Parathyroid function in primary osteoporosis

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Summary

1. Parathyroid hormone and 25-hydroxy-vitamin D concentrations were measured in patients with severe primary osteoporosis and the results were compared with those found in normal subjects and in patients with primary hyperparathyroidism of vitamin D deficiency.

2. The parathyroid hormone concentrations in 19 patients with primary osteoporosis were within the normal range, both in the basal state (215 ± 85 ng/l, mean ± SD) and during a maximal stimulation (460 ± 154 ng/l) induced by the infusion of disodium EDTA (70 mg/kg body weight). Increased serum concentrations of parathyroid hormone were found in patients with primary hyperparathyroidism (821 ± 323 ng/l, n = 33) and nutritional vitamin D deficiency (565 ± 144 ng/l, n = 11).

3. Serum 25-hydroxy-vitamin D concentrations (16.8 ± 7.7 pg/l) were found to be normal in patients with primary osteoporosis. Slightly (9.1 ± 2.1 pg/l) or markedly lower (2.2 ± 1.1 pg/l) 25-hydroxy-vitamin D concentrations were found respectively in patients with primary hyperparathyroidism and secondary hyperparathyroidism due to vitamin D deficiency. The serum concentration of the vitamin D-binding protein was normal in all groups.

4. A clearcut separation was therefore obtained between osteoporotic subjects (normal parathyroid hormone and normal 25-hydroxy-vitamin D concentrations) and patients with either primary hyperparathyroidism (increased parathyroid hormone and normal 25-hydroxy-vitamin D) or vitamin D deficiency (high parathyroid hormone and very low 25-hydroxy-vitamin D).

Key words: carrier proteins, 25-hydroxy-vitamin D, parathyroid hormone, primary osteoporosis, vitamin D-binding protein.

Introduction

The aetiology of primary osteoporosis, a frequent and sometimes severe disease of the elderly, is still basically unknown (Avioli, 1976). Although parathyroid hormone hypersecretion can occasionally produce a picture resembling primary osteoporosis, the exact role of parathyroid hormone in the pathogenesis of this disease is still disputed. Indirect arguments have been put forward by some workers for an excessive effect of parathyroid hormone on bone (Heaney, 1965; Jasani, Nordin, Smith & Swanson, 1965; Jowsey & Raisz, 1968; Hossain, Smith & Nordin, 1970). Direct measurement of serum parathyroid hormone in osteoporosis has yielded conflicting results (Fujita, Orimo, Okano, Yoshikawa & Shimo, 1972; Riggs, Arnaud, Jowsey, Goldsmith & Kelly, 1973; Berlyne, Ben-Ari, Galinsky, Hirsch, Kushelevsky & Shaikin, 1974). Histological signs of osteomalacia have been found in some British patients with fractures of the proximal femur and this may suggest that slight vitamin D deficiency could at least contribute to the picture of osteoporosis (Aaron, Gallagher, Anderson, Stasiak, Longton, Nordin & Nicholson, 1974). We therefore
measured parathyroid hormone and 25-hydroxyvitamin D concentrations in a group of severely osteoporotic patients and compared the results with those found in patients with either primary hyperparathyroidism or vitamin D deficiency.

**Material and methods**

**Subjects**

Nineteen patients with primary osteoporosis were selected on the basis of multiple fractures of the vertebrae, absence of known secondary aetiological factors and without medical treatment other than analgesics during at least the year before the study. All patients had normal kidney function. Further characteristics are given in Table 1. Nine normal adults (five females and four men), 48 ± 6 (mean ± SD) years old and 12 patients with surgically confirmed parathyroid adenoma were studied similarly (Bouillon & De Moor, 1977). Basal parameters were also obtained in 11 patients with nutritional hypovitaminosis D (nine children and two adults).

**Test procedure**

Disodium EDTA (70 mg/kg body weight), diluted in 500 ml of aqueous 5% glucose solution, was infused over a 2 h period. Blood was collected before and 1, 2, 3 and 4 h after the start of the infusion. The serum was centrifuged at 4°C and kept at −30°C until use.

**Methods**

Serum parathyroid hormone was measured with carboxyl-terminal anti-parathyroid hormone antisemur according to previously described methods (Bouillon, Koninckx & De Moor, 1974; Bouillon & De Moor, 1977). Serum 25-hydroxy-vitamin D was measured by a competitive protein binding assay after Sephadex LH-20 chromatography of the extracted sample (Bouillon, Van Kerckhove & De Moor, 1976). The serum transport protein for vitamin D was measured by single radial immunodiffusion (Bouillon, Van Baelen & De Moor, 1977). Serum calcium, phosphorus, alkaline phosphatase and creatinine were measured according to standard methods on SMA 12/60 (Technicon Instruments Inc., Tarrytown, U.S.A.). Statistical analysis was performed by means of paired or unpaired Student’s t-tests.

**Results**

**Parathyroid hormone**

Serum parathyroid hormone basal concentrations in patients with primary osteoporosis (215 ± 85 ng/l, mean ± sd) (Fig. 1) were not different from those in normal subjects (214 ± 95 ng/l, n = 31).

No difference in the hormone concentrations was found between female and male osteoporotic patients (Table 1). The present carboxyl-terminal antisemur, however, was able to detect a raised basal serum parathyroid hormone concentration in all patients with primary hyperparathyroidism (737 ± 215 ng/l in 27 patients with single adenoma and 1027 ± 812 ng/l in six patients with primary hyperplasia; Bouillon & De Moor, 1977). A raised serum parathyroid hormone was also found in 11 patients with hypovitaminosis D (565 ± 144 ng/l) (Fig. 1).

During hypocalcaemia, induced by the infusion of disodium EDTA, an increase in the serum parathyroid hormone concentration was observed.

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**Table 1. Characteristics of the male and female osteoporotic patients**

Means ± SD are shown. No significant sex difference was observed.

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 9)</th>
<th>Women (n = 10)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 ± 13</td>
<td>62 ± 12</td>
<td>—</td>
</tr>
<tr>
<td>No. of fractured vertebrae</td>
<td>7 ± 3</td>
<td>6 ± 3</td>
<td>0</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>88.4 ± 17.7</td>
<td>88.4 ± 17.7</td>
<td>53.0–106.1</td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.32 ± 0.12</td>
<td>2.40 ± 0.15</td>
<td>2.25–2.64</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/l)</td>
<td>1.1 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>0.8–1.5</td>
</tr>
<tr>
<td>Serum alkaline phosphatase (units/l)</td>
<td>85 ± 17</td>
<td>95 ± 42</td>
<td>40–140</td>
</tr>
<tr>
<td>Urinary calcium excretion (mmol/day)</td>
<td>3.9 ± 2.0</td>
<td>4.7 ± 3.8</td>
<td>1.2–7.5</td>
</tr>
<tr>
<td>Serum parathyroid hormone (ng/l)</td>
<td>214 ± 84</td>
<td>217 ± 83</td>
<td>&lt;60–400</td>
</tr>
<tr>
<td>Serum 25-hydroxy-vitamin D (μg/l)</td>
<td>14.3 ± 8.8</td>
<td>16.7 ± 7.2</td>
<td>5–22</td>
</tr>
</tbody>
</table>
in all osteoporotic subjects with a mean maximal value of 460 ± 154 ng/l (paired t-test <0.001 above basal value) (Fig. 2). No significant difference from the control group (n = 9) was observed, whereas 12 patients with a parathyroid adenoma had significantly higher parathyroid hormone concentrations at all times during the EDTA infusion (Fig. 3).

25-Hydroxyvitamin D

As indicated in Fig. 1, the serum 25-hydroxyvitamin D concentration in primary osteoporosis (16.8 ± 7.7 µg/l) did not differ from the value obtained in a group of 51 healthy controls (13.4 ± 4.1 µg/l) (Bouillon et al., 1976).

The patients with primary hyperparathyroidism showed slightly lower 25-hydroxy-vitamin D concentrations (9.1 ± 2.1 µg/l), whereas those with nutritional vitamin D deficiency had a value of only 2.2 ± 1.1 µg/l.
Vitamin D transport protein concentration

Serum concentrations of the transport protein for vitamin D in patients with primary osteoporosis (351 ± 40 mg/l) were similar to those of normal subjects (340 ± 61 mg/l, n = 181) (Bouillon et al., 1977) and those of the hyperparathyroid patients (354 ± 27 mg/l).

Discussion

Parathyroid hormone basal concentrations were within the normal range in osteoporotic subjects, whereas the same assay detected increased concentrations of parathyroid hormone in other clinical conditions that can produce bone lesions (primary hyperparathyroidism and vitamin D deficiency). A second argument in favour of normal parathyroid function was found in the normal increase of parathyroid hormone during induced hypocalcaemia. This test, with the use of 70 mg of disodium EDTA/kg body weight, is capable of inducing maximal secretion of parathyroid hormone in normal subjects, since the peak values in the present control group were not different from those obtained in normal subjects stimulated with only 50 mg of disodium EDTA/kg body weight (Bouillon & De Moor, 1977). Patients with primary (Bouillon & De Moor, 1977) or secondary hyperparathyroidism (Llach, Massry, Singer, Kurokawa, Kaye & Coburn, 1975), however, respond to this hypocalcaemic stimulation with enhanced parathyroid hormone secretion. Hypoparathyroidism can also be excluded in our osteoporotic patients since this EDTA test is able to detect functional hypoparathyroidism due to hyperthyroidism (Bouillon & De Moor, 1974) and was unable to increase the (low) parathyroid hormone basal concentration in two patients with primary hypoparathyroidism (R. Bouillon, unpublished results).

The present results are essentially in agreement with previous conclusions from basal parathyroid hormone measurement alone in other groups of osteoporotic patients (Riggs et al., 1973; Goldsmith, Jowsey, Dubé, Riggs, Arnaud & Kelly, 1976; Riggs, Jowsey, Kelly, Hoffman & Arnaud, 1976) but are in contrast with the elevated parathyroid hormone concentrations found by other authors (Fujita et al., 1972; Berlyne et al., 1974; Teitelbaum, Rosenberg, Richardson & Avioli, 1976). In at least some of the latter studies the hyperparathyroidism can be explained by an impaired kidney function; indeed, Berlyne's patients (Berlyne et al., 1974; Berlyne, Ben-Ari, Kushelvsky, Idelman, Galinsky, Hirsch, Shainkin, Yagil & Zlotnik, 1975) had slight renal failure, whereas Fujita et al. (1972) and Fujita, Orimo, Okano & Yoshikawa (1973) did not mention the renal function of their patients. This explanation, however, can only be applied to one of six osteoporotic patients with normocalcaemic hyperparathyroidism studied by Teitelbaum et al. (1976). Although some osteoporotic patients thus seem to have hyperparathyroidism due to an impaired kidney function or due to an unknown mechanism (Riggs et al., 1973; Teitelbaum et al., 1976), the majority of the osteoporotic patients detailed in the literature and all of our osteoporotic subjects had a normal parathyroid function. The increased rate of bone resorption found in most osteoporotic patients therefore cannot be explained by simple hyperparathyroidism but could be due to enhanced sensitivity of bone resorption to normal parathyroid hormone concentrations (Heaney, 1965; Jasani et al., 1965). Arguments for the latter hypothesis can be found in the protective effect of parathyroidectomy on the development of experimental osteoporosis (Jowsey & Raisz, 1968) and the modulation of parathyroid hormone responsiveness of bone by oestrogens and calcitonin (Orimo, Fujita & Yoshikawa, 1972; Parfitt, 1976). Nutritional vitamin D deficiency probably does not play a role in simple osteoporosis since we and others (Lund, Sorensen & Christensen, 1975) found normal serum 25-hydroxy-vitamin D concentrations.

The transport protein of vitamin D in serum was also present in normal amount and therefore the 'free' or 'active' 25-hydroxy-vitamin D concentration is also probably within the normal range. A disturbance, however, in the metabolism or action of the more polar metabolites of vitamin D cannot be excluded by the present data. Indeed, the serum concentration of 1,25-dihydroxy-vitamin D was found to be lower in postmenopausal osteoporotic patients than in non-osteoporotic peers. These preliminary data, however, need to be further confirmed, especially since the difference was small (Riggs & Gallagher, 1977).

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