3.6	13.1	4	2
63	60 F	1	1	0	0	—	4.3	+1.3	+1.8	5.5	5.8	80	106	61	100	—	7.2	—	11.1	29.0	36.1	—	3.6	2	0

*More biopsies performed after four more months of treatment (given after two-year intermission (case 3) or one-year intermission (case 7) followed by six months of treatment at one-third usual dose) yielded trabecular bone volumes of 17.8% and 23.7% in cases 3 and 7 respectively.

†First bone biopsy performed after four months of treatment and second performed after reduction of dose. Kinetic results obtained before treatment and at time of second biopsy.

‡Second set of results obtained after one year of treatment.

§Third biopsy performed after six more months of treatment (with addition of oestrogen replacement treatment at six months) yielded trabecular bone volume of 12.3% (12.7%; Quantimet method).

Conversion: 51 to traditional units—Calcium: 1 mmol/24 h ≈ 40.1 mg/24 h. Hydroxyproline: 1 mmol/24 h ≈ 131.1 mg/24 h.

There was no significant loss of height over the treatment period (mean $-0.2 \pm \text{SEM } 0.2$ cm). Eight of the 21 patients felt sufficiently better to be regraded in the incapacity index, which therefore improved by a mean of 0.48 ± 0.15 points. No patient became more incapacitated.

BIOCHEMISTRY

There were no significant changes in early-morning fasting plasma calcium and phosphate concentrations, but transient mild hypercalcaemia (rises of 0.3 to 0.4 mmol/l (1.2–1.6 mg/100 ml) above baseline 4–6 h after injection) was seen in four patients (cases 8, 21, 22, and 25), in each of whom it was abolished by reducing the dose of hormone fragment. The serum alkaline phosphatase activity increased by a mean of $15 \pm 7\%$ of its baseline value ($p < 0.05$). Values in the table are expressed as a percentage of the local upper limit of normal because each centre measured it by a different method. The 24-hour urinary hydroxyproline excretion likewise increased by a mean of $26 \pm 10\%$ of baseline ($p < 0.02$), although exceeding the normal range only in case 8. Urinary calcium excretion increased by a mean of 0.8 mmol/24 h (32.1 mg/24 h), which was just significant ($p < 0.05$), as was the mean increase in urinary phosphate excretion (2.4 mmol/24 h (74 mg/24 h)).

MINERAL BALANCE

Despite considerable changes in individual values calcium balance did not change significantly in the group as a whole (baseline mean -0.8 mmol/24 h (32.1 mg/24 h), mean change -0.1 mmol/24 h (-4.0 mg/24 h)). Phosphate balances became more positive but this was only of borderline significance (baseline mean $+0.8$ mmol/24 h ($+24.8$ mg/24 h), mean change $+2.9 \pm 1.7$ mmol/24 h ($+89.8 \pm 52.6$ mg/24 h), $p < 0.1$). Magnesium balances remained unchanged (baseline mean -0.2 mmol/24 h (-4.9 mg/24 h), mean change -0.1 ± 0.3 mmol/24 h (-2.4 ± 6.4 mg/24 h)). True calcium absorption calculated as dietary calcium less faecal calcium corrected for its endogenous component did not change significantly (mean change $+0.2$ mmol/24 h ($+8.0$ mg/24 h)).

The mean change in cortical bone density associated with treatment (as estimated by photon absorptiometry) was insignificantly different from zero ($-1.7 \pm 1.8\%$ of baseline value).

BONE FORMATION AND RESORPTION

There were striking increases in the rate of new bone formation as measured by ^{45}Ca -kinetics, the mean increase being $144 \pm 35\%$ ($p < 0.001$)—equivalent to 7.0 ± 1.3 mmol/24 h (280 ± 52.1 mg/24 h). Trabecular osteoid surfaces also increased (mean increase $+11.8\%$ from an initial mean value of 23.3%, $p < 0.02$), which in relative terms was not so much as the ^{45}Ca -whole-body accretion rate. There were nine pairs of biopsy samples in which the tetracycline double label was well visualised and the calcification rate could be measured satisfactorily. The initial mean value of 630 nm/day increased by an insignificant 40 nm/day as a result of treatment, and since the thickness of osteoid seams was normal increased bone formation must have been due to an increase in forming surfaces. In no case was the calcification rate abnormal.

Histomorphometry of the iliac biopsy samples also showed considerable increases in trabecular bone volume in nine out of the ten pairs of biopsy samples satisfactory for this measurement (fig 1). The mean increase was from a mean volume of 9.3% to a mean volume of 17.3% ($+92\%$ of baseline value). Because the data were skewed they were corrected for determining the level of significance by assessing a logarithmic transformation of the ratios of the values of the second biopsy samples to those of the first. The mean increase thus calculated was under 92% ($+70\%$ of baseline). This increase was significant at the 1% level ($t=3.4$; these figures include those of case 62, see footnote to table). The patient who did not respond to treatment was later found to have developed circulating antibodies to the injected hormone. Because of the importance of this observation the biopsy samples were re-examined blind by one of us (PC) using a Quantimet image-analysing computer, which yielded similar results (table).

The striking increases in accretion rate and bone forming surfaces were accompanied by increases in resorption surfaces, from a mean

FIG 1—Two pairs of biopsy samples from trabecular bone (original magnification $\times 12.5$).

(a) In case 6 before treatment, and (b) after treatment. Mean increase in trabecular bone volume (from 9.1% to 16.1%) was typical of whole group.

(c) In case 8 before treatment, and (d) after treatment. Trabecular bone volume rose from 10.0% to 37.9%: above upper limit of normal.

of 3.9% to a mean of 6.2%. For technical reasons it was possible to count osteoclasts in only six pairs of biopsy samples. In all but one case their numbers increased. The seven technically adequate pre-treatment biopsies yielded a mean osteoclast count of $0.19 \pm 0.05/\text{mm}^2$, and the 14 post-treatment biopsies yielded a mean value of $0.62 \pm 0.14/\text{mm}^2$ ($t=2.89$, $p<0.02$).

Discussion

The increases in trabecular bone volume in these patients treated with synthetic human parathyroid hormone fragment (PTH 1-34) resulted from the formation of new bone on the surface of existing trabeculae, which was shown on detailed examination to be fully mineralised and of normal lamellar texture. Vertebrae, which are normally more than three-quarters composed of trabecular bone, are dependent for their resistance to compressive forces on their bone mineral content,¹⁶ and there appears to be greater loss of trabecular bone than cortical bone in osteoporosis.^{3 17 18} Hence the observed increases in trabecular bone volume produced by treatment with this hormone fragment might usefully increase the strength of the vertebrae in patients with axial osteoporosis.

Because of the relatively wide distribution of the values of the trabecular bone volumes at the time of the second biopsy we attempted to find a measured variable that would provide a predictor to the outcome of treatment, using the trabecular bone volume as the endpoint. A close relation was found between the ^{47}Ca -accretion rate achieved before the end of treatment and final trabecular bone volume (fig 2). The

FIG 2—Relation between trabecular bone volume at time of final bone biopsy and maximum recorded ^{47}Ca -accretion rate during period of treatment.

regression line shown was described by the equation: $Y = 0.79x + 4.51 \pm 5.32$ ($t=5.0$, $p<0.001$, $r=0.81$). Individual changes in trabecular bone volume also correlated well with maximum changes in ^{47}Ca -accretion rate. The regression line was described by the equation: $Y = 0.97x - 1.62 \pm 6.07$ ($t=3.9$, $p<0.01$, $r=0.81$). These results strongly suggest that the size of the improvement in trabecular bone volume is somehow related to the size of the maximum change in ^{47}Ca -accretion rate. Further work is planned to test whether measurement of the accretion rate provides a useful indicator for titrating an effective dose in individual patients.

Despite the encouraging changes in trabecular bone, cortical bone density did not show comparable increases. Furthermore, the balance studies showed no net retention of calcium or phosphate, although the pronounced increases in trabecular bone would have consumed an average of at least 12 mmol calcium/24 h (481 mg/24 h) over six months. These data

suggest that the observed increases in trabecular bone were partly at the expense of cortical bone, and some supporting evidence for this is provided by studies on a subgroup of eight patients whose bone density was measured more often than that in the others and in whom changes in calcium balance correlated closely with changes in bone density in the distal femur (Hesp *et al*, unpublished observations). The adverse trend in cortical bone density associated with treatment, however, was small and could account for only a minor part of the increase in trabecular bone.

The implications of this study for treatment are intriguing since the only other treatments so far shown to have increased trabecular bone volume in osteoporosis used sodium fluoride in doses associated with a high incidence of side effects.^{19 20} Compared with our results in rats,²¹ the failure of human parathyroid hormone fragment to increase dietary calcium absorption was surprising and may have limited the ability of our patients to increase cortical bone mass. Perhaps the increases in plasma concentration of hormone fragment associated with our mode of administration were so brief that the renal 1α -hydroxylase responsible for 1,25-dihydroxycholecalciferol synthesis was not stimulated.²²

Calcium and phosphate retention could perhaps be enhanced (by taking advantage of the temporal relation in the normal physiology of Frost's "basic multicellular unit")²³ with a regimen in which treatment is cyclically interrupted so that the prolonged period of osteoblastic activity after each period of activation is unopposed by excess osteoclasts. Alternatively this hormone fragment might best be used in combination with oestrogen, calcitonin, a diphosphonate, or some other agent that will limit resorption while allowing bone formation to continue. We are currently investigating several of these possibilities.

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Effect of propranolol and metoprolol on parathyroid hormone and calcitonin secretions in uraemic patients

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Summary and conclusions

Nine uraemic patients not being treated by dialysis received intravenous propranolol 1 μ g/kg/min for 85 minutes after a priming dose of 1 mg. Fifteen days later, six of them received intravenous metoprolol 1.2 μ g/kg/min after a priming dose of 1.2 mg. Plasma concentrations of parathyroid hormone (PTH) and calcitonin fell significantly after propranolol but not after metoprolol, whereas no change in plasma concentrations of ionised calcium and phosphate occurred with either drug. Heart rate fell similarly with both drugs.

The fact that propranolol acutely suppressed PTH and calcitonin secretion in uraemic patients indicates that further studies are warranted to assess the long-term effects of the drug on the secretion of these hormones and on renal osteodystrophy. The contrast between the responses to propranolol and metoprolol supports the concept that PTH and calcitonin secretion is modulated through specific beta₂-receptors.

Introduction

Most uraemic patients suffer from two potentially serious complications: hypertension and renal osteodystrophy. In about 20% of the hypertensive patients the hypertension persists despite ultrafiltration and they need antihypertensive drugs.¹ Renal osteodystrophy in patients on long-term haemodialysis is caused mainly by osteitis fibrosa secondary to parathyroid hormone (PTH) hypersecretion.² Insufficient secretion of calcitonin has, however, also been incriminated.³

Interactions between β -adrenergic receptors and secretion of PTH and calcitonin have been shown. For example, in-vitro studies with radioactive hydroxybenzylpindolol⁴ have clearly shown the existence of β -adrenergic receptors in the parathyroid tissue. Furthermore, the fact that isoprenaline had a greater effect in stimulating PTH and adenosine monophosphate secretion than epinephrine and epinephrine a greater effect than norepinephrine suggests that these receptors are of β_2 type.⁴ Finally, propranolol has been shown to prevent the increase of PTH secretion by catecholamines but not the increase induced by hypocalcaemia. The results of these in-vitro studies have been confirmed by in-vivo studies in animals,⁵⁻⁶ but studies in man have given inconsistent results.⁷⁻¹²

Direct evidence of the interaction of β_2 -adrenergic receptors and calcitonin secretion has not been produced, but isoprenaline, epinephrine, and salbutamol have been shown to stimulate calcitonin secretion and propranolol to block it in vitro¹³ and in animals¹⁴⁻¹⁵ and normal men.¹⁶⁻¹⁷ In uraemic patients Heynen *et al*¹⁷ have shown that propranolol can prevent the increase of calcitonin secretion induced by alcohol ingestion.

The data in man are therefore contradictory and concern only propranolol and not the newer cardioselective beta-blockers. Because these newer drugs may offer advantages over non-selective drugs (shorter titration duration, less frequent hypoglycaemia on dialysis, and less bronchoconstriction¹⁸) their use is increasingly being considered in the treatment of hypertension in uraemic men. Since uraemic patients also have a secondary hyperparathyroidism the effects of these two types of beta-blockers on their PTH and calcitonin secretion may be relevant

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