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CORRELATIONS AMONG BONE MINERAL DENSITY, INSULIN-LIKE GROWTH FACTORS AND BIOCHEMICAL BONE MARKERS IN HEALTHY FEMALE SUBJECTS

Miyoko SUGITANI, Yoshio MURAKAMI and Yuzuru KATO

First Division, Department of Medicine, Shimane Medical University, Izumo 693-8501, Japan

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Insulin-like growth factor-I (IGF-I) is an anabolic factor for osteoblasts. A positive relationship between bone mineral density (BMD) and circulating IGF-I levels suggest that IGF-I has an endocrine effect on increasing bone mass. In this study, plasma IGF-I and IGF-II were determined in relation to BMD and biochemical bone markers in 228 healthy female subjects. Both BMD and plasma IGF-I levels declined with age. There was no significant correlation between plasma IGF-I levels and BMD, and between plasma IGF-I levels and either plasma carboxy-terminal propeptide of type I procollagen (PICP) or pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) levels. It is suggested, therefore, that the decline in plasma IGF-I levels has little contribution to the decrease in BMD in healthy aged women and that the age-related decrease in plasma IGF-I levels are not associated with changes in biochemical bone markers.

Key words: bone mineral density/insulin-like growth factors/biochemical bone markers

Growth hormone (GH) plays a major role on bone and calcium metabolism. GH effects bone metabolism through hepatic production of insulin-like growth factor-I (IGF-I) as well as by a direct action. It was reported that the patient with GH deficiency of childhood onset presented with a low adult bone mass, suggesting a crucial role of GH in attaining normal peak bone mass (1). The observation that GH replacement therapy resulted in an increase in bone mineral density (BMD) in GH-deficient adult patients (2) indicates that GH or IGF-I might activate bone formation in adulthood as well.

It was demonstrated that plasma IGF-I, IGF-II and IGF-binding protein-3 (IGFBP-3) levels were low in patients with postmenopausal osteoporosis (3). However, a possible role of IGF-I and IGF-II in the postmenopausal decline in BMD in Japanese populations remains to be fully elucidated. In this study, plasma IGF-I and IGF-II were determined in relation to BMD and biochemical bone markers in healthy female subjects to analyze possible correlations among these parameters.

MATERIALS AND METHODS

Subjects

Two hundred twentyeight healthy female subjects aged 20 to 75yrs who received health screening tests at Shimane Institute of Health Science were enrolled in the study. They lived in Izumo city and its surrounding areas in Shimane Prefecture, Japan. All the subjects had no history of such diseases known to affect bone metabolism as diabetes mellitus, rheumatoid arthritis and its related disorders, or glucocorticoid or estrogen administration. Urinary analysis, circulating blood counting and serum biochemistry tests were performed in all the subjects. Eleven subjects out of 239 with high hemoglobin A1c levels (>7%) were excluded from the study. No abnormalities were found in all the other subjects.

Correspondence : Yoshio Murakami, M.D., First Division, Department of Medicine, Shimane Medical University, 89-1 Enya-cho, Izumo 693-8501, Japan.

Determination of BMD

Whole body and lumbar spine BMDs were measured by dual X-ray absorptiometry (DXA) using Hologic QDR-2000 (Hologic, Waltham, MA, USA) under standard conditions according to the manufacturer's instructions.

Assay

Blood samples were obtained at the day of DXA measurement. The serum was separated and stored at -20℃ until assayed.

Plasma IGF-I and IGF-II levels were assayed with specific EIAs (Daiichi Radioisotope, Tokyo, Japan). Plasma carboxy-terminal propeptide of type I procollagen (PICP) and pyridinoline cross-linked carboxy-terminal telopeptide of type I collagen (ICTP) concentrations were determined with commercial RIA kits (Orion Diagnostica, Espoo, Finland).

Statistical analysis

Statistical evaluation was performed by correlation and multiple regression analysis with StatView (J-4.02) on a Macintosh personal computer. A P value less than 0.01 was considered significant.

RESULTS

As shown in Fig. 1, BMD in the lumbar spine and the whole body decreased with age. There was a highly positive correlation between lumbar spine BMD and whole body BMD ($r=0.88$, $P<0.01$).

Plasma PICP but not ICTP levels were elevated in subjects at the age over 50 (Fig. 2). Plasma PICP levels were positively correlated with plasma ICTP levels (Table 1). Plasma IGF-I (Fig. 2) but not IGF-II (data not shown) levels also declined with aging ([plasma IGF-I] $=350.5-3.26\times$[age], $r=-0.623$).

Correlations and partial correlations between whole body BMD, age, IGF-I and IGF-II, and biochemical bone markers were analyzed (Table 1). There was not a

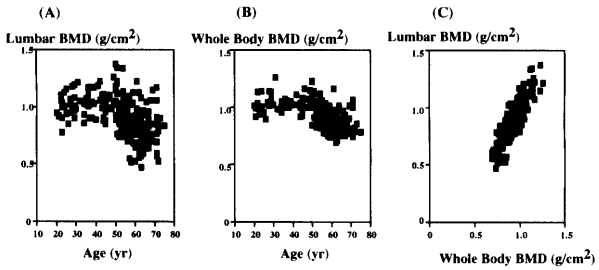

Fig. 1. Correlation among age, lumbar and whole body bone mineral density (BMD) in 228 healthy female subjects at ages of 20 through 75. (A) lumbar spine BMD vs. age. (B) whole body BMD vs. age. (C) lumbar spine BMD vs. whole body BMD.

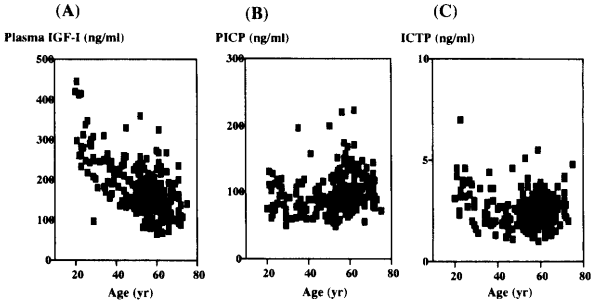

Fig. 2. Plasma IGF-I (A), PICP (B) and ICTP (C) levels in 228 healthy female subjects at ages of 20 through 75.

Table 1. Correlation and partial correlation matrix among whole body BMD, age, and plasma IGF-I, IGF-II, PICP and ICTP levels in 288 healthy female subjects

	BMD	Age	IGF-I	IGF-II	PICP	ICTP
				Correlations		
Whole Body BMD		-0.561	0.373	-0.073	-0.329	0.014
Age	-0.427		-0.632	0.196	0.181	-0.145
IGF-I	0.013	-0.556		0.020	-0.100	0.214
IGF-II	0.062	0.252	0.208		0.078	-0.090
PICP	-0.276	0.009	-0.074	0.110		0.416
ICTP	0.056	-0.026	0.191	-0.133	0.461	
				Partial Correlations		

Table 2. Multiple regression of whole body BMD versus age and plasma IGF-I, IGF-II, PICP and ICTP levels in 228 healthy female subjects

	Coefficient	Standard coefficient	t-value	P-value
Intercept	1.203	1.203	21.241	<0.0001
Age	-0.004	-0.508	-7.045	<0.0001
IGF-I	0.00002255	0.013	0.189	NS
IGF-II	0.00006835	0.052	0.926	NS
PICP	-0.001	-0.261	-4.278	<0.0001
ICTP	0.005	0.051	0.832	NS

significant correlation between IGF-I and IGF-II. A positive correlation was observed between whole body BMD and plasma IGF-I levels. In analyzing a partial correlation, however, there was no significant relationship between these two determinants. There was a negative correlation between whole body BMD and plasma PICP levels. No considerable correlation was observed between plasma IGF-I and PICP or ICTP levels. In multiple regression analysis, age and plasma PICP levels were the only negative factors contributing to whole body BMD ($r=0.610$, adjusted $R2=0.358$) (Table 2).

DISCUSSION

In this study, it was demonstrated that both lumbar spine and whole body BMD declined in female subjects at the age over 50. This observation is on the same line with previous reports (4, 5). There was a positive correlation between lumbar spine and whole body BMD, suggesting systemic metabolic or hormonal factors are involved in a decrease of bone mass in aged female subjects. It is widely accepted that estrogen deprivation is one of key factors in bone loss in postmenopausal women.

Insulin-like growth factor (IGF-I) is an anabolic factor for osteoblasts. A positive relationship between BMD and circulating IGF-I, another index of GH secretion, suggests that IGF-I has an endocrine effect on increasing bone mass (6). Wüster C (3) reported that plasma IGF-I levels were lower in women with primary postmenopausal osteoporosis than in normal subjects and patients with osteoarthritis. In this study, we observed a decline of plasma IGF-I levels with age. Plasma IGF-I levels and age were negatively correlated whereas plasma IGF-I levels did not contribute to the bone mineral density in the multiple regression analysis. The discrepancy between the findings of ours and of Wüster C *et al.* could be due to a difference in the subject groups examined. Healthy female subjects were studied in our study, while Wüster C *et al.* (3) examined patients with established osteoporosis.

Accumulating evidence suggest that GH and IGF-I might be involved in bone remodeling in adult patients with GH-deficiency. It was reported that bone mineral density was increased by the replacement therapy with recombinant human (rh) GH in adult patients with panhypopituitarism (2). Taken together with our observations, it is plausible that bone loss in postmenopausal or senile osteoporosis is different from that in GH-deficiency in the aspect of an involvement of IGF-I.

Plasma PICP and ICTP levels reflect the production and degradation of type I collagen, which were considered as biochemical bone markers for bone formation and resorption, respectively (7). We previously reported that GH replacement therapy increased plasma PICP and ICTP levels in adult patients with GH-deficiency (8). An increase in plasma bone Gla protein levels, a marker of bone formation, during GH administration was also demonstrated in adult patients with panhypopituitarism and isolated GH-deficiency (9). In the present study, however, plasma IGF-I levels were not correlated with either plasma PICP or ICTP levels as well as BMD in healthy female subjects.

We observed a negative correlation between plasma PICP levels and BMD. Plasma PICP levels were elevated in subjects at the age over 50 whereas BMD declined in these subjects. The negative correlation could be attributed to the fact that postmenopausal bone loss is associated with a high turnover of bone metabolism. Thus our findings provide a further evidence that biochemical bone markers, especially plasma PICP levels, might be useful for evaluating the state of bone metabolism.

In summary, our present findings suggest that a decline in plasma IGF-I levels has little contribution to a decrease in BMD in healthy aged women and that the age-related decrease in plasma IGF-I levels are not associated with changes in biochemical bone markers.

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