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3. Recent Advances in the Clinical Research of Osteoporosis

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Key words: bone mineral measurement, osteoporosis, bone metabolic markers

The characteristic loss of bone mass in osteoporosis is a common morbid state in elderly people. As the aged population has grown, the management of osteoporosis had attracted more and more attention, not only as a medical problem but also as a social problem. Since osteoporosis usually deteriorates the patients activity of daily life, the osteoporosis in itself does not have much influence upon the life prognosis, therefore long-term management is necessary.

Recently, in the clinical research of osteoporosis has greatly progressed. In this review, some of these studies will be discussed.

I. Diagnostic criteria of involutional osteoporosis

In 1989, the Research Group of Involutional Osteoporosis authorized and conducted by the Japanese Ministry of Health and Welfare proposed new diagnostic

criteria for osteoporosis (Table 1) and this criteria seems to be widely accepted without any serious criticisms. It contain two characteristics to improve the sensitivity and specificity of the diagnosis of osteoporosis.

Firstly, the item of bone mass measurement is emphasized. When the loss of bone mass is diagnosed on the basis of X-ray film of vertebral column, it is not a sensitive means and too objective. On the other hand, an absorptiometry technique such as dual energy X-ray absorptiometry (DXA) is considered to be the most precise method to detect early bone mineral loss. Recent remarkable pervasion of absorptiometry has allowed assessment of bone mass in patient population.

However, the measured bone mineral density (BMD) values obtained by each machine are different and are not comparable mainly due to the differences in soft ware used. Therefore, the adjustment of BMD values

Table 1. Diagnostic Criteria for Involutional Osteoporosis

Items	Point	Diagnosis
Loss of bone mass	3	Sum of the points of items
Fracture		5 points or more; Definite
one spine fracture	1	4 points; Possible
two or more spine fractures	2	3 points; Probable
femur neck fracture	3	2 points or less; Negative
Colle's fracture	1	
Age		Diseases must be ruled out
female less than 55 y.o.	-1	Primary and Secondary hyperparathyroidism
male less than 75 y.o.	-1	Rheumatic arthritis, Bone metastasis of malignancy, Multiple myeloma, Trauma, Osteomalacia, Secondary osteoporosis
Lumbago	1	
Serum Ca, Pi, & Al-P		
all within normal range	1	
abnormal 1 item	0	
abnormal 2 or more items	-1	

from different equipment is particularly important, and after achievement of this issue, it is necessary to set up a reference value for BMD as well as the cutoff value of BMD for the diagnosis of low bone mass. Such efforts are on going (1).

The latter characteristics of the diagnostic criteria, namely, measurement of serum levels of calcium, phosphorus and Al-p activities, allows us to rule out other metabolic bone diseases such as primary hyperparathyroidism and/or osteomalacia. These two diseases sometimes misdiagnosed as osteoporosis. The bone mineral measurement and/or X-ray findings of these diseases are difficult to distinguish from osteoporosis. Since primary hyperparathyroidism is not a rare metabolic bone disease in the elderly population and the existence of an excess secretion of parathyroid hormone leads to a decrease in bone mass, surgical resection of parathyroid tumor is the only method of treatment of this disease. Thus, the diagnostic specificity of this criteria should be improved by the measurement of these chemical indices.

II. New approach to bone metabolism of osteoporosis

As proposed by Riggs and Melton (2), osteoporosis can be divided into two distinct types, one is type I or postmenopausal osteoporosis and the other is type II or senile osteoporosis. It has been reported that these two types of osteoporosis have different bone turnover rates. For example, type I osteoporosis is frequently seen in women at the early menopausal phase and has a higher bone turnover, while type II is usually observed in elderly men and women and shows a low bone turnover. Histologically, a higher bone resorbing activity induced by osteoclasts and an increase in the number of osteoblasts are observed. In spite of the increase in the number of osteoblasts, bone mass is rapidly decreased by about 2–4% annually, because the function of osteoblasts especially the process of bone matrix calcification is decreased due to the lack of estrogen.

However, the decrease in BMD seems to end at 2 to 3 years after artificial menopause despite the continued lack of estrogen (Fig. 1) (3). The rate of bone mineral density (BMD) loss at the first year of artificial menopause is estimated as -10% a year in a longitudinal study (4), while it decreased to -1.5% a year at 2.5 years after the surgery.

Such a dramatic change in the rate of BMD loss after menopause may involve the change in the rate of bone turnover. In fact, the bone metabolic markers including osteocalcin (bone formation marker) and pyridinoline (bone resorption marker) are increased to 180% of the basal values during 2 years after oophorectomy. However, only the bone resorption marker decreased to the basal values, while the serum level of osteocalcin consistently kept the higher level during 4 years after the oophorectomy (Fig. 2) (3). This observation may indicate that the measurements of bone metabolic mar-

Fig. 1. Changes in L2-4 BMD after operation. The lumbar bone mineral density (L2-4BMD) of a total 347 subjects with hysterectomy (open circle) ($n = 121$), with hysto-oophorectomy (closed circle, $n = 151$), and patients before operation ($n = 75$) was measured with dual energy X-ray absorptiometry using Lunar DPX-L. The vaginal pap smear of hysterectomized subjects was examined as their ovarian function is consistent because of superficial cell dominant finding. The subjects were classified into subgroups according to the duration after operation. Here, the subjects before operation are cases at time 0. The mean body size and age of the subjects in each category at time of operation were completely adjusted.

kers provide insight into the bone metabolic balance between bone resorption and formation.

However, the specificity of the markers is still under investigation because the conventional immunoassay systems crossreact with fragments of osteocalcin. Therefore, we attempted to measure the serum osteocalcin level using site-specific enzyme-linked sandwich immunoassay systems. In order to achieve this aim, the intact osteocalcin as well as N-fragment osteocalcin ELISA systems were developed. The serum level of N-fragment osteocalcin well correlated with the number of osteoclasts in bone biopsy samples (Nakamura T. et al personal communication). This information led us to conclude that N-fragment osteocalcin may indicate bone resorption activity. To confirm this possibility, we have measured intact- and N-osteocalcin levels before and after menopause in humans. The results are shown in Figure 3 (5). As indicated in Fig. 3, serum intact/N-fragment osteocalcin ratios are dramatically changed before and after the menopause, namely, the first 4 years after menopause, a dominant increase in N-fragment osteocalcin was observed. The levels of osteocalcin in serum were returned to the premenopausal level thereafter. This observation strongly suggested that the measurements of osteocalcin provide specific information

Fig. 2. Changes in serum levels of osteocalcin (a) and Al-p activities (b), and urinary excretion of hydroxyproline (c). Open circles and closed circles indicate hysterectomized and hystero-oophorectomized subjects, respectively. Serum levels of osteocalcin and Al-p activities in oophorectomized subjects increased and kept higher levels after the operation. On the other hand, urinary excretion of hydroxyproline increased transiently and decreased to the basal value at 4 years after the operation.

about the bone metabolic balance. These assay systems will be available for clinical use in near future.

III. Treatment of osteoporosis

The aim of osteoporosis treatment is considered to prevent fracture occurrence, because a fracture in the vertebral column or femoral neck deteriorate the patient's ability. However, until now, we do not have any tool to increase bone mass and therefore, the initiation of the treatment of osteoporosis must be started at an early phase of bone mass loss. Figure 4 (6) shows the effect of 1α -OHD₃ treatment in oophorectomized subjects. About 10% loss of BMD was observed in the controls (dietary treatment), while only -2.9% decrease in BMD was found in the patients with 0.75 μ g/day of 1α -OHD₃. This observation indicates that the early

treatment with an active vitamin D₃ analogue may prevent early bone mineral loss after oophorectomy and/or natural menopause.

Since osteoporosis is a heterogeneous syndrome, the mode of therapy must be selected case by case theoretically. To achieve this, the efficacy of the therapy should be monitored by the measurement of bone mass and/or by bone metabolic markers.

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Fig. 3. Relationship between serum levels of intact- and N-fragment osteocalcin with special reference to the duration after menopause. Serum levels of intact- (Y-axis) and N-fragment osteocalcin (X-axis) were plotted in accordance with the duration after menopause. N-fragment osteocalcin dominant increase was found after menopause and this was returned to the level of premenopausal value as seen in the group of 20 years after the menopause.

*; $p < 0.05$ in ANOVA

Fig. 4. Effect of $1\alpha\text{-OHD}_3$ on L2-4 BMD in the subjects with premenopausal bilateral oophorectomy. The premenopausal bilateral oophorectomized subjects were treated with dietary therapy (dietary calcium 800 mg/day or more; control) and with 0.25 or 0.75 $\mu\text{g/day}$ of $1\alpha\text{-OHD}_3$ just after the operation. Significant inhibitory effect on the loss of bone mass after oophorectomy was found in 0.75 μg of $1\alpha\text{-OHD}_3$ treated group.

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4. Uremic Bone Disease and Vitamin D

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Key words: parathyroid hormone, 1,25-dihydroxy vitamin D, chronic renal failure, serum calcium

Bone disease is a major morbidity afflicting most patients with chronic dialysis. The pathogenetic factors include hypersecretion of parathyroid hormone (PTH) or secondary hyperparathyroidism, deficiency of active vitamin D molecule (1,25D), hypocalcemia and hyper-

phosphatemia. Among these factors, PTH excess is thought to be the major factor responsible for uremic bone disease in the majority of patients. It is well known that both hypocalcemia and deficiency of 1,25D underlie the hypersecretion of PTH in uremia. The hypocalcemia