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ORIGINAL RESEARCH

Association Between Osteoporosis Self-Assessment Tool for Asians and Airflow Limitation in Japanese Post-Menopausal Women

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Purpose: This study aimed to reveal the association between the osteoporosis self-assessment tool for Asians (OSTA) and airflow limitation (AL) in post-menopausal Japanese women.

Participants and Methods: This cross-sectional study included 1580 participants undergoing a comprehensive health examination using spirometry and dual-energy X-ray absorptiometry. The OSTA was calculated by subtracting the age in years from the body weight (BW) in kilograms, and the result was multiplied by 0.2. The OSTA risk level was defined as low (>-1), moderate (−4 to −1), or high (<-4). AL was defined as forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) <0.7. The association between the OSTA and AL was assessed using logistic regression analysis.

Results: The prevalence of AL was significantly higher in the high OSTA group (15.3%) than in the low OSTA group (3.1%) ($p<0.001$). In multiple linear regression analysis, the OSTA was independently associated with FEV_1/FVC. In logistic regression models adjusted for smoking status, alcohol consumption, current use of medication for diabetes, hyperglycemia, rheumatoid arthritis, second-hand smoke, and ovary removal showed a significantly higher risk of AL (odds ratio: 5.48; 95% confidence interval: 2.90–10.37; $p<0.001$) in participants with OSTA high risk than in those with OSTA low risk.

Conclusion: These results suggest that the OSTA high risk indicates reduced BMD at the femoral neck and presence of AL in Japanese post-menopausal women aged ≥45 years.

Keywords: airflow limitation, chronic obstructive pulmonary disease, the osteoporosis self-assessment tool for Asians, osteoporosis, post-menopausal women, comorbidity

Introduction

Osteoporosis is a major global public health concern. In Japan, a large observational study identified approximately 10,700,000 and 6,400,000 individuals aged ≥40 years with osteoporosis in the femoral neck or lumbar spine, respectively. This condition is considered a national health issue.[1] The prevalence of osteoporosis in the femoral neck is approximately 12.4% in males and 26.5% in females among Japanese individuals aged 40 years and older.[1] Osteoporosis is a mild disease unless fractures complicate it. Patients with osteoporosis have an increased risk of fractures, particularly fragility fractures.[2] As of 2015, the aging population was the largest worldwide, and the estimated incidence of hip fractures remained unchanged at high rates from 2012 to 2015 in Japan.[3] Therefore, the importance of developing preventive strategies in treating osteoporosis and related fractures that cause disability in older adults is increasing. Identifying low bone mineral density (BMD) early is crucial, particularly in women.

Osteoporosis is also a major and common comorbidity in patients with chronic obstructive pulmonary disease (COPD).[4] Previous studies reported that patients with COPD had a higher risk of death following hip fractures.[5] Nevertheless,

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osteoporosis is frequently underdiagnosed and associated with poor health and prognosis if left untreated.[6–8] Therefore, osteoporosis should be diagnosed and treated using a therapeutic approach in patients with COPD.[8] Osteoporosis occurs in approximately 35% of patients with COPD in Japan; however, most cases are not assessed or treated.[9] COPD was reported by the World Health Organization (WHO) as the third leading cause of death worldwide, causing 3 million deaths in 2016.[10] COPD is a serious health problem and can lead to poor health if complicated by fractures.

Over the past decade, several studies have shown that reduced respiratory function is associated with low BMD and increased fracture risk.[11–14] Spirometry, which is the most widely available and reproducible test of lung function, is required to diagnose COPD; the presence of a postbronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 0.70 confirms the presence of persistent airflow limitation (AL).[6] The spirometric criterion for AL is a postbronchodilator fixed ratio of FEV_1/FVC < 0.70, which is simple and independent of reference values.[6] However, the association between AL and osteoporosis is complex. Although the mechanisms of COPD and osteoporosis remain controversial, starting treatment quickly for patients with osteoporosis and COPD appears to be beneficial.

The OSTA has been used as a simple screening tool for diagnosing low BMD (osteoporosis) without burdening the body.[15] Previous studies have demonstrated that the OSTA is useful for identifying the risk of osteoporosis in each Asian country.[16–20] Recently, the OSTA has been widely used and evaluated in women and men, as well as its association with other comorbidities in some Asian countries.[19,21] If OSTA is related to osteoporosis and AL, it can be used to rapidly diagnose both disorders. However, to our knowledge, no study has been conducted on the association between OSTA and lung function, and data on the relationship between osteoporosis or low BMD and lung function were limited.

Therefore, this study aimed to examine whether OSTA is associated with AL in post-menopausal Japanese women.

Materials and Methods

Participants

This study enrolled 3104 of 15,598 Japanese women aged ≥45 who visited the Japanese Red Cross Kumamoto Health Care Center for medical checkups and underwent a health screening examination, including BMD measurement and spirometry between April 2016 and September 2017.[22] While BMD measurement and spirometry were optional assessments, eligible study Participants included 3104 postmenopausal women who underwent both tests.

As previously described, the screening examinations included physical assessments, questionnaires, and blood collection.[22,23] A trained public health nurse administered questionnaires to collect data on the medical history, including medication use, alcohol consumption, smoking status, and physical activity.

We excluded participants with pre-menopausal (n=1048), the current use of medication for osteoporosis (n=180), those with a history or evidence of thyroid disease (n=103), chronic kidney disease (n=3), respiratory diseases, such as asthma (n=86), tuberculosis or pleurisy (n=11), bronchiectasis (n=4), lung cancer (n=6), other respiratory diseases (n=35), and FEV_1/FVC ≥70% and % FEV_1 <80% predicted (n=48) in this study. None of the participants were diagnosed with COPD in this study.

Overall, 1580 post-menopausal women were included in the final analysis (Figure 1). A physician evaluated all participants and obtained written informed consent.

This study was approved by the Human Ethics Committee of Kumamoto University (approval number 84) and the Japanese Red Cross Kumamoto Health Care Center and was conducted following the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research (partially revised on December 1, 2008, by the Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labor, and Welfare).

BMD Measurement and the OSTA

The left femoral neck BMD was measured using dual-energy X-ray absorptiometry (DXA) (Discovery Ci: Hologic Inc., USA). Participants with a left hip prosthesis or hip fracture were assessed in the right femoral neck.[22]

Osteopenia and osteoporosis were diagnosed according to the WHO criteria.[24] Based on the young adult mean (YAM), the following criteria were used: normal: 88.6% ≤ YAM (−1 SD ≤), osteopenia: 70% < YAM < 88.6% (<-1 SD and >-2.5 SD), and osteoporosis: YAM ≤70% (≤ −2.5 SD). This study defined a reduced BMD as osteopenia and osteoporosis.[22]

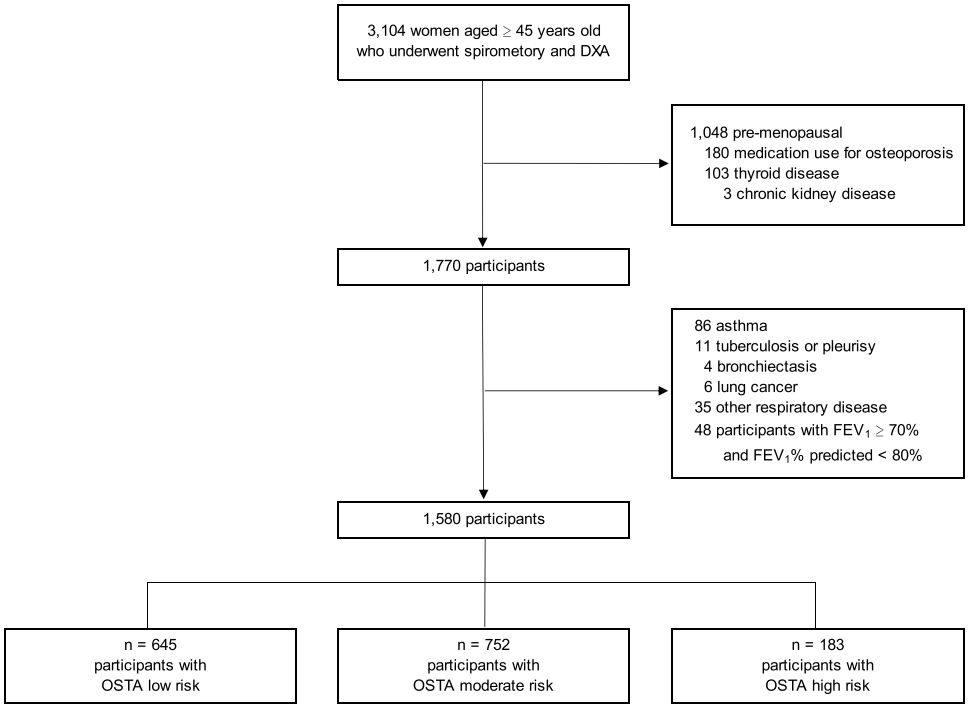

Figure 1 Flow chart for selecting the participants according to the OSTA risk level.
Notes: OSTA index: 0.2 × {BW (kg) - age} OSTA risk level was defined as follows; low (>-1), moderate (−4 to −1), or high (<-4).
Abbreviations: DXA, dual-energy X-ray absorptiometry; FEV1, forced expiratory volume in 1 s; OSTA, the osteoporosis self-assessment tool for Asians.

The OSTA was calculated by subtracting the age in years from the body weight (BW) in kilograms, and the result was multiplied by 0.2.[15] The OSTA risk level was defined as follows: low risk (>-1), moderate risk (−4 to −1), and high risk (<-4), as previously reported.[15,16]

Participants were classified as low-, moderate-, or high-risk based on the OSTA index and normal, osteopenic, and osteoporotic based on BMD.

Pulmonary Function Tests

Pulmonary function tests were performed using an electronic spirometer (DISCOM-21 FX; CHEST MI, Tokyo, Japan), as previously described.[22,23]

The quality criteria and equipment used complied with international recommendations.[25] Spirometry was performed per the American Thoracic Society and the European Respiratory Society guidelines.[25]

AL was defined as an FEV_1/FVC ratio of <70%, according to the Global Initiative for GOPD guidelines.[6] However, bronchodilator reversibility testing was not performed in this study.

Predicted values were determined using the following equations published by the Japanese Respiratory Society: 0.022 × height (cm) - 0.022 × age - 0.005.[9]

Physical Examination and Blood Measurements

Body mass index (BMI) was calculated by dividing the BW (kg) by the square of the height (m^2), classified underweight (<18.5), normal weight (18.5 ≤ BMI <25.0), or overweight (≥25.0).[26]

Abdominal circumference was measured at the end of normal expiration in the standing position, and physical activity was categorized into "regular physical activity", which was defined as engaging in sports or other forms of exercise at least once weekly, and "physical inactivity", which was defined as engaging in irregular physical activity or no form of physical activity.[22]

Alcohol consumption was classified as: "nondrinkers", "consuming alcohol for 1–6 days per week", or "daily drinkers".[22]

Participants were classified based on their smoking status as never smokers, former smokers, or current smokers. Never-smokers included those who had never smoked cigarettes in their lifetime. Former smokers were those who reported smoking cessation before the examination and did not smoke. Furthermore, current smokers were those who smoked during the interviews.[22] The number of pack years was calculated by dividing the average number of cigarettes smoked daily by 20 and multiplying it by the number of years smoked. Second-hand smoke (SHS) was defined as "non", "1–4 h daily", and "≥5 h daily" based on their reported time of exposure to SHS.

Participants, in a rested state, provided blood samples after overnight fasting. Analyses included creatinine, estimated glomerular filtration rate (eGFR), fasting glucose, triglycerides, free thyroxine, thyroid-stimulating hormone (TSH), white blood cell (WBC) count, and high-sensitivity C-reactive protein (hsCRP).

Clinical Information

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using an automatic digital sphygmomanometer (HEM-904; OMRON, Kyoto, Japan) by trained nurses. Placed on the upper arm at the height of the heart, readings were taken with the participants seated.[22]

Before the initial BP measurement, participants rested for at least 5 min, and SBP and DBP were recorded as the average of the two measurements.

Medical histories of rheumatoid arthritis, diabetes, ovary removal surgery, and current medication use were evaluated. Coexisting diabetes was defined as fasting glucose level ≥126 or the use of diabetes medication.

Statistical Analyses

Data are expressed as the number of cases with percentages, means (SD), or medians with interquartile ranges. The normality of the data was assessed using the Shapiro–Wilk test. Analysis of variance, Kruskal–Wallis test, and Chi-squared test were conducted to evaluate the differences in characteristics among the OSTA low-risk level (low), moderate risk level (moderate), and high-risk level (high). A post hoc analysis comparing differences in characteristics between groups was performed using Scheffe's test.

Simple regression analyses assessed correlations between independent variables AL and BMD. Considering clinically related or significant variables and multicollinearity, we performed multiple linear regression analyses to identify the independent factors of BMD and FEV_1/FVC.

We used multivariate logistic regression models to examine the associations between OSTA and BMD, BMD and AL, and OSTA and AL. Statistical significance was set at $p<0.05$. All statistical analyses were performed using the IBM SPSS statistics software (version 22.0; IBM Corporation, Armonk, NY, USA).

Results

Demographic and Clinical Characteristics

This study's participants had a mean age of 60.3 years, 22.4% were diagnosed with osteoporosis, and 5.3% had AL. None of the participants were diagnosed with COPD disease or were taking medication for osteoporosis. Baseline characteristics of the 1580 post-menopausal women aged ≥45 years according to the OSTA risk level (Table 1).

In this study, the low-, moderate-, and high-risk OSTA groups comprised 40.8% (n=645), 47.6% (n=752), and 11.6% (n=183) of the observations, respectively (Figure 1 and Table 1).

The mean age of the high-class group was significantly higher than those of the other groups. The number of underweight participants in the OSTA high-risk group was higher (n = 50, 27.3%) than that in the other groups. SBP was higher in the high-risk OSTA group than in the other groups. The high-risk group included fewer smokers than the other groups. Similarly, the number of participants who were alcohol drinkers and inactive in the OSTA high-risk group was lower than that in the other groups. No differences were observed in the number of participants with SHS exposure,

Table 1 Characteristics of the Participants Based on the OSTA Risk Level

	Low n = 645	Moderate n = 752	High n = 183	*p*-value
Age, yr	56.0 (4.6)	61.2 (5.4)*	72.2 (6.5)* **	<0.001
45–54, n (%)	264 (40.9)	77 (10.3)	0 (0.0)	<0.001
55–64, n (%)	350 (54.3)	471 (62.6)	21 (11.5)	
65–74, n (%)	31 (4.8)	192 (25.5)	89 (48.6)	
75–84, n (%)	0 (0.0)	12 (1.6)	68 (37.2)	
85≥, n (%)	0 (0.0)	0 (0.0)	5 (2.7)	
Height, cm	157.7 (5.0)	154.5 (4.9)*	150.1 (4.7)* **	<0.001
Weight, kg	59.3 (7.7)	49.6 (5.0)*	45.4 (5.3)* **	<0.001
Abdominal circumference, cm	86.5 (8.5)	78.4 (7.1)*	77.7 (8.0)*	<0.001
BMI, kg/m^2	23.9 (3.4)	20.8 (2.4)*	20.2 (2.4)* **	<0.001
BMI classification, n (%)				
Normal: ≤18.5 BMI <25.0	409 (63.4)	593 (78.9)	127 (69.4)	<0.001
Overweight: ≤25 BMI	221 (34.3)	37 (4.9)	6 (3.3)	
Underweight: BMI <18.5	15 (2.3)	122 (16.2)	50 (27.3)	
Systolic blood pressure, mmHg	122.6 (17.5)	121.3 (17.2)	126.2 (17.4)* **	0.003
Diastolic blood pressure, mmHg	72.9 (11.1)	71.0 (10.6)*	69.9 (9.5)*	0.005
Smoking status, n (%)				
Never smokers	545 (84.5)	665 (88.4)	176 (96.2)	0.001
Former smokers	70 (10.9)	61 (8.1)	5 (2.7)	
Current smokers	30 (4.7)	26 (3.5)	2 (1.1)	
Pack-years	2.0 (6.9)	1.5 (7.0)	0.5 (4.2)*	0.026
Exposure to second-hand smoke (n=1521), n (%)	n=615	n=726	n=180	
non	527 (85.7)	618 (85.1)	162 (90.0)	0.284
1–4 hours/day	79 (12.8)	94 (13.0)	18 (10.0)	
≥5 hours/day	9 (1.5)	14 (1.9)	0 (0.0)	
Alcohol consumption, n (%)				
non	392 (60.8)	465 (61.8)	141 (77.1)	<0.001
1–6 days/week	215 (33.3)	226 (30.1)	37 (20.2)	
daily	38 (5.9)	61 (8.1)	5 (2.7)	
Physical activity, n (%)				
Regular activity	288 (44.7)	433 (57.6)	116 (63.4)	<0.001
Inactive	357 (55.3)	319 (42.4)	67 (36.6)	
Diabetes, n (%)	40 (6.2)	32 (4.3)	14 (7.7)	0.105
History of rheumatoid arthritis, n (%)	13 (2.0)	8 (1.1)	1 (1.0)	0.186
Removal of the ovary, n (%)	42 (6.5)	48 (6.4)	6 (3.3)	0.241
Lung function				
FVC, mL	2913.0 (403.5)	2709.6 (349.6)*	2335.5 (341.8)* **	<0.001
FEV_1, mL	2284.6 (321.6)	2105.5 (309.7)*	1753.2 (280.5)* **	<0.001
FEV_1/FVC, %	78.6 (4.9)	77.8 (5.8)*	75.2 (6.0)* **	<0.001
FEV_1% predicted, %	102.3 (11.9)	103.0 (13.1)	103.0 (14.8)	0.835
Laboratory data				
(interquartile range)				
Creatinine, mg/dL	0.63 (0.57–0.69)	0.62 (0.56–0.68)	0.63 (0.56–0.70)	0.545
eGFR, mL/m/1.73m^2	75.2 (67.0–83.4)	74.4 (66.5–82.3)	70.1 (62.2–78.0)* **	<0.001
Fasting glucose, mg/dL (n = 1469)	n=610 97.0 (91.0–103.0)	n=692 95.0 (89.5–100.5)*	n=167 97.0 (90.5–103.5)	0.006
Thyroid hormone (n = 915)	n=397	n=425	n=93	
FT4, ng/dL	0.93 (0.85–1.01)	0.94 (0.87–1.02)	0.95 (0.86–1.04)	0.624
TSH, μU/mL	1.51 (0.96–2.06)	1.76 (1.09–2.44)*	1.94 (1.29–2.60)	0.030
Triglycerides, mg/dL	89.0 (57.5–120.5)	76.0 (53.5–98.5)*	74.0 (52.0–96.0)*	<0.001
White blood cell count, /μL	4800 (4050–5550)	4500 (3800–5200)*	4500 (3650–5350)	<0.001
hsCRP, mg/L (n=1577)	n=642 0.07 (0.03–0.12)	0.04 (0.01–0.07)	0.05 (0.02–0.09)	0.092

Notes: Data are expressed as means (standard deviation), median (interquartile range), or as number (n) (percentage) ack year = (number of cigarettes smoked per day × number of year smoked)/20 * **Significantly different from low and moderate, respectively ($p < 0.05$).

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; FT4, free thyroxine; hsCRP, hypersensitivity C-reactive protein; TSH, thyroid stimulating hormone.

diabetes, history of rheumatoid arthritis, or history of ovary removal. FVC, FEV_1, FEV_1/FVC, and eGFR were significantly lower in the OSTA high group than in the other groups.

Table 2 shows the baseline characteristics classified as normal BMD, osteopenia, and osteoporosis according to WHO criteria. Participants with osteoporosis were older and had a lower BMI than those in the other groups. The number of alcohol drinkers and individuals with diabetes was lower in participants with osteoporosis than those with normal BMD. In contrast, smoking status, pack years of exposure to SHS, physical activity, number of rheumatoid arthritis cases, and ovary removal were not significantly different among the three groups. Significant differences were found in FVC, FEV_1, creatinine, fasting glucose, and triglycerides levels among participants with osteopenia and osteoporosis compared with those with normal BMD.

Table 2 Characteristics of the Participants Based on Bone Mineral Density According to the WHO Diagnostic Criteria

	Normal = 340	Osteopenia n = 886	Osteoporosis n = 354	*p*-value
Age, yr	58.2 (6.0)	60.1 (6.8)*	63.1 (8.2)* **	<0.001
45–54, n (%)	96 (28.2)	197 (22.2)	48 (13.6)	<0.001
55–64, n (%)	189 (55.6)	481 (54.3)	172 (48.6)	
65–74, n (%)	50 (14.7)	176 (19.9)	86 (24.3)	
75–84, n (%)	5 (1.5)	29 (3.3)	46 (13.0)	
85≥, n (%)	0 (0.0)	3 (0.3)	2 (0.5)	
Height, cm	156.7 (5.4)	155.6 (5.1)*	153.1 (5.7)* **	<0.001
Weight, kg	58.4 (9.6)	52.9 (7.1)*	48.3 (6.2)* **	<0.001
Abdominal circumference, cm	85.5 (10.1)	81.3 (8.0)*	78.8 (8.0)* **	<0.001
BMI, kg/m^2	23.8 (3.9)	21.9 (2.9)*	20.6 (2.7)* **	<0.001
BMI classification, n (%)				
Normal: ≤18.5 BMI <25.0	209 (61.5)	665 (75.1)	255 (72.0)	<0.001
Overweight: ≤25 BMI	114 (14.2)	126 (14.2)	24 (6.8)	
Underweight: BMI <18.5	17 (5.0)	95 (10.7)	75 (21.2)	
Systolic blood pressure, mmHg	125.3 (17.1)	121.3 (17.4)*	122.4 (17.3)	0.002
Diastolic blood pressure, mmHg	73.7 (10.9)	71.1 (10.7)*	70.9 (10.5)*	0.001
Smoking status, n (%)				
Never smokers	295 (86.8)	785 (88.6)	306 (86.4)	0.770
Former smokers	30 (8.8)	72 (8.1)	34 (9.6)	
Current smokers	15 (4.4)	29 (3.3)	14 (4.0)	
Pack-years	2.0 (7.4)	1.3 (5.2)	2.0 (9.0)	0.390
Exposure to second-hand smoke (n=1521), n (%)	n=325	n=857	n=339	
non	283 (87.1)	734 (85.6)	290 (85.5)	0.349
1–4 hours/day	39 (12.0)	112 (13.1)	40 (11.8)	
≥5 hours/day	3 (0.9)	11 (1.3)	9 (2.7)	
Alcohol consumption, n (%)				
non	186 (54.7)	569 (64.2)	243 (68.6)	0.002
1–6 days/week	123 (36.2)	267 (30.1)	88 (24.9)	
daily	31 (9.1)	50 (5.7)	23 (6.5)	
Physical activity, n (%)				
Regular activity	181 (53.2)	480 (54.2)	176 (49.7)	0.362
Inactive	159 (46.8)	406 (45.8)	178 (50.3)	
Diabetes, n (%)	31 (9.1)	46 (5.2)	9 (2.5)	0.001
History of rheumatoid arthritis, n (%)	7 (2.1)	13 (1.5)	2 (0.6)	0.234
Removal of the ovary, n (%)	23 (6.8)	55(6.2)	18 (5.1)	0.632
Lung function				
FVC, mL	2864.5 (414.7)	2764.7 (396.6)*	2600.3 (404.1)* **	<0.001
FEV_1, mL	2236.1 (343.0)	2151.2 (337.0)*	2009.9 (357.5)* **	<0.001
FEV_1/FVC, %	78.1 (5.1)	77.9 (5.4)	77.3 (6.1)	0.125
FEV_1% predicted, %	103.4 (12.0)	102.8 (12.9)	101.9 (13.3)	0.245

(*Continued*)

Table 2 (Continued).

	Normal = 340	Osteopenia n = 886	Osteoporosis n = 354	*p*-value
Laboratory data (interquartile range)				
Creatinine, mg/dL	0.64 (0.58–0.70)	0.62 (0.56–0.68)*	0.61 (0.56–0.66)*	0.003
eGFR, mL/m/1.73m^2	73.2 (65.1–81.3)	74.7 (66.9–82.5)	74.7 (67.1–82.4)	0.083
Fasting glucose, mg/dL (n=1469)	n=315 97.0 (90.5–103.5)	n=830 96.0 (90.5–101.5)*	n=324 95.0 (89.5–100.5)*	<0.001
Thyroid hormone (n=915)	n=211	n=523	n=181	
FT4, ng/dL	0.93 (0.85–1.02)	0.94 (0.86–1.03)	0.93 (0.86–1.01)	0.426
TSH, μU/mL	1.73 (1.02–2.44)	1.56 (0.97–2.16)	1.81 (1.18–2.45)	0.580
Triglycerides, mg/dL	86.0 (54.0–118.0)	79.0 (54.0–104.0)*	79.0 (56.5–101.5)*	0.001
White blood cell count, /μL	4800 (4100–5500)	4600 (3850–5350)	4600 (3850–5350)	0.058
hsCRP, mg/L (n=1577)	0.06 (0.02–0.11)	n=883 0.05 (0.02–0.09)	0.05 (0.02–0.09)	0.210

Notes: Data are expressed as means (standard deviation), median (interquartile range), or as number (n) (percentage) Pack year = (number of cigarettes smoked per day × number of year smoked)/20 * **Significantly different from normal and osteopenia, respectively ($p < 0.05$).
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; FT4, free thyroxine; hsCRP, hypersensitivity C-reactive protein; TSH, thyroid stimulating hormone; WHO, World Health Organization.

OSTA and BMD

A. Correlates of BMD

BMD significantly correlated with age, BW, OSTA, height, abdominal circumference, BMI, FEV_1, FVC, creatinine, eGFR, fasting glucose, and hsCRP (Supplementary Table 1). In contrast, the FEV_1/FVC ratio did not significantly correlate with BMD.

B. Multiple Linear Regression Analysis for BMD

Multivariate analyses were performed to identify the independent factors of BMD, considering multicollinearity. Several models were evaluated in the multivariate analyses because of multicollinearity between FEV_1 and FVC (r=0.904). In the multiple regression analysis, age and the OSTA were independently associated with BMD in all models (Supplementary Table 2). Moreover, FEV_1 and FVC were independently associated with BMD in a multiple linear regression model adjusted for age, BMI, creatinine, fasting glucose, and hsCRP. In contrast, FEV_1/FVC was not significantly associated with BMD. No significant associations were observed between FEV_1 and BMD and FVC and BMD in the models that included the OSTA index instead of age and BMI.

C. Prevalence of Osteopenia and Osteoporosis According to the OSTA Risk Level

A higher prevalence of osteoporosis (n=90, 49.2%) was observed in the high-risk OSTA group than in the low- and moderate-risk groups ($p<0.001$). In contrast, few differences were found in the prevalence of osteopenia among the groups (Supplementary Table 3).

D. Association Between the OSTA and Reduced BMD

In the logistic regression analysis, the unadjusted odds ratio (OR) of reduced BMD in participants with the OSTA high risk was significantly higher than in those with normal BMD [OR: 6.86 (3.82–12.34)] ($p<0.001$). Additionally, after adjusting for confounding factors, a significant difference was found in the OSTA high-risk and reduced BMD [OR: 6.80 (3.74–12.35)] ($p<0.001$) (Table 3).

BMD and AL

A. Multiple Linear Regression Analysis for FEV_1/FVC

In the multiple regression analysis, including significant variables of correlates of FEV_1/FVC, age, the OSTA, and pack year were independently associated with FEV_1/FVC, respectively ($p<0.001$) (Table 4).

Table 3 Association Between OSTA Risk Level and Reduced Bone Mineral Density

	OSTA risk level				
	Low n=645	**Moderate n=752**	***p*-value**	**High n=183**	***p*-value**
Crude	Reference	3.23 (2.49–4.21)	<0.001	6.86 (3.82–12.34)	<0.001
Adjusted	Reference	3.31 (2.52–4.36)	<0.001	6.80 (3.74–12.35)	<0.001

Notes: Adjusted for physical activity, alcohol consumption, smoking status, the current use of medication for diabetes and hyperglycemia, the current use of medication for rheumatoid arthritis, exposure to second-hand smoke, and removal of the ovary. According to the WHO diagnostic criteria, reduced bone mineral density was defined as osteopenia and osteoporosis. OSTA index: 0.2 × {BW (kg) - age} OSTA risk level was defined as follows; low (>-1), moderate (−4 to −1), and high (<-4).
Abbreviations: OSTA, the osteoporosis self-assessment tool for Asians; WHO, World Health Organization.

Table 4 Multivariable Linear Regression Analyses of FEV_1/FVC

	Model 1		Model 2		Model 3		Model 4	
	β	***p*-value**	***β***	***p*-value**	***β***	***p*-value**	***β***	***p*-value**
Age	−0.285***	<0.001	−0.278***	<0.001	–	–	–	–
Body weight	−0.030	0.227	–	–	–	–	–	–
Abdominal circumference	–	–	−0.027	0.268	–	–	−0.214***	<0.001
OSTA index	–	–	–	–	0.174***	<0.001	0.287***	<0.001
Pack year	−0.082***	0.001	−0.083**	0.001	−0.094***	<0.001	−0.085**	0.001
eGFR	0.027	0.277	0.029	0.237	0.073**	0.003	0.056*	0.022
hsCRP	−0.019	0.440	−0.018	0.451	−0.046	0.065	−0.018	0.456

Notes: *p-value < 0.05; **p-value < 0.01; ***p-value < 0.001.
Abbreviations: eGFR, estimated glomerular filtration rate; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; hsCRP, hypersensitivity C-reactive protein; OSTA, osteoporosis self-assessment tool for Asians.

Table 5 Prevalence of AL According to Bone Mineral Density Test

	Bone mineral density			
	Normal n = 340	**Osteopenia n = 886**	**Osteoporosis n = 354**	***p*-value**
AL (-)	327 (96.2)	843 (95.1)	326 92.1)	0.037
AL (+)	13 (3.8)	43 (4.9)	28 (7.9)	

Notes: Data are expressed as number (n) (percentage). Osteopenia and osteoporosis were diagnosed according to the WHO diagnostic criteria. Based on the young adult mean (YAM), the following criteria were used: normal: 88.6% ≤ YAM (−1 SD ≤), osteopenia: 70% < YAM < 88.6% (<-1 SD and >-2.5 SD), and osteoporosis: YAM ≤70% (≤ −2.5 SD). AL was defined as FEV_1/FVC <0.7.
Abbreviation: AL, airflow limitation.

B. Prevalence of AL According to BMD Categories

The prevalence of AL in participants with osteoporosis (7.9%) was significantly higher than that in those with normal BMD (3.8%) (p=0.037) (Table 5).

C. OR of AL in Participants According to BMD Categories

Unadjusted OR of AL in participants with osteoporosis [OR: 2.16 (1.10–4.25)] was significantly higher than that in those with normal BMD (p=0.025). However, the logistic regression analysis found no significant association in osteoporosis and AL after adjusting for confounding factors, including age and BMI (Supplementary Table 4).

OSTA and AL

A. Correlates of the OSTA

Significant correlations existed between the OSTA and height, abdominal circumference, BMI, FEV_1/FVC, FEV_1, FVC, pack years, eGFR, fasting glucose, TSH, WBC, and hsCRP (Supplementary Table 1).

Table 6 Prevalence of AL According to OSTA Risk Level

	OSTA risk level				
	Lown = 645	**Moderate n = 752**	**High n = 183**	**Total n = 1580**	***p*-value**
AL (-)	625 (96.9)	716 (95.2)	155 (84.7)	1496 (94.7)	<0.001
AL (+)	20 (3.1)	36 (4.8)	28 (15.3)	84 (5.3)	

Notes: Data are expressed as number (n) (percentage) OSTA index: 0.2 × {BW (kg) - age} OSTA risk level was defined as follows; low (>-1), moderate (−4 to −1), and high (<-4). AL was defined as FEV_1/FVC <0.7.
Abbreviations: AL, airflow limitation; OSTA, osteoporosis self-assessment tool for Asians.

Prevalence of AL in Participants According to the OSTA Risk Level

The prevalence of AL in participants with a high OSTA risk (15.3%) was significantly higher than that in those with a low OSTA risk (3.1%) (p<0.001) (Table 6).

ORs of AL in Participants According to the OSTA Risk Level

The OR of AL in participants with the OSTA high risk [OR: 5.65 (3.10–10.29)] was significantly higher than that in those with the OSTA low risk in the crude model (p<0.001). Moreover, the OR of AL in participants with the OSTA high risk remained significantly higher than that in those with the OSTA low risk after adjusting for confounding factors in logistic regression analysis [OR: 5.48 (2.90–10.37)] (p<0.001) (Table 7).

Discussion

This study evaluated the relationship between OSTA and BMD, BMD and AL, and OSTA and AL in Japanese post-menopausal women aged ≥45 years old. The OSTA high-risk group had a higher prevalence of osteoporosis and AL than the OSTA low-risk group. Furthermore, the risk of AL was higher in the OSTA high group than in the OSTA low group. Therefore, our findings suggest that high-risk OSTA is a characteristic of post-menopausal women with osteoporosis and AL. To the best of our knowledge, this is the first study to demonstrate an association between the OSTA and AL. Considering that participants with OSTA high risk have a high prevalence of fractures[27] and patients with COPD have a higher risk of death following a hip fracture,[5] the relationship between OSTA and AL is also important for preventing fractures in those with decreased pulmonary function.

Our Results are consistent with those of previous studies that have focused on BMD and pulmonary function. Previous observational studies enrolling post-menopausal women aged ≥50 have indicated that VC and FVC were independent predictors of femoral neck BMD in addition to age and BMI. At the same time, FEV_1/FVC was not associated with BMD.[5] The Cambridge General Practice Health Study, which included women aged 45–76 years, has demonstrated that lower FEV_1 was positively and independently related to femoral neck BMD measured using DXA.[12] Similarly, we found that FVC and FEV_1 were independent determinants of BMD in forced multiple linear regression

Table 7 Multivariate Regression Analyses Between OSTA Risk Level and AL

	OSTA risk level				
	Low n = 654	**Moderate n = 752**	***p*-value**	**High n = 183**	***p*-value**
Crude	Reference	1.57 (0.90–2.74)	0.112	5.65 (3.10–10.29)***	<0.001
Model 1	Reference	1.60 (0.91–2.83)	0.103	5.67 (3.03–10.60)***	<0.001
Model 2	Reference	1.56 (0.89–2.75)	0.124	5.60 (3.00–10.47)***	<0.001
Model 3	Reference	1.39 (0.77–2.53)	0.277	5.48 (2.90–10.37)***	<0.001

Notes: ***p-value < 0.001 Model 1: Adjusted for smoking status, alcohol consumption, and physical activity. Model 2: Adjusted for covariates in Model 1 plus the current use of medication for diabetes and hyperglycemia and the current use of medication for rheumatoid arthritis. Model 3: Adjusted for covariates in Model 2 plus exposure to second-hand smoke and ovary removal. AL was defined as FEV_1/FVC <0.7. OSTA index: 0.2 × {BW (kg) - age} OSTA risk level was defined as follows; low (>-1), moderate (−4 to −1), and high (<-4).
Abbreviations: AL, airflow limitation; OSTA, the osteoporosis self-assessment tool for Asians.

analyses adjusted for age and BMI. In contrast, the relationship between BMD and FEV_1/FVC was not significant in multiple linear regression analysis. A previous study, which recruited post-menopausal women aged ≥50 years with diagnosed COPD and age-matched past smokers, demonstrated that moderate-to-very severe airway obstruction were related to osteopenia and osteoporosis BMD in patients with COPD.[28] Moreover, research conducted using data from the Third National Health and Nutrition Examination Survey reported that severe AL is a risk factor for osteopenia and osteoporosis.[29] We evaluated more participants and FEV_1/FVC using prebronchodilator spirometry; however, there were no participants with severe or very severe AL and a small number of moderate AL (n=19) and current smokers (n=58). Therefore, more women with moderate or severe COPD or AL are needed to examine the relationship between pulmonary function and BMD. Our results suggest that participants with mild AL might have a low risk of reduced femoral neck BMD. However, investigating individuals without COPD and osteoporosis is vital to diagnose them earlier and to prevent osteoporosis-related fractures in the general population with asymptomatic disease because AL is also present in non-smokers[30] and loss of lung function is accelerated at the stage of moderate AL.[31] Considering that the OSTA index was an independent predictor of FEV_1/FVC in forced multiple linear regression analyses adjusted for pack-years, a lower OSTA index might indicate both low FEV_1/FVC and osteoporosis in this study.

An observational study evaluating non-smoking healthy pre-and post-menopausal women aged 53–67 in Asia showed that proximal femur BMD was closely associated with pulmonary function parameters, such as FEV_1/FVC, FVC, and FEV_1 in post-menopausal women rather than in pre-menopausal women.[14] Although confounding factors of BMD were not evaluated and analyzed in multivariate analyses, post-menopausal women had decreased BMD and pulmonary function. Intriguingly, a cross-sectional study conducted in Asia suggested that FVC and FEV_1 were associated with BMD at the femoral neck in healthy non-smoking pre-menopausal women rather than in post-menopausal women; FEV_1 (%) correlated with BMD at the femoral neck and total hip only in post-menopausal women, and FEV_1/FVC was not related to BMD in either group.[11] The population age of our study probably affected BMD because our study population was older than the study participants. Moreover, a previous study among Caucasians in the United States has demonstrated that the risk of osteoporosis increased linearly to the severity of airflow obstruction in patients with airflow obstruction.[29] However, data on menopause were not shown. Therefore, we should consider age, menopause, and smoking status to deeply understand the associations between BMD and AL in women.

Generally, aging causes a decrease in BMD and pulmonary function. Although FVC and FEV_1 were lower in the osteoporosis and OSTA high-risk groups, who were older than the other groups, FEV_1/FVC was lower only in the OSTA high-risk group (Tables 1 and 2). Therefore, the common characteristics of participants with osteoporosis and AL were probably reflected in the OSTA high-risk level. By generation, approximately 20% of each of those aged 75–84 years old and >85 years old had AL, whereas 44 (52.4%) of the total 84 participants with AL were 64 years old or younger in this study (data not shown).

Our results suggest that the OSTA index might be used for screening AL in Japanese post-menopausal women.

Tsuji et al suggested that aging may influence the progression of COPD.[32] Epidemiologic studies have shown that the prevalence of AL defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria tends to be higher in older generations, and AL was observed in participants in their 40s.[23,33] It is unclear whether the high prevalence of AL in older patients is caused by long-term exposure to factors that induce AL or aging effects. Although the use of FEV_1/FVC<70% for diagnosing COPD in the elderly is controversial, a fixed FEV_1/FVC <70% value is widely regarded as a diagnostic criterion according to the GOLD.[6] In fact, a cohort study, which enrolled the general population aged ≥45 years old, has demonstrated that definition of FEV_1/FVC <70% had been related to hospitalization and mortality due to COPD and supported the use of FEV_1/FVC <70% to identify individuals at risk of COPD related burden.[34] Therefore, it is important to identify individuals with FEV_1/FVC<70% in the general population with non-diagnosed COPD. Assessing the association between BMD and AL seemed to be difficult because natural menopause and aging affect both BMD and pulmonary function in post-menopausal women. Menopause leads to imbalanced bone remodeling and a decline in lung function,[35] whereas previous observational studies reported no changes in FEV_1/FVC and AL in post-menopausal women compared with pre-menopausal women.[36] If both FEV_1 and FVC decrease, the FEV_1 /FVC ratio may not significantly change before or after menopause. Therefore, it is necessary to consider the participants' age at menopause and duration of menopause[36] in the study population to understand the relationship between BMD and

pulmonary function in post-menopausal women. In contrast to previous studies, we evaluated the AL criteria and FEV_1/FVC. AL is a standard diagnostic criterion for COPD. AL was observed in 15.3% of the high-risk OSTA group in this study participants. Although the effects of aging and menopause on BMD and pulmonary function are complex, and the mechanisms of osteoporosis comorbid with COPD are unclear currently, OSTA high risk consisting of older age and lower body weight might represent the characteristics of post-menopausal women with obstructive pulmonary disease. Considering that menopausal status was associated with bone remodeling as well as accelerated lung function decline,[35] identifying pulmonary dysfunction in menopausal women with a high risk of osteoporosis might be beneficial.

This study has some limitations. First, data on vitamin D levels, sunlight exposure, corticosteroid use, work environment, and occupational factors were not evaluated. Therefore, additional research is required to confirm whether the OSTA, including these factors, is associated with BMD and AL in post-menopausal women. Second, participants with AL could have included those with a postbronchodilator FEV_1/FVC ratio >70% because we could not employ reversibility testing because of the absence of high suspicion of COPD. Participants diagnosed with asthma or other respiratory diseases were excluded from this study. However, these excluded individuals could have had COPD or asthma; thus, we expressed "AL" instead of COPD.[22,23] Third, the sample size of the study population was limited. Moreover, the modest size of the study population and sampling bias as participants were recruited from among those who underwent optional BMD measurement (DXA). The relatively small sample size for the high OSTA risk group could have had less statistical power than that for the low-risk group. In addition, recruiting participants with more than moderate AL who met the study inclusion criteria proved difficult despite screening large numbers of participants. The prevalence of moderate AL was only 3.3% in the OSTA high-risk group, although it was significantly higher than that in the other groups; severe AL was not observed in this study population (Supplementary Table 5). A previous study reported that participants with severe AL have a higher prevalence of osteoporosis than those without AL in the general population.[29] Consequently, further studies with large sample sizes, including participants with a wider range of AL severities, are needed. In two studies conducted in a general population sample, the estimated prevalence of AL diagnosed according to GOLD was 5.0%[33] and 5.8%[37] in Japanese women aged 40 years. Although sampling bias was present, the prevalence of AL in our study was consistent with this rate. Among the three OSTA risk groups, AL severity was the mildest (n=65, 77.4%) in this study. Moreover, the OSTA high-risk group included 22 and 6 participants with mild and moderate AL, respectively. Clinicians should be aware of AL and respiratory symptoms in thin patients with osteoporosis. Finally, the detailed mechanisms underlying osteoporosis in patients with COPD remain unclear. Increased serum concentrations of pro-inflammatory cytokines, including bone resorption,[38] are caused by airway inflammation in COPD.[39] AL occurs in the alteration of airways and emphysema,[40] and whether the inflammatory processes associated with emphysema can reduce BMD remains unclear. Pablo et al showed that CRP levels are closely associated with BMD in a US general population sample.[41] In this study, hsCRP levels did not differ among the groups classified according to BMD. Although the mechanisms and causal factors of reduced BMD in women vary, populations with systemic inflammation and risk of AL, such as smoking and environmental factors, including exposure to dust, gases, and fumes, should be examined to clarify the relationship between AL and osteoporosis and to evaluate the usefulness of OSTA for AL.

Despite these limitations, OSTA may be beneficial for early diagnosis and treatment of osteoporosis or COPD in Japanese post-menopausal women because it is associated with reduced BMD and the presence of AL. None of our participants were diagnosed with COPD or received osteoporosis treatment. Although no relationship between BMD and AL was observed, individuals at risk of osteoporosis and those with AL shared common characteristics. Evaluating OSTA for other symptoms or osteoporosis-related diseases such as COPD is also worthwhile.

Conclusion

We found an association between the OSTA and AL in post-menopausal women in Japan. However, further research is needed to examine the possible association between BMD and AL. Our findings suggest OSTA high risk as a screening criterion for AL in post-menopausal Japanese women.

Ethical Approval

This study was approved by the Human Ethics Committee of Kumamoto University (Number 84) and the Japanese Red Cross Kumamoto Health Care Center.

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