Observational Study

Association Between Abdominal Obesity and Subsequent Vertebral Fracture Risk

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Background: Obesity had been previously considered to be a protective factor against osteoporosis or fractures; however, recent research indicates that obesity, especially abdominal obesity, may increase the risk of some types of fractures.

Objective: We explored the effects of abdominal obesity on subsequent vertebral fracture (SVF) after percutaneous vertebral augmentation (PVA).

Study Design: A prospective observational cohort study.

Setting: Department of Spinal Surgery of a hospital affiliated with a medical university.

Methods: A total of 390 women and 237 men aged > 50 years suffering from osteoporotic vertebral fracture (OVF) were included. Weight, height, bone mineral density (BMD), abdominal circumference, and other basic information were measured at baseline and 1-year follow-up visit.

Results: During follow-up, 80 (33.7%) men and 143 (36.7%) women incurred SVF. Greater waist circumference (WC) and waist-to-hip ratio (WHR) increased the risk of SVF in men (WC: HR 1.83, $P = 0.016$; WHR: HR 1.63, $P = 0.045$) and women (WC: HR 2.75, $P = 0.001$; WHR: HR 2.63, $P = 0.001$) after adjustment for BMD and other potential confounders. Compared with normal BMI, being overweight was associated with lower SVF risk (women: HR 0.55, $P = 0.044$; men: HR 0.46, $P = 0.046$), and obesity was associated with greater SVF risk (women: HR 4.53, $P < 0.001$; men: HR 3.77, $P < 0.001$) in both genders. We observed a nonlinear relationship between BMI and SVF with a U-shaped curve; after adjusting BMD, this became a reverse J-curve.

Limitations: There was no further statistical analysis of the relationship between abdominal obesity and other fracture sites. Asymptomatic SVF may underestimate the impact of abdominal obesity on the occurrence of SVF.

Conclusions: Abdominal obesity was significantly associated with a higher risk of SVF after PVA. Management of body type after PVA may be an effective prevention strategy against SVF.

Key words: Subsequent vertebral fracture, percutaneous vertebral augmentation, abdominal obesity, overweight, waist circumference

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Obesity and fractures are both important public health issues. The interrelation between obesity and fracture is considered fracture site-dependent (1). Traditionally, low body mass index (BMI) has been thought of as a risk factor for fracture and obesity as a protective factor. However, a recent meta-analysis showed that high BMI increased the risk of osteoporotic fracture after adjustment for bone mineral density (BMD) in women (2); that study did not report the relationship between BMI and the risk of vertebral fracture. Another meta-analysis showed that a higher BMI was related to a decrease in the risk of vertebral fracture in men, but not in women; after adjustment for BMD, higher BMI significantly increased the risk of osteoporotic vertebral fracture (OVF) in women (3).

The distribution of body fat, especially abdominal fat, can potentially affect bone differently and may increase the fracture risk in comparison with peripheral subcutaneous fat (4). Recently, abdominal obesity has been reported to be positively associated with hip fracture, as measured by waist circumference (WC) and waist-to-hip ratio (WHR) (5). In the Tasmanian Older Adult Cohort study, the prevalence of vertebral fractures was positively association with WC in women (6). According to the current literature, WC is negatively related to BMD and might increase the risk of vertebral fracture (7). Moreover, Paik et al (8) reported that a larger WC was independently related to a higher vertebral fracture risk.

As a minimally invasive technique, percutaneous vertebral augmentation (PVA) can rapidly relieve pain, restore vertebral height, and provide biomechanical stability; however, increasingly greater evidence shows that the incidence of new OVF after PVA is significantly increased (9). Many studies have reported the risk factors for SVF, including decreased BMD, leakage of bone cement, excessive volume of bone cement, and BMI, among others (10). One study (11) demonstrated that an increased risk of OVF was related to low BMI (< 22 kg/m^2); however, Ren et al (12) reported that a higher BMI increased the occurrence of new symptomatic OVF after PVP. BMI is considered a controversial risk factor for SVF after PVA owing to a nonlinear relationship.

As far as we know, few studies have investigated the influence of BMI and abdominal obesity on incidence of SVF in patients who receive PVA treatment. In the present study, we explored the effects of BMI and abdominal obesity on SVF after PVA.

Methods

Participants

This was a population-based prospective cohort study conducted at our hospital. We included a total of 627 patients (390 women and 237 men) greater than 50 years of age who were assessed using a self-administered questionnaire and physical measurements. Our study was initiated in January 2015 and followed-up for 4-60 months until December 2020. Participants enrolled in our study had experienced an OVF and received PVA owing to ineffective conservative treatment, severe pain, unstable vertebral compression fractures, and nonunion of vertebral fractures. The study was approved by the ethics committee of our hospital. All participants agreed to the use of their clinical data for this study and provided their written informed consent. All participants met the following inclusion criteria: (1) age above 50 years; (2) experienced a low-energy fracture without bone trauma or developed tuberculosis during the follow-up period; (3) experienced a first OVF and had no prior history of spinal surgery; (4) a single-segment vertebral fracture combined with a unilateral approach PVA; (5) the amount of bone cement injected was 3 mL to 5 mL; and (6) patients were taking calcium, vitamin D, and anti-osteoporosis measures (bisphosphonates or teriparatide) after PVA treatments. Exclusion criteria included: (1) pathological fracture caused by cancer, infection, inflammatory disease, or high-energy trauma; (2) incomplete medical records, imaging data, and other physical measurements; (3) patients who subsequently died owing to an accident or other diseases; (4) imaging evidence showing intervertebral disc cement leakage; (5) patients with malnutrition (BMI < 18.5 kg/m^2); and (6) the presence of metabolic bone disease other than osteoporosis (including Cushing's disease, hyperthyroidism, hyperparathyroidism, thyroid cysts, or hypothyroidism) (Fig. 1).

Measurement

At baseline and at a follow-up visit after 1 year, height and weight were measured using an electronic scale. BMI was calculated as weight (kg) divided by height in meters squared (kg/m^2). Based on the Asia Pacific definition (13) of obesity, individuals with 18.5 kg/m^2 ≤ BMI < 23 kg/m^2 were categorized as "normal weight," those with BMI 23 to 25 kg/m^2 as "overweight," and participants with BMI ≥ 25 kg/m^2 as "obesity." WC was measured at the mid-point between the lowest rib and the iliac crest. Generalized obesity (BMI < 23 kg/m^2) and abdominal obesity (men: WC > 90 cm;

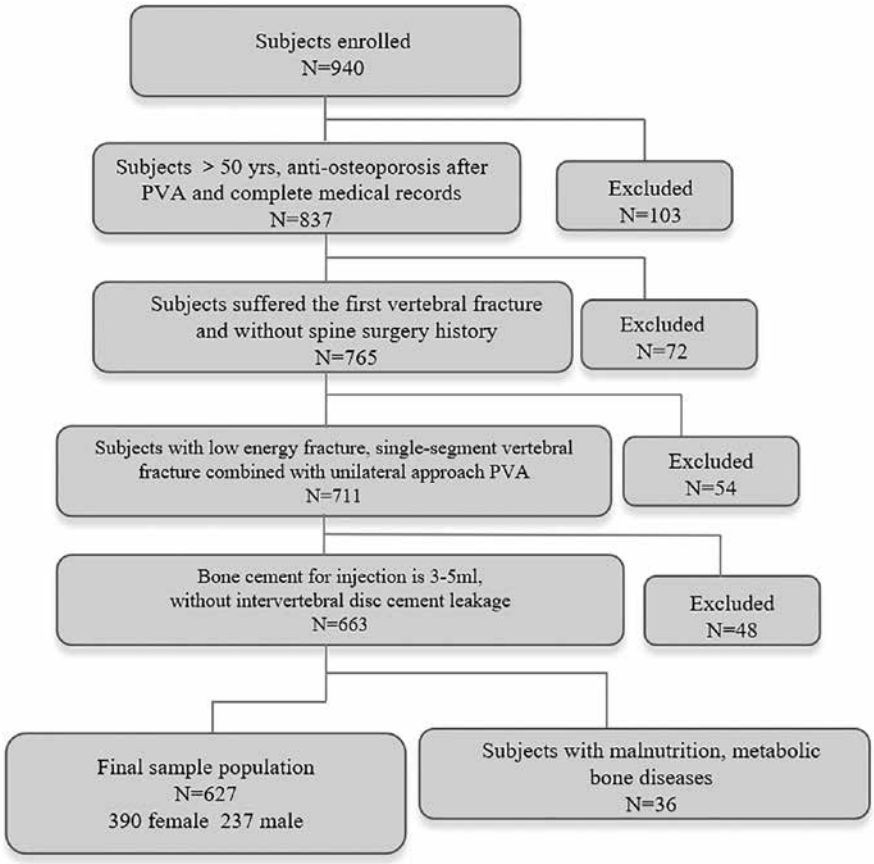

Fig. 1. *Flowchart of participant selection.*

women: WC > 80 cm) were defined according to the World Health Organization Asia-Pacific guidelines (13). Hip circumference (HC) was measured at the point of maximum buttock extension, and the WHR was calculated as WC divided by HC; abdominal obesity (men: WHR > 0.9; women: WHR > 0.85) was defined according to the WHO guidelines (14). Absolute changes in BMI (ΔBMI) were calculated by subtracting the baseline BMI from the BMI measured at 1 year after the baseline visit; the magnitude of ΔBMI was further classified into 3 groups: ± 10% loss/gain, loss > 10%, and gain > 10%.

Dual-energy x-ray absorptiometry (Prodigy GE Healthcare, Chicago, IL) was used to assess femoral neck (FN) BMD. Serum 25(OH)D level was measured by enzyme-linked immunosorbent assay method at enrollment. Potential confounders confirmed in a questionnaire included smoking status (never and current smoker), drinking status, education level, and history of self-reported falls during the previous 1 year. History of hormone replacement therapy (HRT) was also queried, and history of antiosteoporosis drug use was defined as regular use of bisphosphonates or teriparatide. Hypertension history, diabetes history, and coronary heart disease were previously validated using the questionnaire. The Framingham questionnaire was used to assess physical activity and includes 5 aspects of physical activity: basal, sedentary, light activity, moderate activity, and heavy activity (15).

Definition of SVF

In the first 3 months after PVA surgery, patients were followed up monthly at the outpatient department and subsequently at 3-month intervals. Magnetic resonance imaging (MRI) examination was performed in patients with recurrent low back pain and suspected new vertebral fracture. A diagnosis of SVF was made when the imaging outcome met one of the following criteria: x-ray or computed tomography (CT) indicated a

moderate to severe vertebral fracture according to the Genant semiquantitative scale (16), or T1-weighted MRI showed low attenuation and T2-weighted MRI showed high attenuation. We defined SVF to include remote and adjacent vertebral fractures. All SVFs recorded among study participants occurred during the follow-up period; whenever new vertebral fractures were found; an MRI examination was performed and the information about the new fractured vertebral segment was collected.

Statistical Analysis

Continuous variables are shown as mean ± standard deviation. Categorical variables are presented as percentages and analyzed using the Pearson's chi-square test or Fisher's exact test. Results were compared with the Student t-test for normally distributed data; non-normally distributed data were compared using the Mann-Whitney U test. The survival curve was drawn using the Kaplan-Meier method, and a log-rank test was used to compare the survival time of each group.

A Cox proportional hazards model was used to analyze the relationship between BMI, abdominal obesity, and SVF risk in the models. The outcomes taken into account in the models were SVF. The univariate model with BMI/abdominal obesity alone and adjusted models were as follows: (1) adjusted model with abdominal obesity/BMI, and clinical risk factors: age, history of smoking, diabetes, antiosteoporosis drug use, hormone replacement therapy (HRT; in women), and falls, physical activity, treated vertebral level; (2) full model with abdominal obesity/BMI, clinical factors, and FN BMD. The association between ΔBMI and SVF risk was also analyzed using Cox proportional hazard models, and patients who sustained a fracture (or died) within the 1-year visit were excluded. The degree of association between abdominal obesity/BMI/ΔBMI and SVF risk is shown as the hazard ratio (HR) with a 95% confidence interval (CI) in each model.

Possible collinearity between WHR, WC, BMD, and BMI was evaluated using the variance inflation factor (VIF = 1/ (1 – R^2)); a predictor with VIF < 10 is indicative of no obvious collinearity. Interaction terms were used to examine whether WHR and WC interacted with BMI, BMD, age, and gender on SVF risk. A restricted cubic spline (smooth curve) was used to assess nonlinear relationships between BMI and SVF risk. All statistical analyses were performed using the R statistical environment, version 3.0.1 for Windows (The R Project for Statistical Computing, Vienna, Austria). The level of statistical significance was set at $P < 0.05$.

Results

Baseline Characteristics

During follow-up, a total of 627 patients were analyzed; among them, 143 women and 80 men experienced an SVF after PVA, 74 women (51.7%) and 34 men (42.5%) underwent PVA again and others received conservative treatments. Compared with participants without SVF, those with SVF were older, had a higher WHR, and had a lower FN BMD; they were more likely to smoke, to have lower antiosteoporosis drug use and physical activity, and experience a higher occurrence of falls after age 50 years. Women with SVF tended to have used HRT compared with non-SVF patients and had higher HC and BMI. Vertebral fracture at the thoracolumbar junction (TL junction) had a higher incidence of initial fracture (women: 74.8%, men: 68.8%) (Table 1) and was similar in SVF (Fig. 2). In addition, the baseline characteristics of body type change are presented in Table 2. Subjects with SVF were likely to have greater mean changes of height within 1 year, most participants (women: 87.3%, men: 85.5%) had changes in BMI within a 10% range of baseline.

Abdominal Obesity and SVF Risk

When WHR was used to measure abdominal obesity, a higher WHR compared with a lower WHR increased the risk of SVF (women: HR = 2.34, $P = 0.001$; men: HR = 2.89, $P < 0.001$) in the unadjusted analysis. After adjustment for BMI and clinical factors, higher WHR increased the risk of SVF (women: HR = 4.34, $P < 0.001$; men: HR = 1.75, $P = 0.018$), but the relationship was weakened after adjusting for BMD (women: HR = 2.63, $P = 0.001$; men: HR = 1.63, $P = 0.045$). The higher WC increased risk of SVF in women (HR = 2.3, $P < 0.001$) and men (HR = 2.9, $P < 0.001$); additional adjustment for potential confounders did not change the outcome (women: HR = 2.75, $P = 0.001$; men: HR = 1.83, $P = 0.016$) (Table 3).

Association Between BMI and SVF

Table 4 shows that in the unadjusted analysis, compared with a normal BMI, overweight was associated with a lower SVF risk (women: HR = 0.37, $P < 0.001$; men: HR = 0.33, $P = 0.002$) but obesity was associated with greater SVF risk (women: HR = 2.16, $P< 0.001$; men: HR = 2.58, $P < 0.001$) in both genders. This relationship was also demonstrated after adjusting for clinical factors (women: HR = 0.35, $P < 0.001$; men: HR = 0.39, $P =0.015$ in overweight; women: HR = 2.09, $P = 0.013$; men: HR = 4.11, $P < 0.001$ in obesity). With fur-

Table 1. *Baseline characteristics of the initial fracture participants in the study stratified by subsequent vertebral fracture incidence.*

	Male			Female		
	SVF (n = 80)	Non-SVF (n = 157)	*P*	SVF (n = 143)	Non-SVF (n = 247)	*P*
Age, Years	71.09 ± 2.38	67.83 ± 3.35	< 0.001	71.06 ± 3.30	68.44 ± 3.31	< 0.001
Height, m	1.69 ± 0.16	1.75 ± 0.16	0.005	1.60 ± 0.03	1.61 ± 0.03	0.094
Weight, kg	69.11 ± 10.55	73.12 ± 9.33	0.003	66.06 ± 11.51	62.53 ± 9.87	0.002
BMI, kg/m^2	24.42 ± 4.14	23.91 ± 3.09	0.293	25.36 ± 4.35	24.01 ± 3.68	0.001
Waist circumference, cm	101.13 ± 7.82	100.79 ± 8.22	0.764	82.37 ± 5.60	79.59 ± 5.45	< 0.001
Hip circumference (cm)	95.59 ± 7.57	95.01 ± 8.01	0.592	95.76 ± 4.94	94.40 ± 4.73	0.007
Waist/hip ratio (cm/cm)	0.91 ± 0.09	0.87 ± 0.08	0.001	0.85 ± 0.03	0.84 ± 0.03	< 0.001
Diabetes, yes	32 (40.0%)	43 (27.4%)	0.048	72 (50.3%)	60 (24.3%)	< 0.001
Hypertension, yes	28 (35%)	47 (29.9%)	0.428	47 (32.9%)	85 (34.4%)	0.756
Coronary heart disease	14 (17.5%)	25 (15.9%)	0.757	22 (15.4%)	37 (15%)	0.914
Smoking, yes	60 (75.0%)	83 (52.9%)	0.001	74 (51.7%)	47 (19%)	< 0.001
Drinking, yes	24 (30%)	40 (25.5%)	0.458	28 (19.6%)	45 (18.2%)	0.740
25(OH)D, ng/mL	18.66 ± 8.87	19.97 ± 9.36	0.299	20.05 ± 8.54	18.75 ± 7.58	0.123
History of falls, yes	32 (40%)	27 (17.2%)	< 0.001	48 (33.6%)	60 (24.3%)	0.049
Physical activity, METs	25.12 ± 1.86	28.08 ± 2.41	< 0.001	22.11 ± 3.28	27.57 ± 4.31	< 0.001
Education levels (High school, yes)	40 (50.0%)	79 (50.3%)	0.963	76 (53.1%)	127 (51.4%)	0.742
Anti-osteoporosis drugs use, yes	44 (55.0%)	117 (74.5%)	0.002	83 (58%)	211 (85.4%)	< 0.001
HRT (%)	-	-	-	6 (4.2%)	42 (17%)	< 0.001
FN BMD, g/cm^2	0.72 ± 0.12	0.92 ± 0.11	< 0.001	0.72 ± 0.095	0.847 ± 0.16	< 0.001
Treated vertebral level			0.213			< 0.001
Non-TL junction	25 (31.3%)	62 (39.5%)		36 (25.2%)	120 (48.6%)	
TL junction	55 (68.8%)	95 (60.5%)		107 (74.8%)	127 (51.4%)	

BMI, body mass index; FN BMD, femoral neck bone mineral density; Physical activity, METs, metabolic equivalents; HRT, hormone replacement therapy.

ther adjustment for BMD, the risk of SVF increased in both men and women (women: HR = 0.55, *P* = 0.044; men: HR = 0.46, *P* = 0.046 in overweight; women: HR 4.53, *P* < 0.001; men: HR = 3.77, *P* < 0.001 in obesity). Obese and abdominal obesity in people have a higher cumulative incidence of SVF (Fig. 3). Furthermore, in the unadjusted analysis, compared to ± 10% changes in BMI, the group of BMI gain > 10% had an increased risk of SVF (women: HR = 1.83, P = 0.024; men: HR = 4.35, *P*< 0.001). After multivariable adjustment, changes of BMI were not statistically significant.

More importantly, we observed a nonlinear relationship between BMI and SVF with a U-shaped curve; after adjusting for BMD, the shape became a reverse J-curve (Fig. 4).

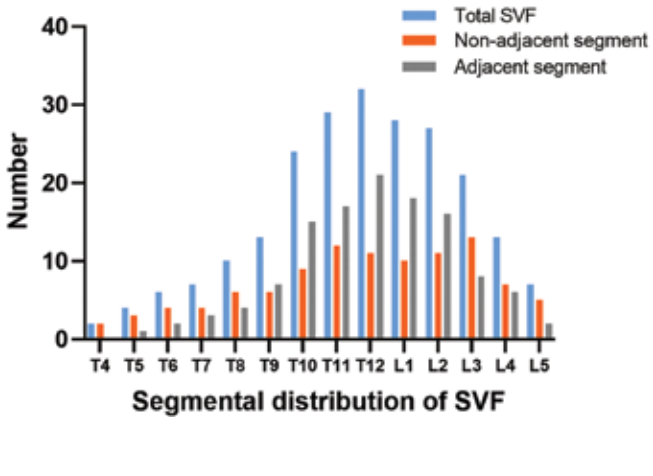

Fig. 2. *Segmental distribution of subsequent vertebral fracture.*

Collinearity and Interaction Analysis

In women, the VIF was 2.00 for WHR, 2.03

Table 2. *Body type change from the baseline (ΔBMI).*

1-year [a]	Male			Female		
	SVF (n = 55)	Non-SVF (n = 153)	*P*	SVF (n = 109)	Non-SVF (n = 213)	*P*
ΔHeight, cm	-1.34 ± 0.56	-0.87 ± 0.47	< 0.001	-1.34 ± 0.58	-0.84 ± 0.46	< 0.001
ΔWeight, kg	-0.77 ± 4.20	-1.03 ± 3.43	0.657	-1.63 ± 4.19	-1.11 ± 4.36	0.304
ΔBMI, kg/m^2	0.10 ± 1.48	-0.11 ± 1.21	0.284	0.56 ± 1.26	-0.09 ± 1.16	0.294
ΔWaist circumference, cm	-0.21 ± 1.85	-0.52 ± 1.99	0.314	-0.46 ± 1.27	-0.24 ± 1.28	0.142
ΔHip circumference (cm)	-0.08 ± 0.68	-0.17 ± 0.63	0.359	-0.31 ± 0.62	-0.12 ± 0.62	0.01
ΔWaist/hip ratio (cm/cm)	-0.001 ± 0.014	-0.004 ± 0.016	0.299	-0.001 ± 0.009	-0.002 ± 0.009	0.638
Relative ΔBMI (Proportion%)			< 0.001			< 0.001
> 10% loss	7 (12.7%)*	7 (4.6%)*		7 (6.4%)#	12 (5.6%)#	
± 10%	35 (63.6%)	143 (93.5%)		85 (78%)	196 (92%)	
> 10% gain	13 (23.6%)*	3 (2%)*		17 (15.6%)*	5 (2.3%)*	

[a] Patients who sustained a fracture (or died) within the 1-year visit are excluded. *Pairwise comparisons to group of ± 10%, P < 0.05. #Pairwise comparisons to group of > 10% gain, P < 0.05.

Table 3. *Association between abdominal obesity and subsequent vertebral fracture risk stratified by gender: multivariable cox regression analysis.*

	Crude model	*P*	Adjusted (BMI + clinical factors)	*P*	Adjusted (BMI + clinical factors + BMD)	*P*
Female						
WHR ≤ 0.85	1		1		1	
WHR > 0.85	2.34 (1.66-3.29)	0.001	4.34 (2.44-7.70)	< 0.001	2.63 (1.49-4.64)	0.001
WC ≤ 80cm	1		1		1	
WC > 80cm	2.3 (1.63-3.25)	< 0.001	3.47 (1.99-6.07)	< 0.001	2.75 (1.52-4.96)	0.001
Male						
WHR ≤ 0.9	1		1		1	
WHR > 0.9	2.89 (1.85-4.51)	< 0.001	1.75 (1.1-2.81)	0.018	1.63 (1.01-2.65)	0.045
WC ≤ 90cm	1		1		1	
WC > 90cm	2.9 (1.85-4.55)	< 0.001	1.82 (1.13-2.92)	0.013	1.83 (1.12-3.02)	0.016

WC, waist circumference; WHR, Waist/hip ratio; BMD, femoral neck BMD; Clinical factors: age, history of smoking, diabetes, anti-osteoporosis drugs use, HRT (in women) use, falls, physical activity, and treated vertebral level.

for WC, and 1.03 for BMD on BMI; we observed similar results in men (VIF for WHR, WC, and BMD on BMI was 1.95, 1.94, and 1.01, respectively).

No statistically significant interaction was detected between WHR and BMI for the risk of SVF. There was also no significant interaction between WC and BMI. Age, gender, and BMD showed no interaction with WHR and WC.

Discussion

Recently, there has been increasing evidence demonstrating a nonlinear association between BMI and risk of fracture among different genders and ages (17,18). Some studies have demonstrated that higher BMI has an adverse effect on fracture risk after adjusting for BMD (19). However, few studies (20) have confirmed the BMI influence on the occurrence of SVF in patients who receive PVA treatment. Our results proved nonlinear relationships between BMI and SVF, with a U-shaped curve, which became a reverse J-shaped curve after adjusting for BMD. Abdominal obesity tended to be a high risk for SVF in both women and men.

Comparison With Previous Studies

Many studies have revealed that different patient populations with different fracture sites may produce divergent results. In a meta-analysis (2) of 398,610 women followed up for a mean of 5.7 years, people with obe-

Table 4. *Association between body mass index, relative ΔBMI and subsequent vertebral fracture risk stratified by gender: multivariable cox regression analysis.*

	Crude model	*P*	Adjusted (clinical factors)	*P*	Adjusted (clinical factors + BMD)	*P*
Female						
Normal	1		1		1	
Overweight	0.37 (0.23-0.59)	< 0.001	0.35 (0.19-0.61)	< 0.001	0.55 (0.31-0.98)	0.044
Obesity	2.16 (1.47-3.14)	< 0.001	2.09 (1.16-3.75)	0.013	4.53 (2.35-8.70)	< 0.001
Relative ΔBMI (category)(1-year) [a]						
> 10% loss	1.82 (0.83-3.97)	0.13	1.53 (0.69-3.37)	0.291	1.12 (0.50-2.51)	0.782
± 10%	1		1		1	
> 10% gain	1.83 (1.08-3.09)	0.024	0.96 (0.53-1.73)	0.885	0.89 (0.49-1.60)	0.689
Male						
Normal	1		1		1	
overweight	0.33 (0.16-0.66)	0.002	0.39 (0.18-0.83)	0.015	0.46 (0.22-0.99)	0.046
obesity	2.58 (1.58-4.21)	< 0.001	4.11 (2.33-7.26)	< 0.001	3.77 (2.13-6.65)	< 0.001
Relative ΔBMI (category)(1-year) [a]						
> 10% loss	2.26 (0.98-5.22)	0.055	2.31 (0.91-5.83)	0.077	1.05 (0.36-3.01)	0.927
± 10%	1		1		1	
> 10% gain	4.35 (2.26-8.38)	< 0.001	2.32 (1.11-4.86)	0.026	1.73 (0.82-3.68)	0.153

BMD, femoral neck BMD; Clinical factors, age, history of smoking, diabetes, anti-osteoporosis drugs use, HRT (in women) use and falls, physical activity, treated vertebral level.

[a]For 1-year samples, the follow-up starts from the 1-year visit, and the follow up time is 4 years; patients who sustained a fracture (or died) within the 1-year visit are excluded.

sity had a lower risk of hip and osteoporotic fractures than overweight women; however, when adjusted for BMD, obesity significantly increased the risk of fracture. Low BMI is a risk factor for hip and osteoporotic fractures; even after adjustment for BMD, it was still a risk factor for hip fracture but showed a protective effect against osteoporotic fracture. Another meta-analysis (3) among 105,129 participants followed for nearly 20 years showed that in a model without adjustment for BMD, a higher BMI decreased the risk of vertebral fracture only in men. After adjustment for BMD, BMI elevated the risk of vertebral fracture in women.

Older people with osteoporotic vertebral fractures will lose their height faster. It is not clear if this is a valid measurement to use for BMI as height loss is part of a vertebral compression fracture in older patients (21). In order to demonstrate the initial validity of BMI, we also explored the effect of changes in body height and weight on the risk of SVF. Height and weight were measured at baseline and at follow-up visits after 1 year. We observed that participants who suffered SVF were likely to have greater height loss and increased BMI within 1 year. The group of BMI gain > 10% increased the risk of SVF only in women. Wilsgaard et al (22) also found that taking a 10-year BMI (kg/m^2) change 0 to < 1 as a reference, ΔBMI < –1 loss or > 3 gain in a 10-year follow-up substantially increased the risk of non-vertebral fracture in elderly men.

Considering the insufficient evidence from studies only investigating BMI, some scholars have focused on the relationship between the type of obesity with incidence of vertebral fracture. A study among 54,934 Nurses' Health Study participants (8) showed that a larger WC was related to higher vertebral fracture risk. Although few studies have reported, the relationship between body composition and vertebral fracture, Karen et al (23) demonstrated that greater (+1 SD) visceral adipose tissue (OR = 2.50) than total fat mass (OR = 1.06) increased the odds of any grade vertebral fracture in women but not in men. Regardless of BMD, total and visceral adiposity were related to a higher incidence of vertebral fracture only in women. Similarly, our studies showed that a higher abdominal fat mass increased the risk of SVF.

Recently, some studies (24) offered strong evidence that cement leakage, lower BMI, and BMD were risk factors for SVF after PVP. The high fracture risk among individuals with a low BMI is mainly mediated by a low

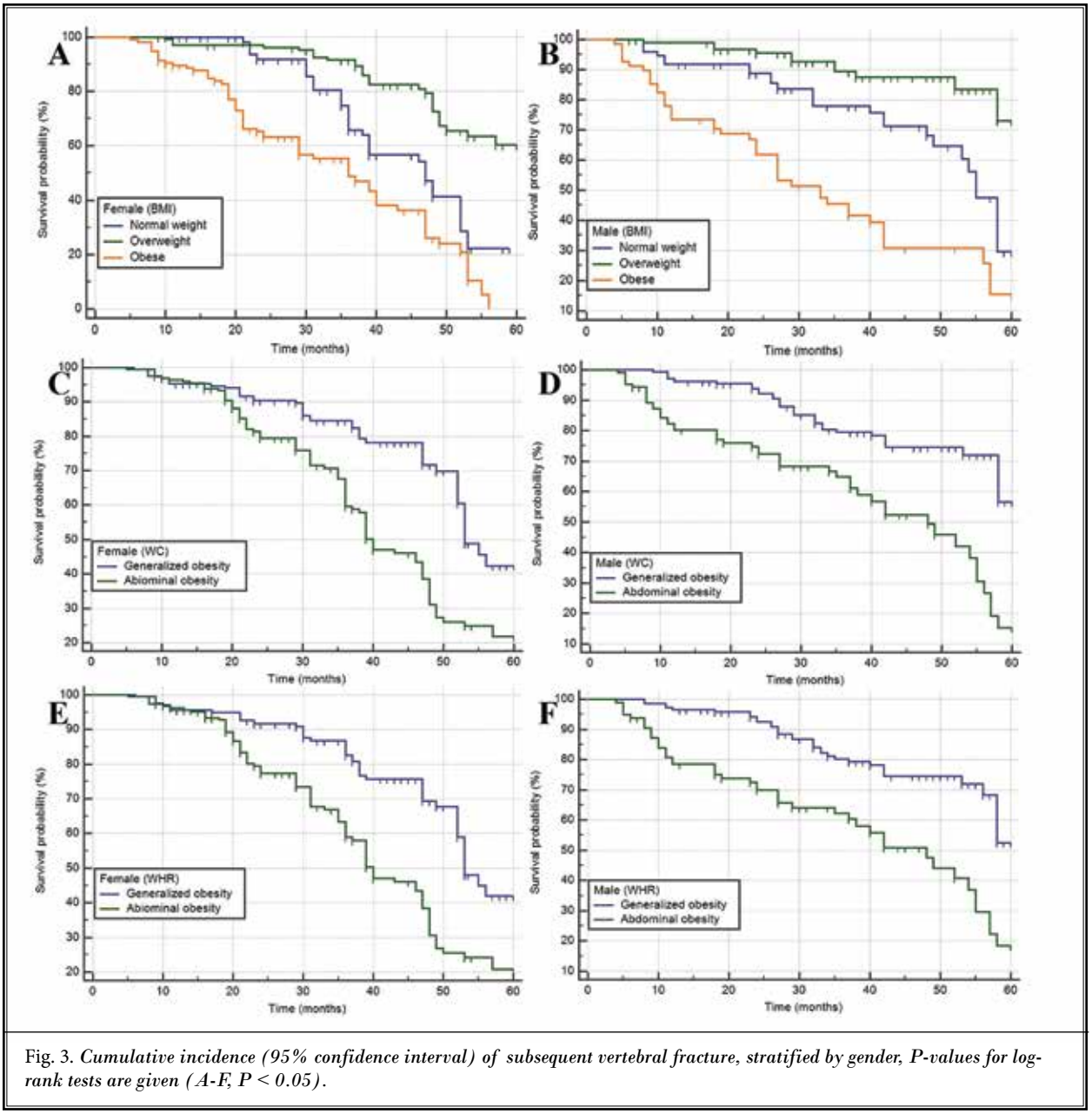

Fig. 3. *Cumulative incidence (95% confidence interval) of subsequent vertebral fracture, stratified by gender, P-values for log-rank tests are given (A-F, $P < 0.05$).*

BMD value (19); however, Hai-long et al (12) demonstrated that a high BMI (OR = 1.268) was significantly associated with SVF after PVP. Greater attention has been paid to surgical factors, included surgical levels, cement leakage, amount of cement, and degree of kyphosis. However, patient-related factors such as BMI have not been studied in-depth among patients with PVA. Therefore, we only included patients with single-segment vertebral fracture and non-cement leakage in the current study to avoid introducing bias.

Possible Explanations, Implications, and Unanswered Questions

With the widespread use of PVA, it has been reported that the incidence of SVA could be as high as 11% to 52% (25,26). The occurrence of SVF is affected by many factors. Previous studies have confirmed that bone mineral density reduction and surgery-related factors, such as cement volume and cement leakage, increase the incidence of SVF after PVA (24). However, few studies have confirmed the influence of BMI on

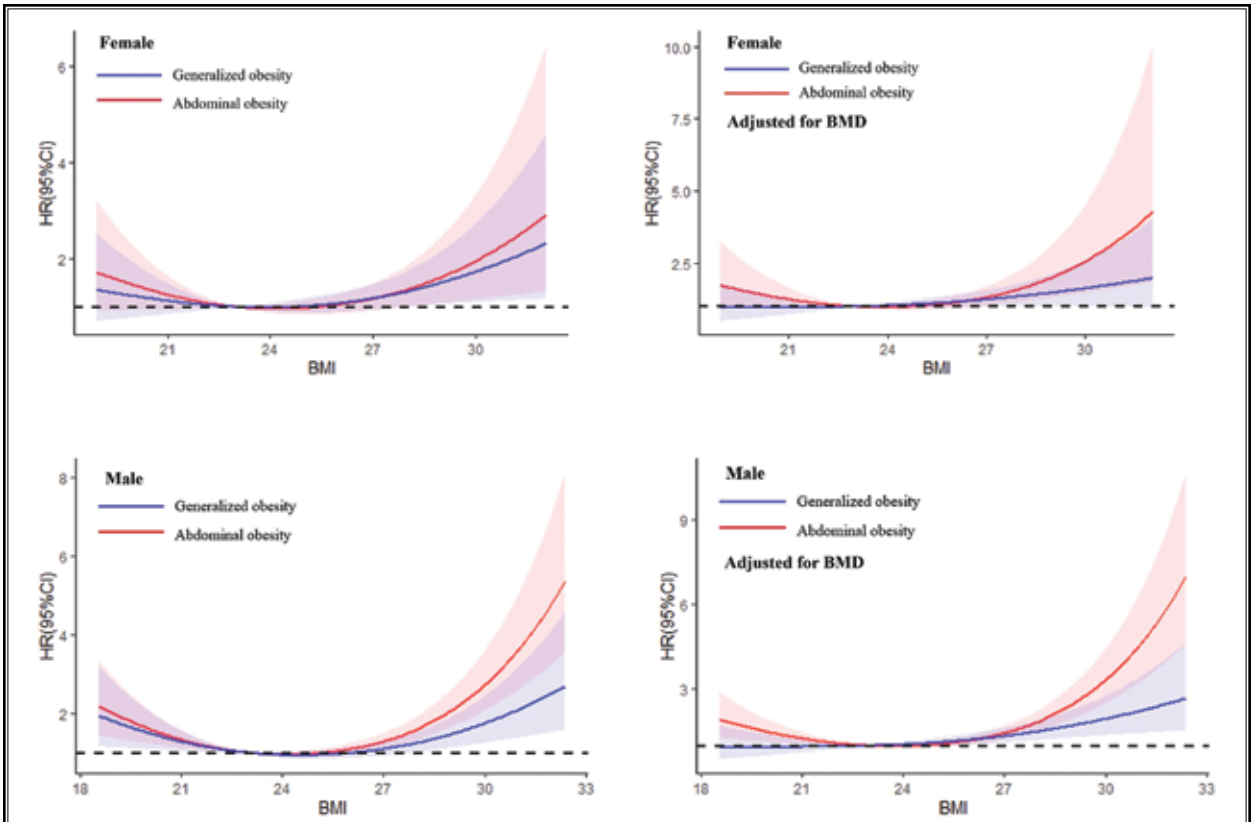

Fig. 4. *Hazard ratios for subsequent vertebral fracture incidence, different gender groups, using restrictive cubic spline analysis and 23.0 kg/m² as a reference. Adjustment for age, history of smoking, diabetes, anti-osteoporosis drugs use, HRT (in women) use and falls, physical activity, treated vertebral level.*

the occurrence and mechanism of SVF. Inconsistencies in obesity fracture rates are probably owing to differences in study population, fracture type, study design, and available covariates (3). Differences in the distribution of lean mass, proportion of fat mass, and the method used to measure obesity among studies could also account for the differing results (27,28).

The relationship between obesity and osteoporotic fracture is complex, even called "the obesity paradox" (29). For obesity in osteoporotic fracture, we may briefly describe the underlying theory as follows. First, obesity is associated with an increased BMD, suggesting an increased bone mass is stimulated by a greater skeletal loading (30). Second, fat mass is associated with the release of bone active hormones (31); obesity often leads to hyperinsulinemia, with increased production of androgens and estrogens in the ovaries and decreased release of hormone-binding globulin in the liver. These result in a rise in free concentration of sex hormones, which may reduce osteoclast activity or have a positive effect on osteoblasts. Increased amylin and preptin also enhance bone mass through the regulation of osteoblasts and osteoclast (32). Lastly, soft tissue pads around the hips absorb impact forces, which may underlie the relatively lower risk of hip and pelvic fractures in women with obesity (33).

Many studies have proposed explanations for the underlying relationship between obesity and increased fracture risk. First, most people with a high BMI have a high BMD; however, this does not guarantee ideal bone mass, this may not be commensurate to increased body mass and fat mass (34). In some overweight and people with obesity, increased bone fragility can lead to a fragility fracture tendency, which may be associated with central adiposity and poor bone quality (lower trabecular bone volume, stiffness, and higher cortical porosity), as well as markedly reduced bone formation (4). The benefit of obesity on bone strength and the protective effect of soft tissue pads are not enough to compensate for the greater fall impact forces (35). Sec-

ond, people with abdominal obesity may be at higher risk of falling than lighter-weight individuals (36). Because people with obesity require more attentional resources to control postural stability, they have a greater tendency to move backward or sideways than forward when standing from a sitting position, which may account for the greater frequency of upper arm and leg fractures than fractures of the hip and pelvis (37). Additionally, obesity is associated with a decreased quality of life and increased frailty (38), which may result in stumbling during ambulation and a higher prevalence of falls (39). Overweight or obese individuals have an instantaneous increase in vertebral load when they fall, which also increases the risk of SVF after percutaneous kyphoplasty surgery. Third, increased visceral fat and inflammatory cytokines in individuals with obesity can adversely affect bone metabolism (40). Obesity-related conditions that compromise bone metabolism reduce 25-hydroxy-vitamin D and increase parathyroid hormone concentrations (41). Previous studies have also shown that inflammation-related factors released by visceral adipose tissue affect bone remodeling by enhancing bone reabsorption and inhibiting bone formation (42). Higher BMI is related to comorbidities that contribute to an increased rate of fracture, such as asthma, emphysema, and diabetes mellitus (43). After the initial vertebral fracture, the patient's height decreases significantly (21), leading to an increase in BMI. So, body height decreases and change in BMI may be useful for prediction of vertebral re-fracture.

Biomechanics may play an essential role in the occurrence of osteoporotic fractures, especially in patients undergoing PVP. In recent years, studies have shown that reduced vertebral body biomechanical strength and an increase in vertebral body yellow marrow are closely related. Thus, people with a high BMI are more likely to experience fracture. Again, a possible mechanism is that in patients with high levels of fat an increased vertebral body conversion of red to yellow marrow can cause a decrease in vertebral body biomechanical strength; bone cement is used to strengthen compression tolerance after excessive load stress, which would otherwise lead to a vertebral body compression fracture.

One study (12) showed that the risk of new adjacent level fractures increases 1.268-fold with every increase in BMI of 1 kg/m^2. Every 12-kg increase in body weight increases spinal load by approximately 11.8%. Higher WC at identical body weights increases spinal forces equivalent to 20 kg of additional bodyweight and increases the risk of OVF by 3 to 7 times compared with a smaller WC (44). Jin et al (45) investigated a total of 502,543 participants in the UK Biobank (229,138 men and 273,405 women) and found that a larger WC was associated with an increase in vertebral fracture risk in men. Until now, it has been considered that a direct pillar effect (the uneven distribution of bone cement resulting in differing forces) may prompt an adjacent level fracture. Obesity limits the relative mobility of adjacent segments and puts greater pressure on the vertebral body, which may lead to subsequent fracture (46). Higher BMI and abdominal obesity may do greater harm to bone and increase the risk of SVF after PVA.

Strengths and Limitations of the Study

A notable advantage of our study is its long-term clinical follow-up as well as the diagnostic standards and exclusion and inclusion criteria, which reduced confounding biases. Our measurement of fat distribution was based on BMI, waist and hip circumference, and body-composition imaging studies; these data are more objective and accurate for the evaluation of future fracture risk. Nevertheless, several potential weaknesses of our study must be acknowledged. First, we only recorded the information of vertebral fracture, and there was no further statistical analysis on information for other fracture sites because the main aim of our paper was to explore the impact of obesity on vertebral re-fracture after PVA. Second, there are many risk factors affecting the recurrence of fracture after PVA, such as the amount of bone cement injected, distribution of bone cement, and cement leakage from the vertebra, among others. Third, to yield more accurate results, we only selected patients with a single-segment vertebral fracture and no cement leakage from the vertebra. Thus, our results may reflect most Asian patients after PVA but may not be generalizable to specific patients or those with different ethnic backgrounds. Forth, there may have been asymptomatic patients with SVF who were not included in this study, which would lead to underestimation of the impact of BMI and abdominal obesity on the occurrence of SVF. However, our strict inclusion criteria ensured a more accurate prediction of the effect of BMI and abdominal obesity on the incidence of SVF in the survival model. Finally, owing to the observational study design, we could not identify an exact mechanism to explain our results. Despite these limitations, our study is the first to demonstrate that lower BMI, abdominal obesity, and excessive BMI gain may increase the incidence of

SVF. We believe that our results and a large number of similar studies in evaluating obesity status are clinically useful for spine surgeons, as well as for the development of new precautionary approaches with respect to preventing SVF in patients with PVA.

Conclusion

Our study showed that being overweight was associated with the lowest risk of SVF after PVA. With adjustment for BMD, lower BMI showed a weak protective effect against SVF in both men and women. Abdominal obesity was associated with a higher risk of SVF in all models. Abdominal circumference can be used as a convenient and inexpensive measure in clinical settings for screening those with greater risk of future SVF after PVA. Large-scale clinical trials are warranted to investigate the clinical efficacy of body type management after PVA for the prevention of SVF.

Authors' contributions:

SJW initiated the idea, HWX and HC wrote the assay, XYF did the data analysis. YYY and TH supervised and reviewed the manuscript. XYG and SBZ gathered the data and helped with the data analysis. All authors read and approved the final manuscript.

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