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Changes in Bone Mineral Density and Metabolism in Women: Evaluation of bodily characteristics, bone metabolic markers and bone mineral density

Tadayuki IIDA[1)], Toshihide HARADA[2,*)], Fumiko ISHIZAKI[2)], Yumiko NITTA[3)], Satomi AOI[2)], Hiromi IKEDA[2)], Chiho CHIKAMURA[2)], Mitsuhisa SHIOKAWA[2)] and Kohsaku NITTA[4)]

1) Department of Public Health, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukakecho, Toyoake, Aichi 470-1192, Japan
2) Faculty of Health and Welfare, Prefectural University of Hiroshima, 1-1 Gakuen-machi, Mihara, Hiroshima 723-0053, Japan
3) Suzugamine Women's College, 4-6-18 Inokuchi, Nishi-ku, Hiroshima 733-8623, Japan
4) Shiraki-no-sato, 230 Shiraki-cho Kogoshi, Asakita-ku, Hiroshima 739-1412, Japan

ABSTRACT

The relationship of bone mineral density (BMD) and bone metabolic markers in women is an interesting field of research. In this study, we aimed to clarify the relationship of body weight, bone metabolic markers and BMD. The subjects were 72 women. The levels of serum bone-specific alkaline phosphatase (BAP), serum type I collagen-cross-linked peptide (s-NTx) and urinary deoxypyridinoline (u-DPD) were measured. The associations between dependent variables (BMD changes/1 or 4 years in the lumbar spine and femoral neck) and explanatory variables (body weight changes/1 or 4 years, the levels of BAP, s-NTx, u-DPD) were evaluated using multiple regression analysis. Changes in the lumbar spine BMD were significantly correlated with changes in height over a year, and those of the femoral neck were significantly correlated with changes in weight over a year. Changes in the lumbar spine BMD over 4 years were significantly correlated with age, BAP and the changes of weight over 4 years. Changes in the femoral neck BMD over 4 years were significantly correlated with the changes in weight for 4 years. These results suggest that BMD changes of different bones correlate with different explanatory variables and that, to predict BMD changes from bone metabolic markers in women, it is necessary to measure BAP levels.

Key words: *Bone mineral density, Bone metabolic marker, BAP, Woman*

Osteoporosis is an important issue in Japan, which is fast becoming a "super-aging" society[1,2,4-9)]. Our previous study showed that menstrual cycle-related changes of estrogen levels were related to changes in bone formation marker levels in menstruating young women[3-5)]. Therefore, it is necessary to identify the menstrual cycle phase before measuring the bone metabolic markers, and then to investigate the association between the bone metabolic markers and BMD reduction. Various studies on changes in the bone mass in women have been performed[1,2,4-10)]. A sufficient bone mass in youth is considered an effective preventive method for osteoporosis[3,8)]. A low body weight affects the bone mineral density (BMD), but no association has been demonstrated between longitudinal changes of body weight and BMD. For all of these reasons, the acquisition of BMD is crucial in women. And thus it is important to detect BMD changes in women promptly, in order to promote osteoporosis prevention. In this study, we investigated the association between changes of BMD and bone metabolic marker levels in women. In addition, we conducted a 1 and 4 year longitudinal study to investigate the effects of changes of body weight and bone metabolic markers on BMD changes.

SUBJECTS AND METHOD

We conducted a survey of 72 healthy middle-aged and older women, of around 40 to 70 years of age. Those with a past history of hospitalization or of being ambulatory patients were excluded. Those with a past history of hysterectomy, oophorectomy and disorders related to bone metabolism (hyperthyroidism, thyrotoxicosis, etc.) were also excluded. Health examinations were carried out once every

*Address correspondence to: Dr. Toshihide Harada
E-mail: hartoshi@pu-hiroshima.ac.jp

Table 1. Height, weight, lumbar spine BMD, femoral neck BMD, BAP, s-NTX and u-DPD in 2007

	2007	
	mean	SD
age	60.5	7.2
Height (cm)	153.5	5.1
Weight (kg)	51.3	7.8
Lumbar spine BMD (g/cm^2)	0.882	0.139
femoral neck BMD (g/cm^2)	0.799	0.144
BAP (U/l)	37.8	11.4
s-NTX (nmolBCE/l)	14.7	6.6
u-DPD (nmol/mmol・ECRE)	4.7	1.4

year from 2007 to 2011. An interview and measurements of physical characteristics, BMD, and biochemical parameters were conducted. Table 1 shows the age, height, weight, lumbar spine BMD, femoral neck BMD, BAP, s-NTX and u-DPD in 2007. The study content and method were sufficiently explained to all subjects, and written consent was obtained before the study. This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of the Hiroshima Prefectural College of Health Sciences.

As physical characteristics, the body weight and height were measured. The BMD (g/cm^2) was measured in the lumbar vertebrae (L2-L4) and left femoral neck using an X-ray BMD measurement system (QDR-4500; Hologic, Bedford, MA, USA). As the biochemical parameters, we measured a bone formation marker, serum bone-specific alkaline phosphatase (BAP), and two bone resorption markers, serum type I collagen-cross linked peptide (s-NTx) and urinary deoxypyridinoline (u-DPD). Blood and urine were collected. Serum samples for BAP and s-NTx measurement were prepared by centrifuging blood at 1,500 × *g* for 10 min. For u-DPD measurement, the urine was collected and centrifuged at 500 × *g* for 5 min, and the supernatant was stored at −20℃. These biochemical measurements were performed by SRL Inc. (Tokyo, Japan) using commercially available kits. The changes in the BMD of the lumbar spine and femoral neck for 1 or 4 years were obtained by subtracting the BMD values measured in 2007 from those measured in 2008, in 2008 from those in 2009, in 2010 from those in 2011, or measured in 2007 from those in 2011. Multiple regression analysis was performed using outcome variables as dependent variables, and the body weight, body weight changes for 1

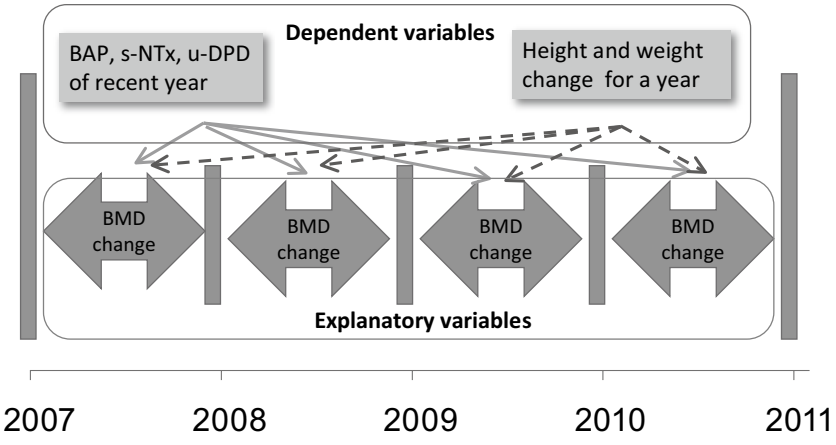

Fig. 1. Multiple regression analysis schedule of BMD changes for a year

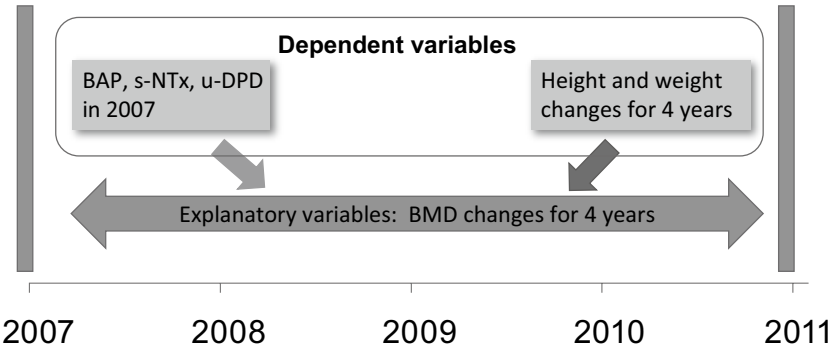

Fig. 2. Multiple regression analysis schedule of BMD changes for 4 years

year, and the levels of BAP, s-NTx and u-DPD of the most recent year as explanatory variables to examine the associations between the variables (Fig. 1). The correlations between the age, height and weight changes for a one year period, and the levels of BAP, s-NTx, u-DPD of a recent year were investigated. No strong correlation (0.7 or higher, $p<0.001$) was noted in any combination of these parameters. In addition, the body weight in 2007 was adjusted as a confounding factor of the multiple regression analysis, because we considered that the BMD would likely be increased by the burden of additional body weight. Multiple regression analysis was performed using outcome variables as dependent variables, and the body weight, body weight changes for 4 years, and the levels of BAP, s-NTx and u-DPD in 2007 as explanatory variables to examine the associations between the variables (Fig. 2). The correlations between the age in 2007, height in 2007, weight in 2007, height and weight changes for a 4 year period, and the levels of BAP, s-NTx, u-DPD in 2007 were investigated. Residual errors of the multiple regression analysis were tested for normal distribution using the Kolmogorov-Smirnov test. The p-values for the lumbar spine and femoral neck were 0.200 and 0.072, respectively, indicating a normal distribution ($p>0.005$). Probability values of 0.05 or lower were regarded as statistically significant in all tests. Statistical analysis was performed using SPSS16.0J software (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Table 2 shows the changes of height, weight and BMD (lumbar spine and femoral neck) for a year. The changes of height for a year were 0.173 ± 1.323 cm/y (2007-2008), -0.267 ± 1.332 cm/y (2008-2009), -0.277 ± 1.320 cm/y (2009-2010) and -0.210 ± 0.472 cm/y (2010-2011). Table 3 shows the changes of height, weight and BMD (lumbar spine and femoral neck) for 4 years. Table 4 shows the results of multiple regression analysis using the age in 2007, height changes for a year, body weight changes for a year, levels of BAP, s-NTx and u-DPD as explanatory variables, and BMD changes as dependent variables. Changes in the lumbar spine BMD were significantly correlated with changes in height for a year ($\beta = 0.204$, $p = 0.022$), and those in the femoral neck were significantly correlated with changes of weight for a year ($\beta = 0.368$, $p<0.001$). Table 5 shows the results of multiple regression analysis

Table 2. Changes of height, weight and BMD for a year (lumbar spine and femoral neck)

	2007–2008		2008–2009		2009–2010		2010–2011	
	mean	SD	mean	SD	mean	SD	mean	SD
Height (cm/y)	0.173	1.323	−0.267	1.332	−0.277	1.320	−0.210	0.472
Weight (kg/y)	−0.900	2.388	0.431	1.670	−2.140	10.113	0.578	5.121
Lumbar spine BMD (g/cm²/y)	−0.050	0.120	−0.019	0.116	−0.010	0.027	−0.010	0.025
femoral neck BMD (g/cm²/y)	0.015	0.051	−0.086	0.147	−0.012	0.018	−0.007	0.018

Table 3. Changes of height, weight and BMD for 4 years (lumbar spine, femoral neck)

	2007–2011	
	mean	SD
Height (cm/4 years)	−0.387	0.970
Weight (kg/4 years)	−1.177	2.173
Lumbar spine BMD (g/cm²/4 years)	−0.049	0.063
Femoral neck BMD (g/cm²/4 years)	−0.063	0.056

Table 4. Multivariate linear regression analysis of the changes of BMD for a year (lumbar spine, femoral neck)

	Lumbar spine BMD (g/cm² /year)			Femoral neck BMD (g/cm² / year)		
	β	p	R^2	β	p	R^2
Age	−0.068	0.460	0.076	−0.019	0.811	0.179
Changes of height for a year (cm/y)	0.204	0.022		−0.060	0.456	
Changes of weight for a year (kg/y)	0.050	0.960		0.368	<0.001	

Table 5. Multivariate linear regression analysis of the changes of BMD for 4 years (lumbar spine, femoral neck)

	Lumbar spine BMD (g/cm² /4 years)			Femoral neck BMD (g/cm² /4 years)		
	β	p	R^2	β	p	R^2
Age in 2007	0.446	0.007	0.285	−0.086	0.598	0.073
Height in 2007 (cm)	−0.006	0.967		−0.026	0.872	
Weight in 2007 (kg)	−0.146	0.341		−0.268	0.104	
BAP (U/l) in 2007	0.327	0.035		−0.053	0.744	
s-NTX (nmolBCE/l) in 2007	−0.175	0.239		−0.008	0.958	
u-DPD (nmol/mmol・CRE) in 2007	−0.034	0.818		0.058	0.727	

Table 6. Multivariate linear regression analysis of the changes of BMD for 4 years (lumbar spine, femoral neck)

	Lumbar spine BMD (g/cm² /4 years)			Femoral neck BMD (g/cm² /4 years)		
	β	p	R^2	β	p	R^2
Age in 2007	0.514	0.001	0.427	−0.027	0.867	0.146
Changes of height for 4 years (cm/4 years)	0.128	0.334		0.008	0.956	
Changes of weight for 4 years (kg/4 years)	0.388	0.006		0.380	0.016	
BAP (U/l) in 2007	0.276	0.050		−0.055	0.742	
s-NTX (nmolBCE/l) in 2007	−0.057	0.678		0.092	0.560	
u-DPD (nmol/mmol・CRE) in 2007	−0.079	0.534		−0.070	0.650	

using the age in 2007, height in 2007, body weight in 2007 and levels of BAP in 2007, s-NTx in 2007 and u-DPD in 2007 as explanatory variables, and BMD changes as dependent variables. The changes in lumbar spine BMD for 4 years were significantly correlated with the age in 2007 ($\beta = 0.446$, $p = 0.007$) and BAP in 2007 ($\beta = 0.327$, $p = 0.035$). Table 6 shows the results of multiple regression analysis using the age in 2007, changes of height for 4 years, changes of weight for 4 years and the levels of BAP in 2007, s-NTx in 2007 and u-DPD in 2007 as explanatory variables, and BMD changes as dependent variables. The changes in the lumbar spine BMD for 4 years were significantly correlated with the age in 2007 ($\beta = 0.514$, $p = 0.001$), the changes of weight for 4 years ($\beta = 0.388$, $p = 0.006$) and BAP in 2007 ($\beta = 0.276$, $p = 0.050$). The changes in the femoral neck BMD for 4 years were significantly correlated with the changes in weight for 4 years ($\beta = 0.380$, $p = 0.016$).

DISCUSSION

Multiple regression analysis showed that the change of the lumbar spine BMD was significantly correlated with the changes of height for a year, and that of the femoral neck was significantly correlated with the changes of weight for a year. Tetraplegia, postoperative bed rest, and weightlessness in space flight were associated with a BMD decrease. We consider that the load of the body weight on different parts of the body mechanically stimulates bones, thereby strengthening the microstructure of bone tissue. In particular, the results of this study suggest that the BMD changes of the femoral neck are at least partly induced by body weight changes in daily life, and that the loss of body weight decreases the BMD of the femoral neck. Accordingly, the maintenance of an appropriate body weight greatly aids in the prevention of osteoporosis in women who are prone to prioritizing their desire for slimness. Meanwhile, based on the results of mouse studies in which BMD changes were accompanied by a body weight change, it is speculated that leptin regulates bone mass via a balance between indirect action through the nervous system and direct action on osteoclasts[3-5]. The epidemiological survey performed a cross-sectional study for men and women and reported a positive correlation between blood leptin levels and the BMD[3-5]. Therefore, the present finding of a BMD change accompanied by a body weight change was tentatively attributed to changes in BMD due to the load of the body weight, as well as the regulation of bone mass by leptin. In order to clarify this result, it is necessary to measure leptin levels on a continuous basis in a longer-term study.

In this four-year-follow-up study on women, the fact that osteoporosis is regarded as a lesion of the entire physiological system suggested that the relationship between BMD levels of the lumbar spine and femoral neck in our study displayed a biological coherence. High s-NTx levels were not found to have a relationship with BMD reductions of the lumbar spine four years later. It is recognized that bone resorption markers are not an absolute index but rather a useful substitute in measuring fracture risk. This can be regarded as biologically coherent because an increase in s-NTx levels reflects an augmentation of bone resorption. Accordingly, s-NTx levels can be utilized not only as diagnostic and therapeutic indices, but also for the actual

prevention of osteoporosis. Higher levels of weight produce a larger load on the spine, consequently preventing bone loss. Higher weight levels were found to increase s-NTx and u-DPD levels over a four year period while preventing BMD reductions of the lumbar spine[2-7]. This may suggest that the increase in spinal load due to the higher weight intensifies the formation and absorption of bone and consequently inhibits bone loss[2-7]. This requires further confirmation by an examination of the levels of bone formation markers. Higher BMD levels of the lumbar spine lowered the risk of incurring abnormally high u-DPD levels four years later[2-7]. As the bone metabolism in women with high BMD levels is still unclear, it is necessary to study changes in bone metabolism markers longitudinally among them. Since our subjects showed almost the same anthropometric (height, weight, and BMI) averages as women of a similar age in Japan, it is suggested that the results of our study can be applied to average healthy women of around 40 to 70 years of age.

Age, weight, 4 year changes and BAP level were correlated with 4 year changes in the BMD of the lumbar spine, suggesting that a high BAP level is associated with an increase in lumbar spine BMD. It has been shown that the BAP level increases earlier than the osteocalcin(OC) level after the first menstruation because it reflects bone growth more markedly than OC[3-5]. The OC level serves as a preventive factor against BMD reduction and reflects osteoblast activity, and the bone-forming activity inhibits BMD reduction[3-5]. One limitation of this study is that the subjects were females participating in a health survey, including a BMD measurement, and therefore it might show a bias toward those who were in good health or had a marked health awareness.

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