

## Research Article

# Divergent Significance of Bone Mineral Density Changes in Aging Depending on Sites and Sex Revealed through Separate Analyses of Bone Mineral Content and Area

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Received 15 June 2012; Revised 27 August 2012; Accepted 24 September 2012

Academic Editor: Harri Sievänen

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Bone mineral density (aBMD) is equivalent to bone mineral content (BMC) divided by area. We rechecked the significance of aBMD changes in aging by examining BMC and area separately. Subjects were 1167 community-dwelling Japanese men and women, aged 40–79 years. ABMDs of femoral neck and lumbar spine were assessed by DXA twice, at 6-year intervals. The change rates of BMC and area, as well as aBMD, were calculated and described separately by the age stratum and by sex. In the femoral neck region, aBMDs were significantly decreased in all age strata by an increase in area as well as BMC loss in the same pattern in both sexes. In the lumbar spine region, aBMDs decreased until the age of 60 in women, caused by the significant BMC decrease accompanying the small area change. Very differently in men, aBMDs increased after their 50s due to BMC increase, accompanied by an area increase. Separate analyses of BMC and area change revealed that the significance of aBMD changes in aging was very divergent among sites and between sexes. This may explain in part the dissociation of aBMD change and bone strength, suggesting that we should be more cautious when interpreting the meaning of aBMD change.

## 1. Introduction

Bone mineral density (aBMD) decreases with age [1] and it is the most significant and widely used index for the diagnosis of osteoporosis and for considering the effects of medication in its treatment [2]. When an aBMD decrease is found, the cause is usually considered to be a decrease in bone mineral content (BMC) in the region measured. ABMD is equivalent to BMC divided by an area. Since areal BMD depends both on bone mineral content and bone dimensions, it is difficult to interpret unambiguously [3]. Dimensional changes occur in long bone by aging [4–6], the shape of the bone, and conditions like osteophytes or vertebral fracture in lumbar spine [7–9] are well known. These can affect the measuring area of DXA examinations, and naturally their results. However, a longitudinal epidemiological DXA study

on aging considering the effect of the area has not been carried out on a large scale, although there have been cross-sectional studies [10–17]. This study was performed in order to reconsider the significance of aBMD change and aging in different anatomical locations, by analyzing the longitudinal changes of both components of aBMD, namely, BMC and the area, and comparing the differences in sex. A large cohort for longitudinal studies of local inhabitants was used for this study.

## 2. Materials and Methods

**2.1. Subjects.** The subjects were selected among people who participated in both the 1st and 4th waves of the National Institute for Longevity Sciences Longitudinal Study

of Aging (NILS-LSA). Details of the NILS-LSA are presented elsewhere [18]. It is a biannual examination checking the physical and mental condition of ordinary Japanese people, so as to clarify the effect of aging. It is conducted by the National Center for Geriatrics and Gerontology (NCGG), in Japan. The National Institute for Longevity Sciences (NILS) is a research section of NCGG. The participants were chosen randomly from the residents of Obu city and Higashiura-cho, in Aichi prefecture, Japan. For this study, data from 1167 persons were analyzed ( $59.2 \pm 10.9$ , mean  $\pm$  SD). Participants were 594 men and 573 women, whose ages ranged from 40 to 79 at the time of the 1st wave. The 1st and 4th waves were from November 1997 to April 2000, and June 2004 to July 2006, respectively.

**2.2. Measurements of Bone Mineral Density.** Areal bone mineral densities (aBMD) were measured using Hologic QDR4500, both at the 1st and 4th wave. Only one DXA scanner was used. Data on the right femoral neck (Figure 1) and the lumbar spine (L2–4) were used for the analysis. Coefficients of variance of the DXA instrument for aBMD were 1.3% (femoral neck), 1.0% (trochanter), and 0.9% (L2,1–4) [19]. ABMD is equivalent to BMC divided by an area, so the following formula was used for the theoretical calculation:  $\text{aBMD (g/cm}^2\text{)} = \text{BMC (g)}/\text{Area (cm}^2\text{)}$ . Therefore, not only aBMD values but also those of BMC and the area measured were used for the analysis in the three different regions above. The annual change rates (CR) were calculated by the following formula.  $\text{CR (\%)} = (\text{the values in the 4th} - \text{the values in the 1st})/\text{the values in the 1st} \times 100/6$ . The CRs of aBMD, BMC, and the area measured were calculated and described separately by the age stratum of 40s, 50s, 60s, and 70s and by sex. All who were 40 to 49 years at baseline belonged to the 40's age stratum, and so forth. Data are presented as the mean  $\pm$  SD, including those in figures. The study protocol was approved by the Committee on Ethics of Human Research of the National Institute for Longevity Sciences. Written informed consent was obtained from each subject.

**2.3. Statistical Analyses.** The statistical analyses were made to test for significance of change (versus no change) in each subgroup defined by age decade and sex, using paired *t*-tests. Also, the trend analyses according to the increase of the age stratum were made for each subgroup using a general linear model procedure. Gender difference was checked for each subgroup. All analyses were conducted using SAS Ver. 8.2 (SAS Institute, Cary, NC, USA).

### 3. Results

Characteristics of subjects were shown in Table 1.

The change rates (CR) from the first to fourth what were expressed as an annual rate. Mean variation between the two DXA measurements was 6 years.

**3.1. Femoral Neck Region.** ABMDs significantly decreased in all age strata both in women ( $-1.1 \pm 1.1\%$  in 40s,  $-1.2 \pm 0.9\%$

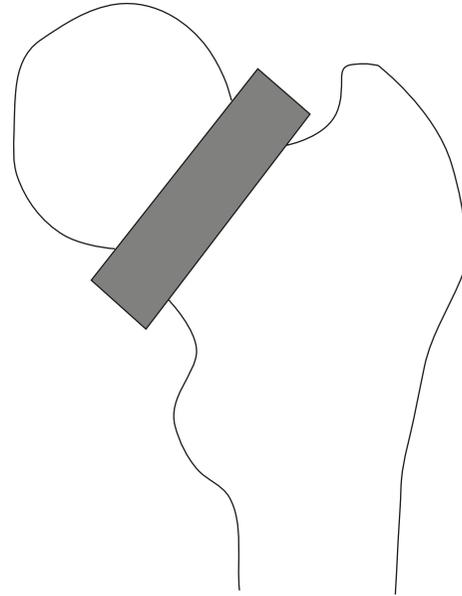
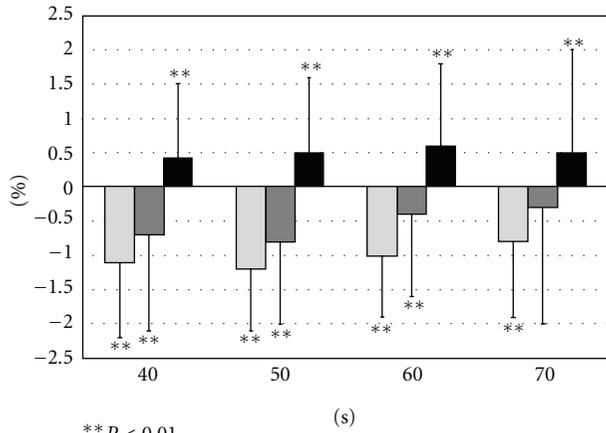


FIGURE 1: Femoral neck region of interest, derived from the Hologic QDR 4500 Operator's Manual.

in 50s,  $-1.0 \pm 0.9\%$  in 60s, and  $-0.8 \pm 1.1\%$  in 70s, all  $P < 0.01$ ) and in men ( $-0.4 \pm 0.8\%$  in 40s,  $-0.5 \pm 0.7\%$  in 50s,  $-0.6 \pm 0.9\%$  in 60s, and  $-0.6 \pm 1.0\%$  in 70s, all  $P < 0.01$ ) (Figures 2(a) and 2(b)). These declines were caused not merely by the decrease of BMC in most of the age strata (in women,  $-0.7 \pm 1.4\%$  in 40s,  $-0.8 \pm 1.2\%$  in 50s, and  $-0.4 \pm 1.2\%$  in 60s, all  $P < 0.01$ , and in men,  $-0.2 \pm 0.9\%$  in 50s and  $-0.2 \pm 1.1\%$  in 70s, with  $P < 0.01$  and  $P < 0.05$ , resp.), but also by the constant or significant increase of the area measured (in women,  $0.4 \pm 1.1\%$  in 40s,  $0.5 \pm 1.1\%$  in 50s,  $0.6 \pm 1.2\%$  in 60s, and  $0.5 \pm 1.5\%$  in 70s, all  $P < 0.01$ , and in men,  $0.4 \pm 0.6\%$  in 40s,  $0.3 \pm 0.8\%$  in 50s,  $0.4 \pm 0.8\%$  in 60s, and in  $0.4 \pm 0.8\%$  in 70s, all  $P < 0.01$ ). This trend was the same in both sexes. The change rates (CR) of the aBMD and BMC, however, were different between women and men in their 40s, 50s, and 60s (Table 2). The CR became higher (in absolute value) only in women according to age in aBMD and BMC ( $P$  trend = 0.0126 and 0.0027, resp.). As for the CR of the area, no significant trend according to age was observed in both sexes, and no sex difference was observed (Table 2).

**3.2. Lumbar Spine Region.** ABMDs significantly decreased in women in their 40s, 50s, and 60s ( $-1.1 \pm 1.2\%$  in 40s,  $-1.0 \pm 0.9\%$  in 50s, and  $-0.2 \pm 1.1$  in 60s, with  $P < 0.01$ ,  $P < 0.01$  and  $P < 0.05$ , resp.) (Figure 3(a)). At earlier ages, these declines were caused by a significant decrease in BMC ( $-1.2 \pm 1.5\%$  in 40s and  $-1.2 \pm 1.2\%$  in 50s, both  $P < 0.01$ ) accompanied by a small but significant decrease in the area. After their 60s, however, no further decrease in BMC occurred, and the small but significant increase of aBMD was caused by the significant increase in the area.

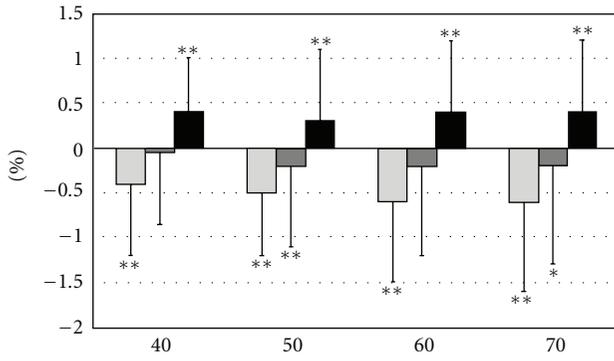
The patterns of aBMD changes were much different in men. BMDs significantly increased in the 50s, 60s, and 70s ( $0.3 \pm 0.8\%$ ,  $0.5 \pm 1.5\%$ , and  $0.3 \pm 1.0\%$ , all  $P < 0.01$ ) due to



\*\*P < 0.01  
 BMD  
 BMC  
 AREA

(s)

(a)



\*P < 0.05, \*\*P < 0.01  
 BMD  
 BMC  
 AREA

(s)

(b)

FIGURE 2: (a) Changes in the femoral neck region by age group in women. Results are the mean ( $\pm$ SD) CR of four different age strata. \*\*P < 0.01. (b) Changes in the femoral neck region by age group in men. Results are the mean ( $\pm$ SD) CR of four different age strata. \*P < 0.05, \*\*P < 0.01.

the significant increase of BMC ( $0.5 \pm 1.0\%$  in 50s,  $1.0 \pm 3.4\%$  in 60s, and  $0.4 \pm 1.2\%$  in 70s, all  $P < 0.01$ ) (Figure 3(b)). The areas significantly increased in every age stratum ( $0.1 \pm 0.5\%$  in 40s,  $0.2 \pm 0.5\%$  in 50s,  $0.4 \pm 1.2\%$  in 60s, and  $0.2 \pm 0.6\%$  in 70s, all  $P < 0.01$ ). Since the increase of BMD occurred after the 50s, the rates of BMC increase surpassed those of the area. The change rates (CR) of the aBMD, BMC, and area were different between women and men in their 40s, 50s, and 60s (Table 2). And in women the CR increased according to age in aBMD, BMC, and area ( $P$  trend < 0.0001,  $P$  trend < 0.0001, and  $P$  trend = 0.0115, resp.). The CR increased in men according to age in aBMD and BMC ( $P$  trend = 0.006 and  $P$  trend = 0.027, resp.), but not in area (Table 2).

TABLE 1: Characteristics of subjects.

	Women	Men
Age (years)	56.5 $\pm$ 9.9	57.9 $\pm$ 9.9
Height (cm)		
All	152.2 $\pm$ 5.7 (n = 573)	165.4 $\pm$ 5.9 (n = 594)
40s	154.9 $\pm$ 5.0 (n = 168)	168.7 $\pm$ 5.5 (n = 148)
50s	153.3 $\pm$ 4.8 (n = 179)	166.3 $\pm$ 5.7 (n = 183)
60s	150.4 $\pm$ 5.6 (n = 147)	164.0 $\pm$ 4.7 (n = 162)
70s	147.0 $\pm$ 5.0 (n = 79)	161.0 $\pm$ 5.2 (n = 101)
Weight (kg)		
All	53.0 $\pm$ 8.0 (n = 573)	62.8 $\pm$ 8.5 (n = 594)
40s	54.1 $\pm$ 8.0 (n = 168)	66.4 $\pm$ 8.8 (n = 148)
50s	53.7 $\pm$ 7.4 (n = 179)	63.5 $\pm$ 8.1 (n = 183)
60s	53.0 $\pm$ 8.0 (n = 147)	61.2 $\pm$ 7.8 (n = 162)
70s	49.1 $\pm$ 7.9 (n = 79)	58.8 $\pm$ 7.5 (n = 101)
BMI (kg/m <sup>2</sup> )		
All	22.9 $\pm$ 3.2 (n = 573)	22.9 $\pm$ 2.6 (n = 594)
40s	22.5 $\pm$ 3.3 (n = 168)	23.3 $\pm$ 2.6 (n = 148)
50s	22.9 $\pm$ 3.2 (n = 179)	23.0 $\pm$ 2.5 (n = 183)
60s	23.4 $\pm$ 3.1 (n = 147)	22.8 $\pm$ 2.7 (n = 162)
70s	22.7 $\pm$ 3.1 (n = 79)	22.6 $\pm$ 2.5 (n = 101)
BMD at 1st wave		
Femoral neck (g/cm <sup>2</sup> )	0.7 $\pm$ 0.1	0.8 $\pm$ 0.1
Trochanter (g/cm <sup>2</sup> )	0.6 $\pm$ 0.1	0.7 $\pm$ 0.1
Lumbar spine (L2-4) (g/cm <sup>2</sup> )	0.9 $\pm$ 0.2	1.0 $\pm$ 0.2
BMC at 1st wave		
Femoral neck (g)	3.2 $\pm$ 0.6	4.0 $\pm$ 0.7
Trochanter (g)	6.0 $\pm$ 1.3	8.7 $\pm$ 1.6
Lumbar spine (L2-4) (g)	38.1 $\pm$ 9.3	50.7 $\pm$ 10.0
Area at 1st wave		
Femoral neck (cm <sup>2</sup> )	4.6 $\pm$ 0.3	5.3 $\pm$ 0.3
Trochanter (cm <sup>2</sup> )	10.2 $\pm$ 1.2	12.8 $\pm$ 1.4
Lumbar spine (L2-4) (cm <sup>2</sup> )	42.3 $\pm$ 3.9	51.3 $\pm$ 4.5

Values are mean  $\pm$  SD.

#### 4. Discussion

ABMD is equivalent to BMC divided by an area, but when we encounter cases of BMD decline, we simply consider the decline of the BMC at the measured sites without

TABLE 2: *P* trend according to age strata and *P* value of sex difference analyses of subgroup.

		<i>P</i> trend according to age strata		Sex difference analysis			
		women	men	40s	50s	60s	70s
Femoral neck	BMD	0.0126	0.1682	<0.0001	<0.0001	<0.0001	0.0982
	BMC	0.0027	0.2519	<0.0001	<0.0001	0.0298	0.7122
	Area	0.2084	0.9947	0.9436	0.0434	0.0987	0.2391
Lumbar spine	BMD	<0.0001	0.006	<0.0001	<0.0001	<0.0001	0.815
	BMC	<0.0001	0.027	<0.0001	<0.0001	<0.0001	0.4277
	Area	0.0115	0.3383	<0.0001	<0.0001	0.0052	0.0986

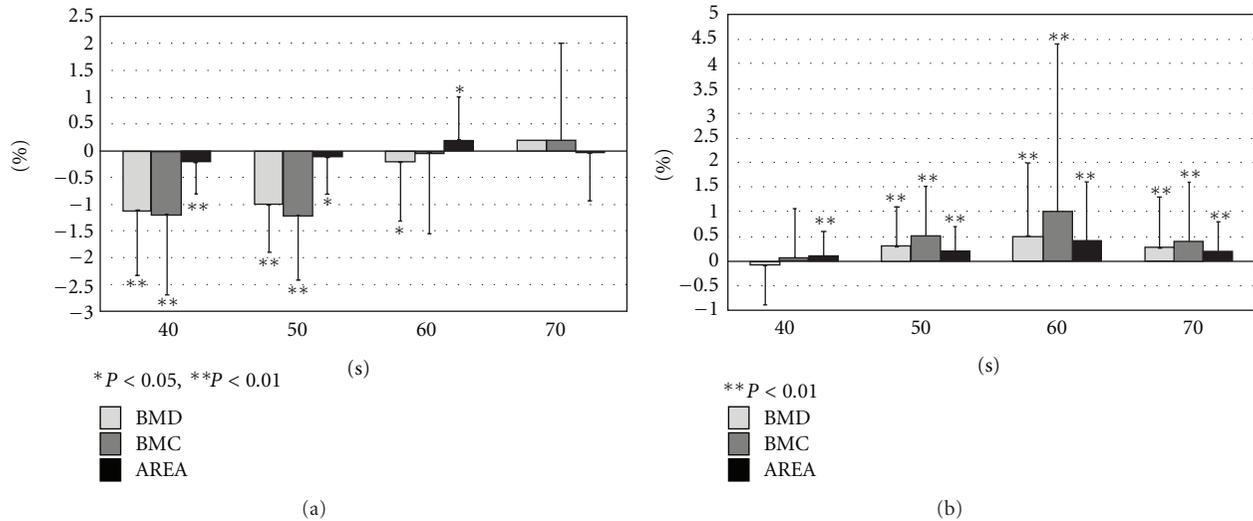


FIGURE 3: (a) Changes in the lumbar spine region by age group in women. Results are the mean ( $\pm$ SD) CR of four different age strata. \* $P < 0.05$ , \*\* $P < 0.01$ . (b) Changes in the lumbar spine region by age group in men. Results are the mean ( $\pm$ SD) CR of four different age strata. \*\* $P < 0.01$ .

incorporating the change of the area (or size), which may represent the change of the shape in the region. The present study demonstrated that in the femoral neck, the aBMD decline in aging occurs not only due to the decline of BMC, but also due to the increase in the area, for both men and women. In fact, the increase of the femoral neck area represents the physiological compensating effect of the weakened bone tolerance [4, 20–23], caused by BMC decline. This may be one of the reasons for the dissociation between the strength of the bone and aBMD values. The widening (or enlargement) of the femoral neck in elderly persons has been demonstrated by the hip structure analyses of DXA [10, 13–15], by computed tomography [23–26], or utilizing both [27, 28]. The annual change rates of aBMD in our study in the femoral neck region were around  $-1\%$  in women (Figure 2(a)) and  $0.5\%$  in men (Figure 2(b)). This is almost equal to the level of the large population-based cohort in Hiroshima Japan,  $-1.14\%$  in women, and  $-0.38\%$  in men [29]. In the lumbar spine, however, a sexual difference was observed in the changes of aBMD and those of BMC or the area as well. The increase in BMC together with the area may be explained by the osteophyte formation found to be more marked in elderly men [7, 9]. This type of change, osteophyte formation, occurs also in

women but later. The significant area increase in women may derive from the osteophyte formation in advanced age. The reason for the significant decrease in the areas in women in their 40s and 50s is unclear at the moment. More detailed studies, using CT scans, are warranted to elucidate the mechanism of the sex difference in the spinal region.

From this perspective, the meaning or significance of aBMD change should be diverse depending on the sites measured and gender. Moreover, the apparent decrease of aBMD may not simply represent the weakness of that measured region (e.g., in the femoral neck), since the greater diameter can make the cylindrical structure stronger [21].

The limitation of this study is that the measurements were carried out by the ordinary DXA method without using elaborate software like hip structure analysis or CT. DXA has an inherent inaccuracy [30–32]. If body composition or weight changed during the followup, it is possible that BMD is inaccurately measured, namely, it may be over- or underestimated. Also, the size measuring by DXA was not very accurate for volumetric analysis. But our method disclosed the differences among sites and between sexes, particularly in terms of longitudinal effect, which have been little investigated.

The strength of our study is its random selection of our samples from people in the local community with very little bias in the process. NILS-LSA is one of the few major epidemiological studies investigating the aging mechanism that is designed to select subjects in a completely random manner. The results of this study should therefore reveal characteristics of the entire Japanese population.

In summary, we investigated the meaning of aBMD changes in aging through separate analyses of BMC and area change. The results revealed that the significance of aBMD changes were very divergent among the sites measured, and between sexes. This may explain the dissociation of aBMD change and bone strength, which encourages one to be more cautious when interpreting the meaning of aBMD change.

## Acknowledgment

This work was supported by the research fund for Longevity Sciences [23–33] from the National Center for Geriatrics and Gerontology (NCGG), Japan.

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