Underweight Young Women Without Later Weight Gain Are at High Risk for Osteopenia After Midlife: The KOBE Study

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ABSTRACT

Background: Although underweight young women are targets for interventions to prevent low bone mineral density (BMD), the relationship between change in body mass index (BMI) from youth to older age and BMD has not been widely investigated in community dwellers.

Methods: In 749 healthy Japanese women aged 40–74 years, BMD was measured by quantitative ultrasound and anthropometric measurements, and BMI was calculated from body weight and height. The BMI of participants at age 20 years was estimated by self-reported body weight and their present height. They were classified into four groups according to the presence of underweight (BMI <18.5 kg/m²) at 20 and/or at present. Logistic regression models were used to estimate multivariate-adjusted odds ratios (ORs) of the presence of underweight at 20 and/or at present for osteopenia (BMD T score <−1 standard deviations) compared with participants with BMI ≥18.5 kg/m² both at 20 and at present.

Results: The participants who were underweight both at 20 and at present had a higher OR for osteopenia compared with those with BMI ≥18.5 kg/m² at 20 and at present (OR 3.94; 95% confidence interval [CI], 1.97–7.89). Those underweight only at present also had significantly increased OR of developing osteopenia (OR 2.95; 95% CI, 1.67–5.24). The OR of those underweight only at 20 was 0.87 (95% CI, 0.51–1.48).

Conclusions: Current underweight was associated with increased risk for osteopenia among Japanese women, especially in those who were underweight both at 20 and at present. To prevent low BMD in the future, maintaining appropriate body weight might be effective for young underweight women.

Key words: bone mineral density; osteopenia; body mass index; underweight

INTRODUCTION

Osteoporosis is a major risk factor for fractures in the elderly. In 2013, fractures were the fourth leading cause of disabilities that subsequently required support for daily living in Japan.1 The estimated prevalence of osteoporosis diagnosed in the proximal femur among people aged 40 years or over in Japan is 12.4% in men and 26.5% in women, and prevalence is higher in women than in men in every generation.2

Previous studies have reported significant positive associations between bone mineral density (BMD) and body weight or body mass index (BMI) in cross-sectional studies.3–7 In cohort studies, Tanaka et al reported that being underweight was a risk factor for osteoporotic fractures,8 and Forsmo et al reported that an increase in body weight was associated with higher BMD after 11 years of follow-up in middle-aged women.9

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The prevalence of underweight among young women is increasing in Japan.\textsuperscript{10,11} The percentages of women in their twenties with BMI less than 18.5 kg/m\texttwosuperscript{2} were 13.5\% in 1979, 20.4\% in 1998, and 21.5\% in 2013.\textsuperscript{10,11} These young underweight Japanese women are considered to have lower BMD compared with those who are not underweight. However, future weight gain might increase BMD in middle or older age.

Development of strategies for preventing future osteoporotic fractures in young underweight women requires investigating the relationship between BMD in middle or older age and BMI both in young and middle-aged or older women. However, few studies have investigated these associations in a general female population. We investigated the relationships between present BMD and BMI both at age 20 years and in middle and older age among healthy females.

**METHODS**

**Study participants**

Data of the present study were based on the baseline survey of the Kobe Orthopedic and Biomedical Epidemiological (KOBE) study. The details of the KOBE study have been described elsewhere.\textsuperscript{12-15} The baseline survey was performed between July 2010 and December 2011. Study participants were healthy volunteers aged 40–74 years who were residents of Kobe City, a major urban area in Japan. From 1117 participants in the baseline survey (341 men and 776 women), we excluded all male participants as well as the 27 female participants in the baseline survey (341 men and 776 women), resulting in 749 women that were healthy volunteers aged 40–74 years who were residents of Kobe City, a major urban area in Japan. From 1117 participants in the baseline survey (341 men and 776 women), we excluded all male participants as well as the 27 female participants in the baseline survey (341 men and 776 women), resulting in 749 women that were included in the study. Written informed consent was obtained from each participant. The study was approved by the Ethics Committee of the Institute of Biomedical Research and Innovation (Committee approval number: 11-12).

**Data collection**

Participants completed a questionnaire that included demographic characteristics, body weight at 20 years old, medical history, menopause status, postmenopausal years, dietary habit, nutritional supplement intake, walking time per day (less than 30, 30–59, 60–119, and 120 or more min), smoking habit (current, ex-, or never), and drinking habit (current, ex-, or never). Height and weight were measured with subjects wearing light clothing, and BMI was calculated as weight (kg) divided by the square of height (m). The BMI data from the survey are described as “present BMI” in the present study. The BMI at 20 years old was estimated using self-reported weight at age 20 and height at the time of the survey. BMD was measured using the quantitative ultrasound method in the right calcaneum (AOS-100NW; ALOKA Ltd., Tokyo, Japan). Blood samples were obtained from all participants and were tested in the commissioned clinical laboratory center (SRL Inc., Tokyo, Japan). Thyroid-stimulating hormone (TSH) was measured using electrochemiluminescence immunoassay, and subclinical hyperthyroidism was defined as TSH <0.5 µIU/mL.\textsuperscript{16}

**Definitions of the main outcome**

BMD was expressed in standard deviation (SD) units relative to the BMDs of young women (T score). Osteopenia was defined according to World Health Organization criteria as a T score less than −1 SD.\textsuperscript{17,18} Although osteoporosis is defined as a T score less than −2.5 SD, osteoporosis was not defined in the present study because there were too few participants with a T score less than −2.5 SD (n= 3).

**Statistical analysis**

Participants were categorized into four groups as follows: Group 1 (normal or overweight\textsuperscript{19} with BMI $\geq 18.5$ kg/m\texttwosuperscript{2} at 20 years old and at present), Group 2 (normal or overweight at 20 years old and underweight\textsuperscript{19} with BMI $<$18.5 kg/m\texttwosuperscript{2} at present), Group 3 (underweight at 20 years old and normal or overweight at present), and Group 4 (both underweight at 20 years old and at present). Characteristics among the four groups were compared by analysis of variance or by Kruskal-Wallis test for continuous variables and by Chi-square tests for categorical variables. Logistic regression models were used to estimate odds ratios (ORs) and 95\% confidence intervals (CIs) of the participants who were underweight at 20 years old for osteopenia compared with those who were normal or overweight at 20 years old. The same analyses were performed using the participants’ present BMI. In these analyses, model 1 was adjusted for age and model 2 was adjusted for age, postmenopausal years, taking calcium supplements, walking time per day, smoking habit, drinking habit, milk or yogurt intake, and hyperthyroidism. Postmenopausal years were defined as zero for menstruating women. For the analysis of BMI at 20 years old, model 3 was adjusted for model 2 variables and present BMI category. For the analysis of present BMI, model 3 was adjusted for model 2 variables and BMI category at 20 years old.

Logistic regression models were also used to estimate ORs of Groups 2–4 for osteopenia compared with Group 1. Variables for adjustment in model 1 and 2 were the same as those mentioned above. The estimated OR of Group 4 for osteopenia was compared with Group 3 after adjusting for the variables in model 2 (additional model). These logistic regression models were also performed after exclusion of participants with BMI $\geq 25.0$ kg/m\texttwosuperscript{2}.

All data were analyzed using Stata, version 13 (IBM Corp., Armonk, NY, USA). All reported \textit{P}-values were two-tailed, and \textit{P} < 0.05 was considered statistically significant.

**RESULTS**

Among all participants, mean (SD) age was 58.0 (8.7) years. The percentages of participants in menopause, currently smoking, currently drinking, and taking calcium supplement...
were 77.7%, 2.0%, 37.0%, and 5.2%, respectively. Of all participants, 302 (40%) had osteopenia. Table 1 shows the characteristics of the four groups classified by the presence of underweight at 20 years old and at present. Mean age of participants in group 4 was relatively low. However, there were no significant differences among the four groups for any variables.

The ORs of being underweight at 20 years old for osteopenia are shown in Table 2. None of the ORs in any adjusted models were significantly increased. In model 3, after additional adjustment for the present BMI category (underweight or not underweight), the OR was slightly attenuated compared with the other models. In Table 2, the ORs of being underweight at present for osteopenia are also shown. The ORs were significantly increased in all models, and the multivariable-adjusted OR of being underweight was 3.39 (95% CI, 2.10–5.46) in model 3. In the analysis of women with BMI <25.0 kg/m² either at 20 years old or at present (Table 3), the results were similar after multivariable adjustment (OR of being underweight at 20 years old, 0.93; 95% CI, 0.59–1.47), and the OR of being underweight at present was 3.23 (95% CI, 1.99–5.23).

The ORs of Groups 2–4 for osteopenia compared with Group 1 are shown in Table 4. Approximately one-third of the participants who were underweight at age 20 were also underweight at present. Compared with Group 1, the ORs of osteopenia in Groups 2 and 4 (OR 2.95; 95% CI, 1.67–5.24 and OR 3.94; 95% CI, 1.97–7.89, respectively) were significantly increased after multivariable adjustment. Group

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**Table 1. Characteristics of participants according to the presence of underweight at 20 years old and/or at present**

<table>
<thead>
<tr>
<th>At 20 years old</th>
<th>Normal or Overweight</th>
<th>Underweight</th>
<th>Normal or Overweight</th>
<th>Underweight</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 4</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>521</td>
<td>74</td>
<td>103</td>
<td>51</td>
<td>0.116</td>
</tr>
<tr>
<td>Age</td>
<td>58.4 (8.5)</td>
<td>57.9 (8.1)</td>
<td>57.2 (9.3)</td>
<td>54.7 (9.5)</td>
<td></td>
</tr>
<tr>
<td>BMI at 20 years old</td>
<td>Median (25th–75th percentile)</td>
<td>20.5 (19.6–21.8)</td>
<td>19.7 (19.2–20.6)</td>
<td>17.7 (17.2–18.1)</td>
<td>18.0 (16.9–18.3)</td>
</tr>
<tr>
<td>Range</td>
<td>18.5–29.1</td>
<td>18.6–23.6</td>
<td>15.5–18.5</td>
<td>15.1–18.5</td>
<td></td>
</tr>
<tr>
<td>BMI at present</td>
<td>Median (25th–75th percentile)</td>
<td>21.4 (20.1–23.2)</td>
<td>17.7 (17.2–18.2)</td>
<td>20.2 (19.4–21.3)</td>
<td>17.7 (16.8–18.2)</td>
</tr>
<tr>
<td>Range</td>
<td>18.5–39.6</td>
<td>13.6–18.5</td>
<td>18.5–26.6</td>
<td>15.2–18.5</td>
<td></td>
</tr>
<tr>
<td>Menopause, %</td>
<td>78.7</td>
<td>79.7</td>
<td>77.7</td>
<td>64.7</td>
<td>0.142</td>
</tr>
<tr>
<td>Hyperthyroidism, %</td>
<td>2.7</td>
<td>1.4</td>
<td>1</td>
<td>2</td>
<td>0.683</td>
</tr>
<tr>
<td>Calcium supplement, %</td>
<td>4.4</td>
<td>6.8</td>
<td>9.7</td>
<td>2</td>
<td>0.096</td>
</tr>
<tr>
<td>Milk or yogurt intake, ml/week</td>
<td>1050 (600–1700)</td>
<td>1365 (560–1960)</td>
<td>1190 (500–1750)</td>
<td>990 (500–1400)</td>
<td>0.630</td>
</tr>
<tr>
<td>Walking time per day, %</td>
<td>less than 30 minutes</td>
<td>5.6</td>
<td>5.4</td>
<td>9.7</td>
<td>3.9</td>
</tr>
<tr>
<td>30–59 minutes</td>
<td>25.9</td>
<td>24.3</td>
<td>23.3</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td>60–119 minutes</td>
<td>36.9</td>
<td>43.2</td>
<td>27.2</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>120 minutes or more</td>
<td>31.7</td>
<td>27</td>
<td>39.8</td>
<td>31.4</td>
<td></td>
</tr>
<tr>
<td>Smoking, %</td>
<td>Current, ex, never</td>
<td>2.3, 6.7, 91.0</td>
<td>1.4, 12.2, 86.5</td>
<td>0.0, 9.7, 90.3</td>
<td>3.9, 7.8, 88.2</td>
</tr>
<tr>
<td>Alcohol drinking, %</td>
<td>Current, ex, never</td>
<td>37.2, 2.7, 60.1</td>
<td>36.5, 2.7, 60.8</td>
<td>35.0, 1.9, 63.1</td>
<td>39.2, 3.9, 56.9</td>
</tr>
</tbody>
</table>

BMI, body mass index. Normal or overweight: BMI ≥18.5 kg/m², Underweight: BMI <18.5 kg/m². Continuous variables are presented as mean (standard deviation) or median (25th–75th percentile). Categorical variables are presented as percentage.

**Table 2. Multivariate-adjusted odds ratios of underweight for osteopenia according to BMI at 20 years old and at present**

<table>
<thead>
<tr>
<th>n</th>
<th>Case (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>BMI category at 20 years old</td>
<td>Underweight</td>
<td>154 (61.96)</td>
</tr>
<tr>
<td>Normal or overweight</td>
<td>595 (40.5)</td>
<td>ref</td>
</tr>
<tr>
<td>BMI category at present</td>
<td>Underweight</td>
<td>125 (69.55)</td>
</tr>
<tr>
<td>Normal or overweight</td>
<td>624 (33.7</td>
<td>ref</td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; OR, odds ratio. Normal or overweight: BMI ≥18.5 kg/m². Underweight: BMI <18.5 kg/m². Osteopenia: T score less than −1 standard deviation.

Model 1: Adjusted for age.
Model 2: Adjusted for age, postmenopausal years, taking calcium supplement, walking time per day, smoking habit, drinking habit, milk or yogurt intake and hyperthyroidism.
Model 3a: Adjusted for model 2 variables and BMI category at present.
Model 3b: Adjusted for model 2 variables and BMI category at 20 years old.
3 had a lower risk of osteopenia than Group 1, although not significantly so (OR 0.87; 95% CI, 0.51–1.48). In the analyses of Groups 3 and 4, the OR of osteopenia in Group 4 compared with Group 3 were significantly increased (multivariable adjusted OR 3.79; 95% CI, 1.57–9.15). In the analysis of women with BMI <25.0 kg/m² at age 20 and at present, the multivariable-adjusted ORs in Groups 2, 3, and 4 were 2.73 (95% CI, 1.53–4.87), 0.80 (95% CI, 0.46–1.38), and 3.66 (95% CI, 1.82–7.39), respectively (Table 5). In Group 4, the OR compared with Group 3 was 3.83 (95% CI, 1.56–9.41).

### DISCUSSION

The present study showed that the OR of osteopenia in women who were underweight at age 20 years and at present compared with women whose weight was normal or overweight at age 20 years and at present were significantly higher. Also, the OR among women who were underweight at 20 years but normal or overweight at present was slightly lower; however, this difference was not significant. In addition, the OR among women who were normal or overweight at 20 years but underweight at present was significantly higher. These results did not change after exclusion of participants with ≥BMI 25.0 kg/m² either at age 20 years or at present.

It has been reported that postmenopausal women with BMI <18.5 kg/m² have low BMD and that they are at high risk of future fractures. Similarly, young underweight women with anorexia nervosa have also been reported to have low BMD compared with healthy young women. Consequently, underweight women should have low BMD regardless of age. Although the BMD measurement sites and severity of being underweight were different in these studies, their results are consistent with the present observations that women who remained underweight had low BMD.

Although there are few studies investigating the effects of weight gain on BMD among healthy young underweight women, some studies have investigated the effects among young women with anorexia nervosa. These studies demonstrated that weight gain does not increase BMD in this population. Further, the study by Misra et al. reported...
that adolescent girls who did not recover from anorexia nervosa had decreased BMD compared with healthy controls, but girls who recovered from anorexia nervosa did not.\textsuperscript{23} Therefore, weight gain among underweight young women might prevent a decrease in BMD. In addition, it has been reported that weight gain increases BMD among perimenopausal women with BMI \(<23.0\ \text{kg/m}^2\).\textsuperscript{24} Therefore, weight gain might increase or stabilize BMD among both young and middle-aged women. Although it is not clear in the present study when the participants with BMI \(<18.5\ \text{kg/m}^2\) at age 20 years and with BMI \(\geq 18.5\ \text{kg/m}^2\) at present gained their weight, it is possible that there was no increase in the OR of osteopenia among these women compared with those with BMI \(\geq 18.5\ \text{kg/m}^2\) both at 20 years old and at present because of weight gain. In addition, the multivariable-adjusted OR for underweight at 20 years old was attenuated after adjustment for present BMI category, but the OR of underweight at present was not attenuated after adjustment for BMI at 20 years old (Table 2). This result indicates that BMD may be more strongly associated with BMI category at present than that at the age 20 years.

In the present study, one-third of the 154 participants who were underweight at 20 years old remained underweight at present. Because the number of young underweight women is increasing in Japan,\textsuperscript{10,11} the number of women who remain underweight in later life may increase in the future. As a consequence, the number of women who are at high risk for osteopenia may increase. In a study investigating the desire for thinness among 631 female university students in Japan, it was reported that nearly half of the underweight and 89% of normal-weight students desired to be thin.\textsuperscript{25} In addition, the National Nutrition Survey in Japan reported that the mean desired BMI values were 18.7 kg/m\(^2\) among young women aged 15–19 years and 19.2 kg/m\(^2\) in women aged 20–24 years.\textsuperscript{25} Because weight gain might prevent osteopenia but the desired body weight is low among underweight women, it is important to educate Japanese young women about a desirable healthy weight.

The present study showed that the OR for osteopenia among women with a BMI \(\geq 18.5\ \text{kg/m}^2\) at age 20 years but \(<18.5\ \text{kg/m}^2\) at present was also high. Weight loss has been reported to lead to bone loss in previous studies,\textsuperscript{11,27} which is consistent with the present results. Thus, maintaining appropriate body weight not only at a young age but also after midlife is important to prevent osteopenia. However, aerobic and weight-bearing exercises are also recommended to prevent osteopenia.\textsuperscript{28} Therefore, if women who are overweight after midlife need to lose weight, these exercises rather than dietary restriction might be effective for improving health status.

The present study has several limitations. First, BMD was not measured by dual-energy X-ray absorptiometry or computed X-ray densitometry.\textsuperscript{18} Although quantitative ultrasound is not an established method for making a definitive diagnosis of osteopenia, it is useful as an examination procedure in screening for osteopenia.\textsuperscript{18,29} Second, BMD was measured only at the calcaneum, while it is usually measured at the lumbar spine, hip, femoral neck, calcaneum, forearm, or whole body. Of these sites, measurement of BMD at the hip or femoral neck is important, because these fracture sites are the leading cause of deterioration of daily living activities. Because the correlation between the BMD of the calcaneum and femoral neck has been reported to be 0.6 among middle-aged and older Japanese women,\textsuperscript{29} BMD measured at the calcaneum could be an index of risk for severe fractures. Similar investigations to the present study should be performed using BMD data in other bone sites, because significant correlations between BMI and BMD at many bone sites other than the calcaneus have been reported.\textsuperscript{5,8,29,30} Third, because body weight at age 20 years was based on self-reported weight, there might have been recall bias. However, the influence of inaccurate recall data might be reduced because we used dichotomized BMI information. Nevertheless, some of the normal or overweight women at 20 years old might have been wrongly classified into the underweight group, because it has been reported that self-reported weights are lower than measured weights.\textsuperscript{31} Thus, ORs of osteopenia among women who were underweight at 20 years old might have been underestimated. In addition, height for estimating the BMI at age 20 years was based on the present data measured at the baseline survey of the KOBE study. Finally, the participants of the present study were not representative of the general Japanese population because the participants of the KOBE study were relatively healthy individuals who did not take medication for diabetes, hypertension, or dyslipidemia and did not have a past history of cardiovascular diseases. Also, the mean Z-score of BMD, which is expressed in SD relative to the BMD of age-matched women was 0.33; in other words, the BMDs of the participants were slightly higher compared with those of age-matched Japanese women. Thus, the participants were considered to be highly health-conscious volunteers. Therefore, the results of the present study should be applied to the general population with caution.

In conclusion, being underweight at present was associated with increased risk for osteopenia in women, especially who were also underweight at age 20. On the other hand, the risk of osteopenia in women with underweight only at 20 years old was not increased compared with women whose weight was normal or overweight at age 20 years and at present. Maintaining appropriate body weight might be effective in preventing future low BMD among young underweight women.
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Conflicts of interest: None declared.

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