Parathyroid Function in Primary Osteoporosis

B. Lawrence Riggs, Claude D. Arnaud, Jenifer Jowsey,
Ralph S. Goldsmith, and Patrick J. Kelly

From the Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901

A B S T R A C T Two major species of serum immuno-
reactive parathyroid hormone (iPTH) were measured
in 47 untreated patients with primary osteoporosis by
using two highly specific radioimmunoassays. Mean
iPTH was normal with one antiserum but was lower
than normal ($P < 0.001$) with the other. iPTH values
did not correlate with biochemical parameters or with
the proportion of bone-resorbing surfaces in iliac crest
bone biopsy specimens. These data suggest that the in-
creased bone resorption is not due to increased para-
thyroid function in most osteoporotic patients. How-
ever, seven of our patients (15%) appear to represent
a separate population because they had increased values
with one or the other of the antisera.

INTRODUCTION

Because of morphometric (1, 2) and biochemical evi-
dence (3) that bone resorption is increased in primary
osteoporosis and because it is believed that bone resorp-
tion is primarily regulated by parathyroid hormone
(PTH),[1] PTH may play a causal or permissive role
in the pathogenesis of osteoporosis (4-7). However,
parathyroid function has not been assessed directly in
this disorder.

We measured serum immunoreactive PTH concen-
trations (iPTH) in normal and in osteoporotic persons
to determine if parathyroid function is abnormal in os-
teoporosis.

METHODS

We studied 47 ambulatory patients with progressive osteo-
porosis of sufficient severity to produce crush fractures of
the spinal column. The 43 women and four men in the
group had a mean age of 64.9 yr (range, 47-79 yr). No

[1] *Abbreviations used in this paper:* CH-14M, chicken anti-
bovine-PTH antiserum; GP-1M, guinea pig anti-porcine-
PTH antiserum; PTH, parathyroid hormone; iPTH, im-
munoreactive PTH.

patient had any evident medical disease that might produce
osteoporosis and none had any clinically evident condition
that might impair calcium absorption, such as liver disease,
previous subtotal gastrectomy, or sprue. All had normal
serum values for calcium, phosphorus, and alkaline phos-
phatase. Formal studies of intestinal absorption were not
made. iPTH was determined in these patients prior to the
initiation of any form of treatment.

The patients remained on their habitual diets; blood for
serum iPTH determinations was drawn at 8:00 a.m. after
an overnight fast. On the same serum sample, calcium was
determined by atomic absorption spectrophotometry and
phosphorus and alkaline phosphatase, by standard methods.
Bone-forming and bone-resorbing surfaces in an iliac crest
biopsy sample were determined by quantitative microradi-
ography (1) in 27 of these patients.

For control values, serum iPTH and calcium were also
determined in 146 normals, none of whom had a history of
back pain (84 women and 62 men with ages distributed
evenly between 20 and 78 yr); these values include previ-
ously reported data from 52 normal persons (8). Bone
densitometry values (9) of the radius, obtained for two-
thirds of the normals more than 50 yr old, were within the
normal range for their age.

iPTH was measured by radioimmunoassay using two
different antisera (GP-1M and CH-14M). The first assay
system used a guinea pig anti-porcine-PTH antiserum (GP-
1M) and has been described in detail previously (8). It
measures iPTH in greater than 95% of normal sera. Sera
from all patients studied were assayed in this system. The
second assay system used a chicken anti-bovine-PTH anti-
serum (CH-14M). This assay system measures iPTH in
greater than 90% of normal sera. The radioimmunoassay
was performed identically except that it was used at a
higher concentration (1:3,000, compared with 1:100,000
for GP-1M) and that approximately five times less [131]I-
labeled bovine PTH was added to the incubation mixtures
(3,000 cpm for CH-14M compared with 15,000 cpm for
GP-1M). Incubation mixtures with CH-14M were counted
for sufficient times to record 10,000 counts. Standard curves
with CH-14M antiserum using both purified human PTH
from hyperparathyroid serum and a standard preparation
of human PTH obtained from the media of cultured para-
thyroid adenoma explants have been published previously
(10, 11). Sera of 20 of the osteoporotic patients and 36
normals (17 more than 50 yr old) were assayed for iPTH
using CH-14M antiserum. In both assays, the criteria for
a measurable iPTH value were those previously published
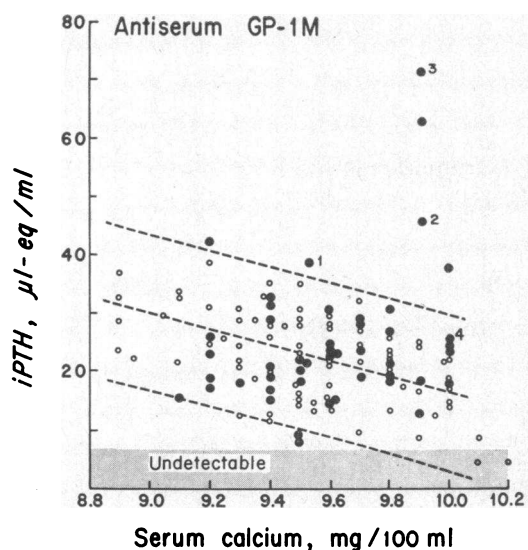(8). Human hyperparathyroid serum was used as a refer-

FIGURE 1 Serum iPTH (antiserum GP-1M) as function of serum calcium. Individual values for normals over age 50 yr are given by (O); regression line and 95% confidence limits are given by broken lines. Individual values for osteoporotic patients are given by (●). Patients designated by numbers 1, 2, and 3 underwent intravenous calcium infusions; iPTH was not suppressed in patients 1 and 2 but was suppressed in patient 3. Patient 4 had high iPTH values with antiserum CH-14M.

ence standard in both assays and the coefficient of interassay variation for replicate determinations was 12–14%.

Two major molecular species of PTH have been previously demonstrated in serum of patients with primary hyperparathyroidism (12, 13). The two antisera used in the present study have markedly different specificities for these two species. Gel-filtration studies of hyperparathyroid sera [2] have demonstrated that antiserum GP-1M predominantly measures PTH immunoreactivity in fractions eluting in a region corresponding to mol wt 7000 whereas antiserum CH-14M predominantly measures immunoreactivity eluting in the region of mol wt 9500. The normal range for iPTH is undetectable to 40 μl-eq/ml measured with GP-1M and undetectable to 250 μl-eq/ml with CH-14M. The difference in the normal ranges obtained with these two antisera probably relates to (a) differences in the specificities of the antisera for the 9500 and 7000 mol wt species of PTH in hyperparathyroid sera and (b) apparent differences in the concentration of these species in the standard hyperparathyroid reference serum. From our studies,[2] there appears to be much less 9500 mol wt than 7000 mol wt species of iPTH in hyperparathyroid serum. Therefore, since CH-14M antiserum is relatively specific for the 9500 mol wt species of iPTH, it would require proportionally more standard hyperparathyroid serum to achieve the same inhibition of the immune reaction than with GP-1M.

RESULTS

iPTH values obtained with antiserum GP-1M. iPTH was measurable in all but four sera from normals;

[2] Arnaud, C. D. Unpublished data.

values did not differ significantly between men and women. There was a small positive regression of iPTH on age ($r = 0.186$, $P < 0.05$). As previously reported (8), there was an inverse correlation of iPTH with serum calcium concentration ($r = -0.53$, $P < 0.001$). For 79 normals more than 50 yr old, mean iPTH ($\pm$SE) was 22.4$\pm$0.9 μl-eq/ml.

For patients with osteoporosis, mean iPTH ($\pm$SE) was 25.1$\pm$1.8 μl-eq/ml (range, 9.0–71.2), not significantly different from that of normals more than 50 yr old. The serum calcium values did not differ significantly in the two groups. There was no significant correlation of iPTH with serum calcium concentration (Fig. 1) or with serum phosphorus or alkaline phosphatase or, in the 27 patients who had iliac crest biopsies, with the proportion of surfaces undergoing formation or resorption.

Six of the 47 osteoporotic patients had iPTH values that were above the 97.5 percentile limit for the regression of iPTH on serum calcium concentration in normals. Three of these six patients subsequently underwent an intravenous infusion of calcium (as the glucoheptonate, 4 mg/kg per h for 4 h in two and 8 h in one); at this time all three were receiving treatment for their osteoporosis (calcium supplements and calcitonin for 6 months in two and phosphate supplements for 3 months in one). iPTH remained unchanged or increased slightly during the 8 h after the beginning of the infusion in two patients; it decreased from 71 to 11 μl-eq/ml in one (Fig. 2). In four normals who received a 4 h infusion of calcium at the same rate, iPTH was undetectable by 2 h and remained so through 12 h (8).

iPTH values obtained with antiserum CH-14M. iPTH was measurable in all but two sera from normals; values did not differ significantly between men and women or between individuals over and under age
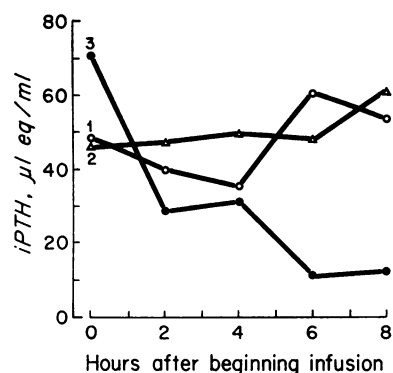

FIGURE 2 iPTH values in three patients who received intravenous calcium infusions (4 mg/kg per h for 4 h in patients 1 and 2 and for 8 h in patient 3). Designation of patients is as in Fig. 1.

50 yr. For these 37 normals, mean iPTH (±SE) was 127.2±9.2 μl-eq/ml. For the 20 osteoporotic patients who also had values determined with this antiserum, mean iPTH (±SE) was 69.9±14.2 μl-eq/ml, significantly lower ($P < 0.001$) than normal. However, one patient had a value higher than normal. In neither normals nor osteoporotic patients was there a significant correlation between iPTH and serum calcium concentration (Fig. 3).

DISCUSSION

iPTH values were not increased in the majority of osteoporotic patients when the assay was based on antiserum GP-1M but they were significantly lower than normal when assayed with antiserum CH-14M. Furthermore, if PTH excess is the sole cause of increased bone loss in osteoporosis, a correlation between iPTH values and the amount of bone-resorbing surface would be expected; this was not found. However, in another study which also used antiserum GP-1M, iPTH values correlated directly with bone-resorbing surface when secondary hyperparathyroidism was induced in osteoporotic patients by chronic therapy with porcine calcitonin (14). Also, iPTH values by either antiserum correlated directly with the osteoclast count and with osteocytic osteolysis in bone from patients with primary hyperparathyroidism.[8] Although it is possible that PTH may play a permissive role, our findings suggest that increased parathyroid function is not a distinguishing feature of most osteoporotic patients and that there may be a partial inhibition of PTH secretion, as previously suggested by us (15).

It is not entirely clear why different results were obtained with the two antisera in the osteoporotic patients. The fraction of iPTH (mol wt ~9500) which CH-14M measures primarily appears to be the principal secretory product of parathyroid glands in vivo (13); this form of iPTH apparently is converted peripherally into a smaller molecule (mol wt ~7000) (13) which GP-1M measures primarily. Our finding that iPTH assayed with CH-14M is lower than normal and iPTH assayed with GP-1M is normal might indicate decreased PTH secretion coupled with decreased rate of metabolism of the lower molecular weight form of the hormone.

The data also suggest that there are two populations of osteoporotic patients—a large majority with normal or decreased parathyroid function and a small minority with increased parathyroid function. The presence of two types of parathyroid function in osteoporosis might explain the failure to observe the expected inverse correlation between iPTH (assayed with antiserum GP-1M) and serum calcium concentration. Of the seven

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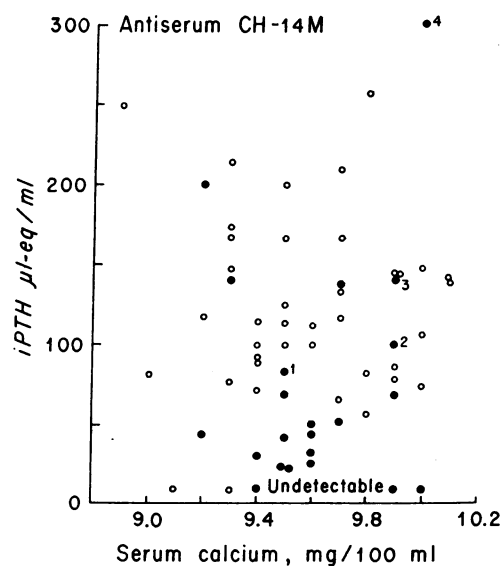[8] Bordier, P., and C. D. Arnaud. Unpublished data.

FIGURE 3 Serum iPTH (antiserum CH-14M) as a function of serum calcium, in normals (○) and in 20 osteoporotic patients (●). Designation of patients 1–4 is the same as in Fig. 1. Patients 1, 2, and 3 were the only patients reassayed with antiserum CH-14M who had higher than normal iPTH values with antiserum GP-1M.

patients with increased iPTH values (six with antiserum GP-1M and one with antiserum CH-14M), five had serum calcium concentrations in the high normal range and it is possible that they represent examples of normocalcemic primary hyperparathyroidism. This possibility is particularly likely in the two patients whose iPTH values were not suppressed by intravenous calcium infusion, although prior treatment may have influenced these results. That more patients had increased values for iPTH with antiserum GP-1M than with CH-14M is consistent with the greater ability of the former antiserum to separate normals from those with primary hyperparathyroidism (16). An alternative possibility is that increased iPTH in these seven patients was due to secondary hyperparathyroidism resulting from occult intestinal malabsorption of calcium.

ACKNOWLEDGMENTS

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