**Genetic and Environmental Factors of Bone Mineral Density Indicated in Japanese Twins**

**Key Words**
Bone mineral density  
Osteoporosis  
Aging  
Twins

**Abstract**
To evaluate the effects of genetic and environmental factors on the bone mass, we determined the bone mineral density (BMD) in the total body, the lumbar spine and in the femoral neck in 23 Japanese twin pairs including 21 monozygotic (MZ) pairs, applying dual-energy X-ray absorptiometry. In MZ pairs aged 20–49 years, highly significant intraclass correlation coefficients, ranging from 0.775 to 0.926, were observed at several sites, including the lumbar spine and the femoral neck, which suggests considerable contributions of genetic factors to the BMD. Neither intraclass correlation coefficients nor intrapair differences were found to change with increasing age in the present analysis. In female MZ pairs, exercises both at the present time and in the past were correlated with the BMD at several sites as well as body mass index in multiple regression analyses.

**Introduction**

The prevention of osteoporosis reduces the risk for fractures in the lumbar spine or in the femoral neck in the elderly [1, 2]. Therefore, it is of great importance to study factors involved in the determination of the bone mass. In the elderly, the bone mass is assumed to be determined by the peak bone mass and the bone loss during aging [2–4]. Various genetic
and environmental factors may influence these two parameters. Contributions of genetic factors determining the bone mass in the radius [5] and in the metacarpal [6] bone have been indicated using twin methods.

Twin studies on weight-bearing bones, utilizing dual-photon absorptiometry, have also disclosed significant influences of genetic factors on these bone masses [7, 8].

As for environmental factors, beneficial effects of exercise [9, 10] and calcium intake [11] have been described. Detrimental effects of smoking [12–14] or alcohol drinking [12, 13] on the bone mass have also been reported.

The present study aims to clarify genetic and environmental factors related to the determination of the bone mass in the total body, the lumbar spine and in the femoral neck, applying a twin method to Japanese twin pairs. For the measurement of the bone mass, we applied a recently developed technique, dual-energy X-ray absorptiometry, which is more precise, decreases the dose of X-ray exposure and is less time-consuming, compared to dual-photon absorptiometry [3].

Materials and Methods

Subjects

Subjects were twin pairs who graduated from high schools affiliated to the University of Tokyo. A total of 23 twin pairs voluntarily participated in the study. Of the 23 pairs, 21 pairs were monozygotic (MZ) and only two pairs were dizygotic. Among the 21 MZ pairs, 16 were female and 5 male pairs. The ages of the twin pairs ranged from 20 to 49 years. Only MZ pairs were included in the present analysis except for an investigation for age-related changes in bone mineral density (BMD).

Measurement of BMD

BMD in the total body, the lumbar spine and in the femoral neck was measured using a dual-energy absorptiometry technique (Lunar DP-X model). BMD of the total body was operationally separated into BMD at five different sites; head, arm, rib, spine and leg. Intraclass correlation coefficients for BMD among the twin pairs were calculated as described by Snedecor and Cochran [15]:

\[ r = \frac{\sum (X - \bar{X})(X' - \bar{X})}{\sqrt{\sum (X - \bar{X})^2 \sum (X' - \bar{X})^2}} \]

where the sums are over the number of pairs and \( \bar{X} \) is the mean of all observations.

Questionnaire to Detect Environmental Factors Affecting BMD

A questionnaire asking various aspects of lifestyles, including factors supposed to influence osteoporosis, such as exercise at the present time, exercise during junior and high schoolers, smoking, drinking, intake of milk, exposure to sunlight, was sent in advance to all of the twin pairs recorded in the alumni association of the schools. The information from the questionnaire was utilized for the analysis of environmental factors affecting BMD. Body mass index (BMI), calculated as weight divided by the square of height was used as an index for obesity.

Results

Correlations for BMD in the total body, the lumbar spine and in the femoral neck, in MZ pairs, are shown in figure 1. At all sites, the BMD exhibited fairly good correlations. Intraclass correlation coefficients for the BMD in MZ and random pairs are summarized in table 1. Random pairs were generated by randomly allocating partner B to each partner A. In MZ pairs, high and significant (p < 0.001) correlation coefficients, ranging from 0.775 to 0.926, were observed in the total body, the lumbar spine, the femoral neck, the head, the spine and in the leg. Slightly lower (0.581 and 0.699), but still significant correlation coefficients were obtained in the arm and in the rib, respectively. Meanwhile, no significant correlations were observed at all sites in the random pairs.

Age-related alterations in the BMD of the total body, the lumbar spine and of the femoral neck were examined for all twin pairs
Table 1. Intraclass correlation coefficients for BMD at various sites of the body among MZ twin pairs and random pairs

<table>
<thead>
<tr>
<th>Site</th>
<th>MZ pair</th>
<th>Random pair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body</td>
<td>0.8765** (n = 20)</td>
<td>-0.1167</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.8566** (n = 15)</td>
<td>0.1923</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.8180** (n = 19)</td>
<td>0.1104</td>
</tr>
<tr>
<td>Head</td>
<td>0.9259** (n = 20)</td>
<td>0.0161</td>
</tr>
<tr>
<td>Arm</td>
<td>0.5811** (n = 20)</td>
<td>0.0578</td>
</tr>
<tr>
<td>Rib</td>
<td>0.6985* (n = 9)</td>
<td>-0.3835</td>
</tr>
<tr>
<td>Spine</td>
<td>0.7750** (n = 20)</td>
<td>-0.0289</td>
</tr>
<tr>
<td>Leg</td>
<td>0.9195** (n = 20)</td>
<td>-0.1221</td>
</tr>
</tbody>
</table>

* p < 0.01, ** p < 0.001.

(fig. 2, table 2). In males, negative correlations, although not significant, were indicated between age and BMD in the lumbar spine and in the femoral neck. Paradoxically, a positive correlation (p < 0.05) was found in females between age and the total body BMD.

Age-related changes in the intraclass correlation coefficients were evaluated as shown in table 3. No differences in the coefficients were apparent between 19–40 years and 40–49 years.

To evaluate the influences of environmental factors on the BMD, relationships between age and intrapair differences [(A−B)/(A+B)] were investigated for the BMD at various sites in MZ pairs (table 4). No significantly positive correlations were found. Conversely, negative correlations, although not significant, were indicated in the femoral neck and in the leg.

Because of the small sample size of males, the effects of several important environmental factors were evaluated only in females, using simple correlation coefficients and multiple regression analysis. Factors significantly

Fig. 1. Correlations of BMD in the total body (a), the lumbar spine (b) and in the femoral neck (c) between the first (A) and the second (B) sib in MZ twin pairs. An intraclass correlation coefficient for each BMD is described.
Correlated with the BMD at various sites are listed in Table 5. While BMI was significantly correlated with the BMD at all sites except the femoral neck in simple correlations, BMI was only correlated with the BMD of the total body and of the spine in multiple correlation analysis. Exercises both in the past and at the present time were frequently associated with the BMD, in both simple correlations and multiple regression analysis.
Table 5. Environmental factors significantly correlated with the BMD at various sites in female MZ pairs (n = 32)

<table>
<thead>
<tr>
<th>Site</th>
<th>Simple correlation coefficients</th>
<th>Multiple regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body</td>
<td>BMI*** (0.6247) exercise (present)* (0.3645)</td>
<td>exercise (present)** BMI*</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>BMI* (0.4166) exercise (past)* (0.4328)</td>
<td>exercise (present)*</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>BMI** (0.5426) exercise (present)* (0.5549)</td>
<td>exercise (past)**</td>
</tr>
<tr>
<td>Head</td>
<td>BMI* (0.3579) exercise (present)* (0.7786)</td>
<td>smoking*</td>
</tr>
<tr>
<td>Arm</td>
<td>BMI*** (0.7549) exercise (present)* (0.5023)</td>
<td>BMI***</td>
</tr>
<tr>
<td>Rib</td>
<td>BMI** (0.4179) exercise (past)* (0.3845)</td>
<td>exercise (present)**</td>
</tr>
<tr>
<td>Spine</td>
<td>BMI*** (0.7549) exercise (present)* (0.5023)</td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td>BMI** (0.5023) exercise (past)* (0.3845)</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, ***p < 0.001.

Discussion

The present study indicated strong correlations for BMD at all sites, except in the arm and in the rib, between MZ twin pairs. These results, particularly those observed in the weight-bearing bones, are in accordance with previous reports for the BMD of the lumbar spine [7, 8] and of the femoral neck [8]. Significant correlations for the arm BMD are also consistent with previous results [5–8]. It is of interest to note that even non-weight-bearing bones, such as the head bone, exhibited considerably high coefficients. Therefore, some genetic determinants affecting the whole body, like the regulation of hormonal factors [1], may be involved in the determination of the bone mass. In contrast, in the present study, the coefficients for the arm BMD were relatively lower compared to other sites, which might suggest an importance of environmental factors in the arm BMD. Nonsignificant correlations of the forearm BMD in premenopausal [8], young [7] or adult groups [5] are in line with the present results. To identify high-risk populations which have genetic predispositions to bone loss is of great importance for the prevention of osteoporosis. Recently, a mutation in a gene for type I procollagen (COL1A2) was found in a woman with postmenopausal osteoporosis [16]. This gene could be one of the candidate genes which determine BMD. Further analyses in more samples would substantiate the causal significance of this gene.

The present study is the first report which examined contributions of genetic factors to BMD in Japanese twins. Although lower average BMD values have been reported in Japanese compared to Caucasians [17], the obtained intrapair correlation coefficients in the present study indicate that genetic factors influence BMD in Japanese as much as in Caucasians.

Age-related decreases in BMD values were implicated only in males and not in females. A considerable fraction of young women, aged 20–29 years, exhibited lower BMD val-
ues in the total body (fig. 2b), the lumbar spine and in the femoral neck (data not shown), which greatly contributed to the observed paradoxical changes in females. The lower BMD values in young women might indicate some nutritional problems derived from oversensitivity for their looks or ovulatory disturbances, which have been implicated as a significant causal factor for the spinal bone loss in premenopausal women [18]. These possibilities remain to be elucidated in further analyses.

In a previous report [7], genetic determinants for the spinal bone mass were only found in an age group younger than 25 years and not in the older group, whereas those for the radial bone mass were only found in the older group. We, however, observed similar correlation coefficients for the BMD at three different sites. The present study included only subjects younger than 50 years, which may partly explain the observed discrepancy.

To evaluate contributions of genetic factors, correlations between the intrapair differences of BMD and age were examined. No positive correlations between them were indicated, which suggests the relatively smaller influence of environmental factors on BMD, at least in the age group younger than 50 years.

Multiple regression analysis selected exercise at the present time, exercise in the past and BMI as major determinants for BMD. These results suggest the usefulness of exercise in premenopausal ages as well as in postmenopausal ages [10]. Since a reduced peak bone mass is considered to be one of the major risk factors for osteoporosis [4], the importance of exercise before menopause should be stressed.

Although smoking [12–14] and drinking [12, 13] might be potential factors influencing BMD, smoking was only correlated with the rib BMD and drinking was not associated with BMD in the present study. Since only females were analyzed, studies including larger numbers of male pairs are required for drawing a conclusion.

Acknowledgements

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References


