Endocrine Factors in Senile Osteoporosis

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Synopsis

Serum 1, 25-dihydroxyvitamin D \( [1, 25(OH)_2D] \), parathyroid hormone (PTH), calcitonin (CT), calcium, inorganic phosphorus and alkaline phosphatase (Al-P'ase) levels were determined in 24 patients with senile or postmenopausal osteoporosis, which was diagnosed by lateral X-ray film of lumbar vertebrae and divided into 3 stages, porosis score I, II and III according to its severity. Serum calcium in osteoporotic group with porosis score II or III was within normal limits but significantly increased compared to that of the age-matched normal group. There was no significant difference in serum inorganic phosphorus and serum Al-P'ase levels between osteoporotic groups and age-matched normal group. Serum 1, 25(OH)_2D level determined by radioreceptor assay was significantly decreased in the osteoporotic group with porosis score III compared to that of normal group. Serum PTH was supernormal or higher than normal level in all of osteoporotic groups, while serum CT was within normal limits in those osteoporotic groups. There was no significant correlation among serum 1, 25(OH)_2D, PTH and CT or between any of these calcium-regulating hormones and serum calcium, inorganic phosphorus and Al-P'ase, either in osteoporotic groups or in normal group. From these results, it is presumable that a decrease in serum 1, 25(OH)_2D is not the only factor for the pathogenesis of senile osteoporosis, and some abnormality in the receptors of the target organs to 1, 25(OH)_2D_3 or some other factor than 1, 25(OH)_2D_3 might be playing a role for an increase of serum PTH level leading to an increase of bone resorption.

Recently, an abnormality of vitamin D metabolism has been regarded as one of the pathogenesis for senile or postmenopausal osteoporosis. Okano et al. (1976) reported that serum 25-hydroxyvitamin D (25-OH-D) was decreased in senile osteoporosis, while some other group reported that it was normal or rather increased in that disease (Lund et al., 1975). However, the role of 1, 25-dihydroxyvitamin D \([1, 25(OH)_2D_3]\), an active vitamin D metabolite, in the pathogenesis of senile osteoporosis has not been completely elucidated yet.

In the present study, serum 1, 25(OH)_2D level was determined in parallel with the determinations of serum parathyroid hormone (PTH), calcitonin (CT) and other parameters in senile or postmenopausal osteoporosis, in order to elucidate the pathogenesis for senile or postmenopausal osteoporosis from an endocrine standpoint of view.

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Materials and Methods

Osteoporotic patients were consisted of 23 postmenopausal women and one man all above 60 years of age. Normal group included 10 age-matched normal volunteers and patients with nonendocrine diseases all of whom had porosis score 0±. A diagnosis of osteoporosis was made using X-ray film of lumbar vertebrae, and the degree of its severity was divided into 3 stages, porosis score I, II and III. Porosis score I is featured with a decrease in horizontal trabeculae and more prominent vertical trabeculae in the vertebral bodies, porosis score II with further decrease in horizontal trabeculae and coalesced vertical bodies, and porosis score III with hollow vertebral bodies outlined by the shell of cortical bone. Serum PTH, CT, 1, 25(OH)_{2}D, calcium, inorganic phosphorus and Al-P'ase levels were determined in those osteoporotic groups and in normal group.

Serum PTH was determined by radioimmunoassay. Highly purified bovine 1-84 PTH for labeling (Inolex Co., Ltd.) was iodinated with ^{125}I-Na by the chloramine-T method followed by purification through Bio-Gel P-10 column chromatography. Mixture of 100μl antitbovine PTH guinea pig serum specific for both C- and N-terminal region of bovine PTH (Wellcome Research Laboratories, 211/32) diluted with 0.05 M Veronal buffer (pH 8.6) containing 2.5% normal guinea pig serum to initial dilution of 1:40,000, 100μl of unknown sample or highly purified 1-84 bovine PTH (Inolex Co., Ltd.) diluted serially with charcoal-treated human serum, 300μl of 0.05 M Veronal buffer (pH 8.6) containing 1% charcoal-treated serum and 0.05% thimerosal was incubated at 4° for 4 days. After addition of 100μl of ^{125}I-PTH, the mixture was further incubated at 4° for 2 days. For the separation of bound and free of PTH, 100μl of 20 times-diluted antiguinea pig γ-globulin goat serum (Antibodies Incorporated) was added, and the mixture was centrifuged at 4° for 30 min after further 1 day incubation at 4°. Ten % fall from 0 standard in a standard curve of CT was 0.08 ng/ml.

Serum CT was determined by radioimmunoassay. Human CT (Armour Co., Ltd.) was iodinated by chloramine-T method followed by purification through Bio-Gel P-10 column chromatography according to Defios (1974). Mixture of 100μl of antihuman CT rabbit serum (Teikoku Zoki Co., Ltd., final dilution 1:200,000), 200μl of unknown sample or human CT standard diluted serially with charcoal-treated human serum, and 400μl of 0.04M phosphate buffer (pH 7.3) containing 1% charcoal-treated serum, 0.01 M EDTA-Na₄ and 0.01% thimerosal was incubated at 4° for 1 day, and further incubated at 4° for 2 days after addition of 100μl

Results

A. Corrected serum calcium, serum inorganic phosphorus and serum Al-P'ase levels in senile osteoporosis

As shown in Fig. 1, corrected serum calcium levels in senile osteoporosis showed a significant decrease compared to the normal group. The difference was statistically significant at the p<0.05 level.

Fig. 1. Corrected serum calcium levels in senile osteoporosis. Difference from normal group porosis score 0±: * p<0.05, ** p<0.01.
calcium level in the osteoporotic group with porosis score II or III, was within normal limits but significantly increased compared to that in the age-matched normal group (P<0.05, P<0.01, respectively). As shown in Fig. 2 and Fig. 3, there was no significant difference between normal group and osteoporotic groups either in serum inorganic phosphorus or in serum Al-P'ase, although serum Al-P'ase tended to decrease in the osteoporotic group with porosis score III.

B. Serum PTH and serum CT in senile osteoporosis

As shown in Fig. 4, the detection rate of serum PTH was increased in all stages of senile osteoporosis and some patients revealed high PTH levels, while it was detected only in 3 of 10 normal subjects. As shown in Fig. 5, serum CT level did
Fig. 5. Serum CT levels in senile osteoporosis.

Fig. 6. Correlation between serum 1, 25(OH)₂D and serum PTH or CT in osteoporotic group and in normal group.

Table 1. Serum 1, 25(OH)₂D levels in senile osteoporosis

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of cases</th>
<th>Serum 1, 25(OH)₂D (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal group</td>
<td>10</td>
<td>49.6±18.8*</td>
</tr>
<tr>
<td>Osteoporosis with porosis score I</td>
<td>9</td>
<td>51.7±19.9</td>
</tr>
<tr>
<td>Osteoporosis with porosis score II</td>
<td>7</td>
<td>48.5±23.4</td>
</tr>
<tr>
<td>Osteoporosis with porosis score III</td>
<td>4</td>
<td>26.3±10.4**</td>
</tr>
</tbody>
</table>

* Mean±S.E.
* and ** p<0.02.

Fig. 8. Correlation between serum PTH and corrected serum calcium, inorganic phosphorus and Al-Pase in osteoporotic group and in normal group.
not show significant changes in osteoporotic groups compared to that of normal group.

C. Serum 1,25(OH)$_2$D level in senile osteoporosis

As shown in Table 1, serum 1,25(OH)$_2$D level was 51.7±19.9 pg/ml, 48.5±23.4 pg/ml and 26.3±10.4 pg/ml in osteoporotic group with porosis score I, II and III, respectively, while it was 49.6±18.8 pg/ml in normal group, indicating a significant decrease in the osteoporotic group with porosis score III compared to that in normal group (P<0.02).

D. Correlation among serum 1, 25(OH)$_2$D, PTH and CT in senile osteoporosis

As shown in Fig. 6, there was no significant correlation among serum 1, 25-(OH)$_2$D, serum PTH and serum CT levels either in normal group or in osteoporotic groups.

E. Correlation between serum 1, 25-(OH)$_2$D, PTH or CT and corrected serum calcium, inorganic phosphorus or Al-P'ase

As shown in Fig. 7, 8 and 9, there

![Fig. 7. Correlation between serum 1, 25(OH)$_2$D and corrected serum calcium, inorganic phosphorus and Al-P'ase in osteoporotic group and in normal group.](image)

![Fig. 9. Correlation between serum CT and corrected serum calcium, inorganic phosphorus and Al-P'ase in osteoporotic group and in normal group.](image)
was no significant correlation between any of serum 1, 25(OH)₂D, PTH or CT and any of corrected serum calcium, serum inorganic phosphorus or serum Al-Pase either in normal group or in osteoporotic groups.

Discussion

Osteoporosis in the aged human subjects is called senile osteoporosis and especially in women postmenopausal osteoporosis. The incidence of osteoporosis starts to increase around the age of 50, and its incidence is much higher in women than in men. Recently, we reported that serum 25-OH-D decreased with advancing age and in senile osteoporosis (Okano et al., 1976), suggesting an abnormality in vitamin D metabolism as one of the pathogenesis for senile osteoporosis, while it was reported that serum 25-OH-D was normal or rather increased in osteoporosis (Lund et al., 1975). Such an inconsistency in serum 25-OH-D level in osteoporotic patients prompted us to determine serum 1, 25(OH)₂D level in parallel with the determinations of serum PTH and CT levels in senile osteoporosis, in order to elucidate the pathogenesis for senile osteoporosis from an endocrine standpoint of view.

Our present result that serum 1, 25(OH)₂D level is decreased in advanced senile osteoporosis with porosis score III often accompanied by vertebral compression fractures, coincides with a report by DeLuka (1978). However, a decrease of serum 1, 25(OH)₂D level seems not to be the only factor in the pathogenesis of senile osteoporosis, because serum 1, 25(OH)₂D was not necessarily decreased in a slight to moderate degree of senile osteoporosis in the present study. Davies et al. (1977) reported that no abnormality in vitamin D metabolism was detected in osteoporotic patients with vertebral compression fractures in his study observing the response of bone to a small dose of 1, 25(OH)₂D₃. Supernormal or high level of serum PTH in all stages of senile osteoporosis in the present study coincides with a report by Teitelbaum et al. (1976). The present data that serum calcium is significantly increased and serum PTH is relatively higher than normal in advanced osteoporosis, implies a possibility that a decrease in serum 1, 25(OH)₂D level, directly (Okano et al., 1979) or indirectly through a decrease of intestinal calcium absorption, would induce an increase of PTH secretion leading to an increase of bone resorption. On the other hand, normal serum 1, 25(OH)₂D level and rather increased serum PTH level in a slight to moderate degree of senile osteoporosis in the present study would imply a probability that some abnormality in the receptors of the target organs to 1, 25(OH)₂D₃ and/or some other factors than 1, 25(OH)₂D₃, for instance, a decrease of calcium intake, age-dependent decrease of intestinal calcium absorption and a lack of oestrogen, might be playing a role for an increase of serum PTH level leading to an increase of bone resorption.

As to the role of estrogen in the pathogenesis of senile or postmenopausal osteoporosis, it is known that estrogen mainly inhibits bone resorption. It is also reported that the sensitivity of bone to PTH would be increased in postmenopausal osteoporosis as a result of a decrease of serum estrogen level. Recently, Tanaka et al. (1976) reported that estradiol in combination with testosterone promoted the conversion of 25-OH-D₃ to 1, 25(OH)₂D₃ in chick kidney. Rigs (1978) reported that an administration of estradiol to osteoporotic patients increased serum 1, 25(OH)₂D level and improved intestinal calcium absorption. On the other hand, it is also reported that estrogen preparation administered for long period eventually decreased bone formation (Riggs et al., 1972). Even in the osteoporotic patients given estrogen preparation,
progressive bone demineralization was observed, although estrogen seems clearly to delay bone loss lasting at least 10 to 15 years (Davis et al., 1966). In fact, we could not observe a significant difference in serum estradiol level between osteoporotic patients and age-matched normal controls in spite of a significant decrease of serum 25-OH-D level in these osteoporotic patients (Okano et al., 1976).

Contrary to the present results and the report by Teitelbaum et al. (1976) as to the complication of secondary hyperparathyroidism in osteoporosis, it was reported that serum PTH was low in senile osteoporosis (Rigge et al., 1973) and that only about 10% of osteoporotic patients represented secondary hyperparathyroidism (Riggs, 1978). Furthermore, Riggs (1978) proposed to classify osteoporosis into several categories from a standpoint of vitamin D metabolism: 1) disturbance of 25-hydroxylase in liver (decreased serum 25-OH-D), 2) disturbance of 1α-hydroxylase in kidney (increased serum 25-OH-D), 3) insufficient substrates due to nutritional deficiency (decreased serum 25-OH-D), and 4) unrelated to vitamin D metabolism. However, further detailed investigation covering a large number of cases of osteoporosis seems to be necessary for the validation of this proposal. For the time being, it appears to be appropriate to regard osteoporosis as a syndrome induced by various causes. And it will be mandatory to classify osteoporosis by the age of its onset, the sex and nutritional conditions of the osteoporotic patients and so forth for the further elucidation of its pathogenesis.

Furthermore, recent reports that 24, 25-dihydroxyvitamin D₃ [24, 25(OH)₂D₃] is indispensable for normal hatching of chick embryo (Henry and Norman, 1978) and directly inhibited PTH secretion (Okano et al., 1979) and the recent isolation of a low molecular-weight Gla containing protein from bone (Hauschka et al., 1975) would necessitate the investigations on the role of 24, 25(OH)₂D₃ and other unknown vitamin D metabolites as well as vitamin K-dependent bone protein in osteoporosis for further elucidation of its pathogenesis.

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References
