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ORIGINAL RESEARCH

Clinical Manifestations and Factors Associated with Osteosarcopenic Obesity Syndrome: A Cross-Sectional Study in Koreans with Obesity

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Abstract

Demonstrating the clinical consequences of osteosarcopenic obesity (OSO) is complex. This study evaluated clinical manifestations and factors associated with bone and muscle loss in Koreans with obesity. This cross-sectional observational study enrolled Koreans with obesity aged ≥ 50 years from the Korea National Health and Nutrition Examination Survey. Clinical manifestations were compared among four groups: obesity (O), sarcopenic obesity (SO), osteopenic obesity (OO), and OSO. Factors associated with appendicular skeletal muscle mass (ASM) or bone mineral density (BMD) were evaluated. OSO increases with age in both sexes. Men with SO and OSO had increased cardiometabolic diseases and markers, percentages of body fat (BF %), and trunk fat (TF %), and decreased limb fat percentage (LF %). Women with SO and OSO had increased metabolic markers, BF %, and TF % but those with OSO had increased cardiometabolic diseases and lower LF %. Both sexes with OSO had decreased ASM and vitamin D, and higher vitamin D deficiency. BF % was negatively associated with ASM and femur BMD in both sexes. TF % was negatively and LF % was positively associated with ASM in both sexes and with femur BMD in women. Vitamin D was positively associated with femur BMD in men and with ASM and BMD at all sites in women. ASM and BMD were positively associated with each other. Appendicular muscle loss is metabolically significant regardless of bone loss in men; however, appendicular muscle loss with bone loss is metabolically more significant in women. Regional body composition, fat distribution, and vitamin D deficiency were associated with OSO phenotype in both sexes.

Keywords Appendicular skeletal muscle mass · Bone mineral density · Body fat · Bone loss · Muscle loss · Osteosarcopenic obesity

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Abbreviations

ALT	Alanine aminotransferase
ASM	Appendicular skeletal muscle mass
AST	Aspartate aminotransferase
BF %	Body fat percentage
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
Cr	Creatinine
CVA	Cerebrovascular accident
DBP	Diastolic blood pressure
DXA	Dual-energy X-ray absorptiometry
FM	Fat mass
H	Hours
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HL	Hyperlipidemia
HOMA-IR	Homeostasis model assessment of insulin resistance
Ht	Height

HTN	Hypertension
iPTH	Intact parathyroid hormone
KNHANES	Korea National Health and Nutrition Examination Surveys
LDL-C	Low-density lipoprotein cholesterol
LF %	Limb fat percentage
LM	Lean mass
MetS	Metabolic syndrome
MI	Myocardial infarction
Min	Minutes
O	Obesity
OA	Osteoarthritis
OO	Osteopenic obesity
OSO	Osteosarcopenic obesity
SBP	Systolic blood pressure
SD	Standard deviation
SO	Sarcopenic obesity
T-C	Total cholesterol
TF %	Trunk fat percentage
TG	Triglycerides
T2D	Type 2 diabetes
WC	Waist circumference
Wt	Weight
25OHD	25-hydroxyvitamin D

Introduction

Globally, aging is associated with increasing obesity, sarcopenia, and osteopenia/osteoporosis, which may lead to increased cardiometabolic morbidity and mortality [1]. Although obesity is well known as a strong risk factor for metabolic diseases and subsequent cardiovascular complications, the association between obesity and bone or muscle loss remains controversial. In aging individuals, bone and muscle mass generally decrease with increasing fat mass, which subsequently leads to the development of a combined comorbid condition known as osteosarcopenic obesity (OSO) syndrome [2]. However, proper prevention and treatment of OSO, as well as its clinical consequences related to cardiometabolic diseases and fracture risk, have not been well documented given its complex nature [3].

Obesity is characterized by increased fat mass, which has been proven to be difficult to assess without analyzing body composition. Thus, fat mass index or body fat percentage (BF %) is considered a more appropriate measure of obesity when data on body composition analysis are available [4]. Although the cutoff point of body mass index (BMI) for obesity recommended by the World Health Organization is generally lower for Asians than that for Caucasians, the BF % cutoff point for obesity has yet to be clearly defined among the various ethnicities [5].

Besides obesity, bone and muscle losses are of great concern among the elderly population. Generally, bone or muscle mass and strength peak during the 20–40 s and decline thereafter. Accordingly, a decrease in bone or muscle mass below −1 SD of the normal peak level could lead to osteopenia or sarcopenia [6]. The age-related decline in muscle mass and strength has been associated with increased disability and falls as well as low bone mass [7]. However, it remains unclear whether the decline in bone mineral density (BMD) decreases appendicular skeletal muscle mass (ASM), which can accelerate sarcopenia. Moreover, it is still unclear whether the loss of bone and muscle masses in obese state influences each other to develop OSO syndrome among elderly [3, 8].

Given that the coexistence of sarcopenia and obesity, i.e., sarcopenic obesity (SO), is considered as a significant body composition change, SO has been found to increase the risk of metabolic syndrome (MetS), physical disability, and subsequent morbidity [9]. Obesity or increased overall BF with aging results in fat infiltration into bone and muscle, which may lead to decreased bone and muscle masses or qualities and possibly increased frailty [10, 11]. OSO, defined as the deregulation of bone, muscle, and fat tissues, is inevitably a significant health concern. Based on its underlying pathophysiology, it has a greater potential of the risk of cardiometabolic diseases, falls, and fractures than SO.

The number or percentages of elderly individuals in obesity categories considerably differ as various criteria for the diagnosis of OSO syndrome are being developed. Moreover, the clinical significance of each obesity category has not been well compared with other categories. Therefore, this cross-sectional study evaluated clinical manifestations and factors associated with bone and muscle losses among Koreans with obesity.

Methods

Participants

This cross-sectional observational study recruited individuals who were enrolled in the Korea National Health and Nutrition Examination Survey (KNHANES), which was annually conducted by the Korea Centers for Disease Control and Prevention from 2008 to 2011 to assess the health and nutritional status of non-institutionalized, civilian population [12]. Data were collected via household interviews using individual surveys and through standardized physical examinations at mobile examination centers. Individuals with obesity over the age of 50 years who underwent body composition and BMD analyses using dual-energy X-ray absorptiometry (DXA) were enrolled. All participants in the KNHANES signed informed consent forms.

Among the 3566 individuals with obesity included from KNHANES, those with chronic liver or renal failure, neoplastic diseases, increased serum creatinine (Cr) levels (≥ 1.6 mg/dL), type 2 diabetes (T2D) with exogenous insulin use, or missing demographic information were excluded from this study ($n = 299$). Prevalent diseases among the individuals, such as T2D, hypertension (HTN), hyperlipidemia (HL), myocardial infarction (MI), angina, cerebrovascular accident (CVA), osteoarthritis (OA), and fracture at any site including the wrist, vertebra, and hip, were identified from their individual surveys. Menopause history for women was obtained through individual surveys.

Anthropometric and Biochemical Measurements

Age, height (Ht), body weight (Wt), waist circumference (WC), smoking history, alcohol consumption, and physical activity level were obtained, and subsequently BMI (kg/m^2) was calculated. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured thrice on the upper arm using an electronic sphygmomanometer, and average values were used. Smoking history and alcohol consumption were considered positive if the individual had ever smoked tobacco or consumed alcohol. Physical activity level was considered positive when the individual regularly exercised at moderate (> 30 min at a time and more than five times per week) or vigorous (> 20 min at a time and more than three times per week) levels.

Fasting blood samples from individuals were immediately refrigerated, transported to the Central Testing Institute in Seoul, Korea, and analyzed within 24 h. Fasting plasma glucose, total cholesterol (T-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen, and Cr levels were measured using the Hitachi Automatic Analyzer 7600 (Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Serum fasting insulin was measured through immunoradiometric assay (Biosource, Nivelles, Belgium) using the 1470 WIZARD γ-counter (PerkinElmer, Turku, Finland). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the reference formula [13]. Intact parathyroid hormone (iPTH) level was measured using the LIAISON N-tact PTH assay (DiaSorin, Stillwater, MN, USA). Serum 25-hydroxyvitamin D (25OHD) level was measured using radioimmunoassay (DiaSorin) using a 1470 Wizard γ-counter (PerkinElmer) with the reference level for 25OHD deficiency set at < 20 ng/mL [14]. Glycated hemoglobin (HbA1c) was analyzed in subjects who had a personal history of T2D through high-performance liquid chromatography using HLC-723G7 (Tosoh, Tokyo, Japan).

DXA Measurements for BMD and Body Composition Analyses

DXA (QDR 4500A; Hologic, Inc., Waltham, MA) analyses were conducted by trained technicians at mobile examination centers and were periodically calibrated using an internal referencing system using methods detailed in previous reports [4, 15]. DXA examination provided absolute BMD (g/cm^2) and T scores for each anatomical site, such as lumbar spine (LS), femur neck (FN), and total hip (TH). The in vivo precision of DXA was approximately 1.5%. Individuals whose weight or height exceeded the limit of the DXA scanning table (136 kg for Wt and 196 cm for Ht) were excluded from DXA analyses.

Body composition analysis using DXA provided the absolute values for total fat mass (FM), total lean mass (LM), and ASM in kilograms. Regional body composition was quantified using indices such as BF % and ASM index (ASM/Wt), while percentages of trunk fat (TF %) and limb fat (LF %) including both upper and lower extremities, were calculated based on FM [4].

- (1) ASM/Wt (%) = ASM (kg) × 100/Wt (kg).
- (2) TF % = TF (kg) × 100/FM (kg).
- (3) LF % = Right and left LF (kg) × 100/FM (kg).

Definition of Obesity Groups and MetS

Obesity was defined using BF % cutoff points modified from recent studies conducted on Asian populations, such as ≥ 25% for men and ≥ 35% for women, to overcome the limitation associated with defining obesity using BMI [16, 17]. Sarcopenia was defined as ASM/Wt > 1 SD below the sex-specific mean of the young, healthy, reference group [18]. Osteopenia was defined as a T score of ≤ −1.0 for LS, FN, or TH BMD determined using DXA. The obesity groups were further divided into the following four categories according to the coexistence of sarcopenia or osteopenia: obesity without sarcopenia nor osteopenia (O), sarcopenic obesity (SO), osteopenic obesity (OO), and OSO.

MetS was defined based on the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria [19]. Accordingly, following Korean-specific cutoffs for abdominal obesity defined by the Korean Society for the Study of Obesity [20], MetS was confirmed when three or more of the following components were present: (1) fasting glucose level ≥ 100 mg/dL or previously diagnosed T2D; (2) TG level ≥ 150 mg/dL; (3) HDL-C level < 40 mg/dL for men or < 50 mg/dL for women; (4) SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, or treatment with antihypertensive agents; and (5) WC ≥ 90 cm for men or ≥ 85 cm for women.

Statistical Analysis

All statistical analyses were conducted using the IBM SPSS software (version 22.0; SPSS, Chicago, IL). Demographic characteristics, laboratory and body composition factors, and prevalent diseases were compared between sexes or among obesity groups, men and women separately, using *t* tests and analysis of variance (ANOVA) for continuous variables or Chi-square tests for categorical variables followed by Tukey's HSD post hoc tests. The relationships between laboratory or regional body composition parameters and ASM or BMD were analyzed using multiple linear regression analyses in adjusted models. A P value of <0.05 was considered statistically significant.

Results

Participant Characteristics

The demographic characteristics and prevalent diseases of the individuals stratified by sex are shown in Table 1. The mean age was higher in men (64.6 ± 9.1 years; range 50–93 years) than women (63.8 ± 8.9 years; range, 50–91 years). Postmenopausal women comprised 92.4% of all women (2021/2187; data not shown). A comparison of baseline characteristics by sex showed that the average Ht, Wt, WC, smoking experience, alcohol consumption, exercise habit, DBP, glucose, TG, AST, ALT, and 25OHD levels were higher in men, whereas BMI, T-C, HDL-C, LDL-C, and iPTH levels were higher in women (Table 1). Insulin and HOMA-IR, as well as HbA1c (7.2% ± 1.2% for both men and women with a personal history of T2D; data not shown), did not differ between men and women. A comparison of body composition factors revealed that TF %, LM, ASM, ASM/Wt, and BMDs were higher in men, whereas FM, BF %, and LF % were higher in women (Table 1). Mean T scores for LS, FN, and TH were higher in men than in women (−0.5 ± 1.3, −0.8 ± 0.9, −0.1 ± 0.9 vs. −1.6 ± 1.2, −1.6 ± 1.0, −0.6 ± 1.0, all $P<0.01$; data not shown). MetS, T2D, MI/angina, and CVA were more prevalent in men, whereas HL, OA, vitamin D deficiency, and fractures were more prevalent in women (Table 1).

Sex and Age-specific Proportion of Obesity Groups

The proportion of obesity groups stratified by sex and age are shown in Fig. 1 and Supplementary Table 1. Accordingly, the OO and OSO groups comprised 36.3% and 36.1% of the total study population and 42.3% and 40.1% of women, respectively, the proportions of which were higher than those of the O and SO groups. Only small differences were found between such groups in men (Fig. 1a). The

Table 1 Baseline characteristics and prevalent diseases among the individuals stratified by sex

	Men (n = 1080)	Women (n = 2187)
General characteristics		
Age (years)	64.6 ± 9.1*	63.8 ± 8.9
Ht (cm)	166.5 ± 5.8†	153.1 ± 5.7
Wt (kg)	70.9 ± 8.8†	60.8 ± 8.1
BMI (kg/m^2)	25.5 ± 2.6	25.9 ± 2.9†
WC (cm)	91.0 ± 7.0†	87.1 ± 8.2
Smoking (ever, *n* or %)	865 (80.7%)†	153 (7.0%)
Alcohol (ever, *n* or %)	971 (90.6%)†	1409 (64.7%)
Exercise (≥ moderate, *n* or %)	584 (54.5%)†	1038 (47.7%)
SBP (mmHg)	129.9 ± 16.9	130.0 ± 17.8
DBP (mmHg)	80.4 ± 10.2†	79.0 ± 9.7
Glucose (mg/dL)	107.5 ± 24.4†	101.9 ± 21.7
Insulin (μIU/mL)	11.4 ± 6.3	11.4 ± 7.7
HOMA-IR	3.1 ± 2.2	3.0 ± 3.3
T-C (mg/dL)	189.8 ± 37.0	204.6 ± 37.1†
HDL-C (mg/dL)	45.8 ± 11.2	51.4 ± 11.8†
LDL-C (mg/dL)	112.4 ± 35.9	128.7 ± 33.8†
TG (mg/dL)	176.1 ± 125.3†	144.2 ± 78.5
AST (IU/L)	25.1 ± 8.7†	22.7 ± 7.5
ALT (IU/L)	26.3 ± 14.2†	20.6 ± 10.3
iPTH (pg/mL)	68.8 ± 24.7	71.0 ± 29.7*
25OHD (ng/mL)	19.9 ± 6.6†	17.9 ± 6.8
Body composition factors		
FM (kg)	19.9 ± 3.4	23.5 ± 4.1†
BF %	28.2 ± 2.6	38.7 ± 2.9†
TF %	58.2 ± 3.7†	55.1 ± 4.5
LF %	36.4 ± 3.5	41.0 ± 4.5†
LM (kg)	50.5 ± 6.1†	36.9 ± 4.6
ASM (kg)	20.5 ± 2.8†	13.9 ± 2.0
ASM/Wt (%)	28.9 ± 1.8†	22.9 ± 1.6
LS BMD (g/cm^2)	0.96 ± 0.16†	0.82 ± 0.14
FN BMD (g/cm^2)	0.75 ± 0.12†	0.63 ± 0.11
TH BMD (g/cm^2)	0.93 ± 0.13†	0.79 ± 0.12
Prevalent diseases		
MetS (*n*, %)	748 (74.6)†	1030 (51.9)
T2D (*n*, %)	223 (21.7)†	332 (16.2)
HTN (*n*, %)	533 (49.7)	1025 (47.1)
HL (*n*, %)	166 (15.5)	447 (20.5)†
MI, angina (*n*, %)	83 (7.7)†	89 (4.1)
CVA (*n*, %)	63 (5.9)†	80 (3.7)
OA (*n*, %)	96 (9.0)	787 (36.2)†
Vitamin D deficiency (*n*, %)	577 (56.2)	1381 (67.6)†
Fracture (*n*, %)	69 (6.4)	192 (8.8)†

*$P<0.05$; †$P<0.01$, considered significant parameters by *t* test and Chi-square test comparing values between men and women. Values are shown in mean ± SD or *n* and percentage (%) within each sex

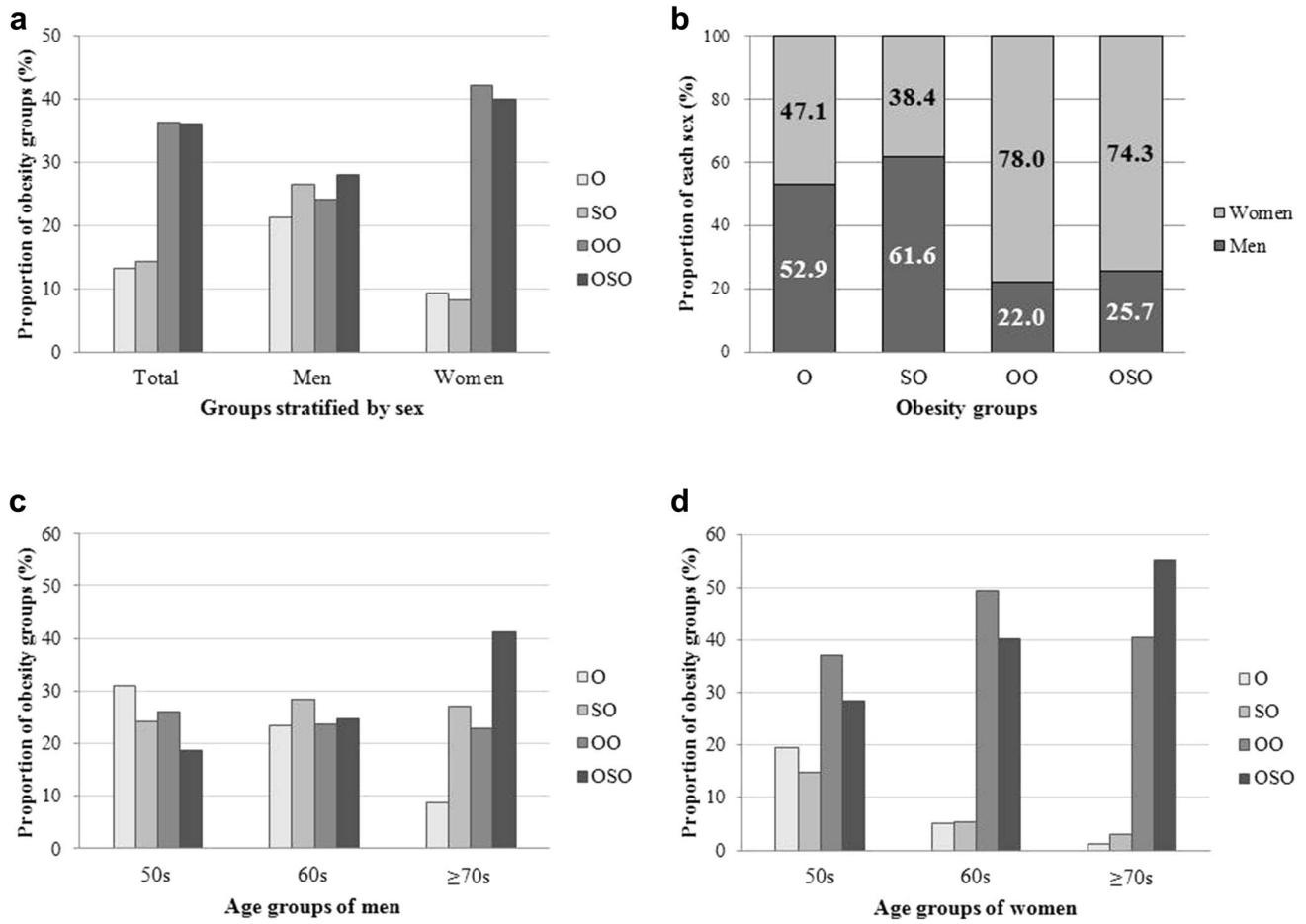

Fig. 1 Proportion of obesity groups by sex and age groups. The proportion of total subjects, men, and women (**a**), the proportion of men and women in each obesity group (**b**), and the proportion of men and women in the obesity groups stratified by age (**c**, **d**)

proportion of men was higher than women in both the O and SO groups; moreover, the proportion of women was as high as 78.0% and 74.3% in the OO and OSO groups, respectively (Fig. 1b). With regard to the proportion of individuals in the obesity groups by age, the proportion of men in the OSO group increased from 18.7% for those aging 50 years to 41.3% for those ≥ 70 years. In addition, the proportion of men in the O group decreased to 8.8% for those ≥ 70 years (Fig. 1c). The proportion of women in the OSO group increased from 28.4% for those aging 50 years to 55.2% for those aging ≥ 70 years, while the proportion in the O and SO groups decreased to 1.3% and 3.1% in women aging ≥ 70 years, respectively (Fig. 1d).

Sex-Specific Comparison of Clinical and Body Composition Factors among Obesity Groups

A comparison of clinical and biochemical parameters among obesity groups in men showed that the lowest and highest age of men was in the O and OSO groups, respectively. Moreover, the lowest Ht was observed in the OSO group, whereas the highest Wt, BMI, and WC were observed in the SO group. The lowest exercise habit was observed in the OSO group, while smoking experience and alcohol consumption were similar among all four obesity groups. SBP was high in the SO and OSO groups, while DBP was high in the O and SO groups. The highest metabolic marker values, such as glucose, insulin, TG levels, and HOMA-IR were observed in the SO group, while ALT level was higher in the O and SO groups than that in the other groups. The level of iPTH was similar among all obesity groups, whereas the lowest 25OHD level was in the OSO group. A comparison of body composition factors revealed that the highest FM and the lowest LF % were observed in the SO group, whereas BF % and TF % were higher in the SO and OSO groups than those in the other groups. The lowest LM and ASM were observed in the OSO group, while BMD was lower in the OO and OSO groups than that in the other obesity groups (Table 2).

Table 2 Comparison of clinical and body composition factors among obesity groups in men

	O (n = 229)	SO (n = 287)	OO (n = 261)	OSO (n = 303)
General characteristics				
Age (years)	61.0 ± 8.0	64.5 ± 8.6[a]	64.5 ± 9.2[b]	67.7 ± 9.1[c,e,f]
Ht (cm)	168.0 ± 5.7	167.3 ± 5.6	166.3 ± 5.4[b]	164.9 ± 6.0[c,e,f]
Wt (kg)	73.3 ± 8.1	74.7 ± 9.1	67.7 ± 7.3[b,d]	68.2 ± 8.5[c,e]
BMI (kg/m^2)	25.9 ± 2.1	26.7 ± 2.5[a]	24.5 ± 2.3[b,d]	25.1 ± 2.6[c,e,f]
WC (cm)	90.7 ± 6.2	94.1 ± 7.1[a]	88.2 ± 6.2[b,d]	90.7 ± 7.2[e,f]
Smoking (ever, *n*, %)	174 (76.3%)	228 (79.7%)	211 (82.1%)	252 (83.7%)
Alcohol (ever, *n*, %)	208 (91.2%)	261 (91.3%)	234 (91.1%)	268 (89.0%)
Exercise (≥ moderate, *n*, %)	136 (59.6%)	165 (57.7%)	137 (53.3%)	146 (48.5%)[c,e]
SBP (mmHg)	129.0 ± 16.0	130.8 ± 15.9	127.1 ± 15.0[d]	132.0 ± 16.4[f]
DBP (mmHg)	82.1 ± 10.7	80.9 ± 10.0	79.7 ± 10.0[b]	79.3 ± 10.0[c]
Glucose (mg/dL)	106.2 ± 19.4	112.2 ± 31.1[a]	103.6 ± 22.4[d]	107.3 ± 21.4
Insulin (μIU/mL)	10.9 ± 5.1	12.7 ± 8.1[a]	10.2 ± 4.5[d]	11.8 ± 6.4[f]
HOMA-IR	2.9 ± 1.6	3.7 ± 3.2[a]	2.7 ± 1.5[d]	3.1 ± 1.9[e]
T-C (mg/dL)	190.6 ± 25.8	191.0 ± 38.7	188.7 ± 36.9	188.8 ± 36.4
HDL-C (mg/dL)	46.0 ± 10.6	45.2 ± 11.0	46.9 ± 11.9	45.4 ± 11.3
LDL-C (mg/dL)	114.1 ± 35.7	111.0 ± 36.9	111.7 ± 35.6	112.9 ± 35.3
TG (mg/dL)	170.6 ± 99.4	195.2 ± 153.9[a]	165.8 ± 113.1[d]	171.2 ± 121.6[e]
AST (IU/L)	25.0 ± 8.1	25.5 ± 8.4	24.5 ± 8.5	25.3 ± 9.7
ALT (IU/L)	27.7 ± 14.7	27.6 ± 13.9	25.1 ± 13.6[b,d]	25.0 ± 14.3[c,e]
iPTH (pg/mL)	67.1 ± 24.5	69.1 ± 24.0	68.9 ± 26.5	69.8 ± 24.0
25OHD (ng/mL)	20.4 ± 6.7	20.1 ± 6.5	20.4 ± 6.7	18.8 ± 6.4[c,f]
Body composition factors				
FM (kg)	19.4 ± 2.5	21.8 ± 3.7[a]	18.1 ± 2.4[b,d]	19.9 ± 3.6[e,f]
BF %	26.6 ± 1.3	29.4 ± 2.7[a]	26.8 ± 1.5[d]	29.3 ± 2.8[c,f]
TF %	57.8 ± 3.6	59.4 ± 3.6[a]	57.4 ± 3.8[d]	58.3 ± 3.6[e,f]
LF %	36.7 ± 3.4	35.6 ± 3.4[a]	37.0 ± 3.6[d]	36.5 ± 3.5[e]
LM (kg)	53.4 ± 5.7	52.1 ± 6.1	49.2 ± 5.0[b,d]	47.7 ± 5.6[c,e,f]
ASM (kg)	22.3 ± 2.6	20.6 ± 2.7[a]	20.6 ± 2.3[b]	18.8 ± 2.5[c,e,f]
LS BMD (g/cm^2)	1.06 ± 0.11	1.09 ± 0.13[a]	0.85 ± 0.10[b,d]	0.87 ± 0.12[c,e,f]
FN BMD (g/cm^2)	0.83 ± 0.08	0.84 ± 0.09	0.68 ± 0.09[b,d]	0.67 ± 0.08[c,e]
TH BMD (g/cm^2)	1.02 ± 0.09	1.02 ± 0.10	0.86 ± 0.10[b,d]	0.85 ± 0.09[c,e]

$P < 0.05$, considered significant difference by ANOVA and Chi-square tests comparing parameters among obesity groups in men

[a]O versus SO; [b]O versus OO; [c]O versus OSO; [d]SO versus OO; [e]SO versus OSO; [f]OO versus OSO are marked with significant differences among the groups by post hoc analysis using Tukey's HSD. Values are shown in mean ± SD or *n* and percentage (%) within each obesity group in men

A comparison of the parameters in women revealed that the lowest age was recorded in the O and SO groups and the highest in the OSO group. The lowest Ht was observed in the OSO group, whereas Wt was higher in the O and SO groups than that in the other obesity groups. Moreover, the highest BMI and WC were observed in the SO group. Alcohol consumption was higher in the O and SO groups than that in the other obesity groups. The lowest exercise habit was observed in the OSO group. The highest SBP and DBP were observed in the OSO and OO groups, respectively. Unlike those in men, the highest metabolic marker values were observed in the OSO group, while ALT level was higher in the O and SO groups than that in the other obesity groups. The level of iPTH was the highest and 25OHD level was the lowest in the OSO group. A comparison of the body composition factors in women showed that the highest FM was observed in the SO group, with BF % and TF % being higher in the SO and OSO groups than those in the other obesity groups, whereas the lowest LF % was observed in the OSO group. The lowest LM and ASM were observed in the OSO group, while BMD was lower in the OO and OSO groups than that in the other obesity groups, similar to the results found in men (Table 3).

Table 3 Comparison of clinical and body composition factors among obesity groups in women

	O (n = 204)	SO (n = 179)	OO (n = 926)	OSO (n = 878)
General characteristics				
Age (years)	56.2 ± 5.8	57.9 ± 7.3	64.3 ± 8.4[b,d]	66.3 ± 8.7[c,e,f]
Ht (cm)	156.9 ± 5.2	155.5 ± 5.0[a]	153.4 ± 5.5[b,d]	151.4 ± 5.5[c,e,f]
Wt (kg)	64.8 ± 7.8	66.3 ± 9.4	59.4 ± 6.9[b,d]	60.4 ± 8.2[c,e,f]
BMI (kg/m^2)	26.3 ± 2.7	27.4 ± 3.6[a]	25.2 ± 2.5[b,d]	26.3 ± 3.1[e,f]
WC (cm)	87.1 ± 8.4	89.0 ± 10.0[a]	85.6 ± 7.6[b,d]	88.3 ± 8.4[f]
Smoking (ever, *n*, %)	13 (6.4%)	5 (2.8%)	71 (7.7%)	64 (7.3%)
Alcohol (ever, *n*, %)	148 (72.9%)	136 (76.0%)	585 (63.4%)[b,d]	540 (61.9%)[c,e]
Exercise (≥ moderate, *n*, %)	113 (55.7%)	86 (48.3%)	465 (50.4%)	374 (43.0%)[c,f]
SBP (mmHg)	125.9 ± 17.9	129.3 ± 17.7	129.3 ± 17.5	131.9 ± 17.9[c,f]
DBP (mmHg)	79.6 ± 9.9	80.8 ± 9.6	89.6 ± 9.5[d]	79.0 ± 9.9
Glucose (mg/dL)	98.1 ± 16.0	102.5 ± 22.9	100.9 ± 20.1	103.7 ± 24.0[c,f]
Insulin (μIU/mL)	10.5 ± 4.2	11.2 ± 4.3	10.9 ± 4.8	12.3 ± 10.9[c,f]
HOMA-IR	2.6 ± 1.2	2.9 ± 1.7	2.8 ± 1.5	3.3 ± 4.9[c,f]
T-C (mg/dL)	203.4 ± 36.5	202.8 ± 37.4	203.0 ± 36.3	207.1 ± 38.0
HDL-C (mg/dL)	52.1 ± 12.3	52.8 ± 12.3	51.1 ± 11.7	51.2 ± 11.6
LDL-C (mg/dL)	129.4 ± 31.5	126.0 ± 34.6	127.6 ± 33.6	130.2 ± 34.3
TG (mg/dL)	133.4 ± 85.6	141.9 ± 72.7	141.3 ± 76.6	150.5 ± 80.0[c]
AST (IU/L)	22.7 ± 7.2	23.1 ± 8.2	22.4 ± 7.2	23.0 ± 7.8
ALT (IU/L)	22.7 ± 11.2	22.4 ± 12.3	19.9 ± 9.8[b,d]	20.5 ± 10.0[c]
iPTH (pg/mL)	64.5 ± 23.7	67.6 ± 27.3	70.6 ± 29.5[b]	73.9 ± 31.3[c,e]
25OHD (ng/mL)	18.6 ± 6.6	17.6 ± 6.5	18.3 ± 6.9	17.2 ± 6.8[c,f]
Body composition factors				
FM (kg)	23.9 ± 3.5	26.7 ± 5.0[a]	21.9 ± 2.9[b,d]	24.3 ± 4.4[e,f]
BF %	37.1 ± 1.7	40.4 ± 2.8[a]	37.1 ± 1.5[d]	40.4 ± 2.9[c,f]
TF %	53.6 ± 4.2	55.3 ± 4.3[a]	54.5 ± 4.4	56.1 ± 4.5[c,f]
LF %	42.5 ± 4.2	41.2 ± 4.2[a]	41.5 ± 4.4[b]	40.2 ± 4.5[c,e,f]
LM (kg)	40.4 ± 4.5	37.1 ± 4.8[a]	37.0 ± 4.1[b,d]	35.6 ± 4.3[c,e,f]
ASM (kg)	15.7 ± 2.0	14.3 ± 2.1[a]	14.3 ± 1.8[b]	13.0 ± 1.8[c,e,f]
LS BMD (g/cm^2)	1.02 ± 0.11	1.02 ± 0.08	0.77 ± 0.11[b,d]	0.79 ± 0.11[c,e,f]
FN BMD (g/cm^2)	0.79 ± 0.07	0.79 ± 0.08	0.60 ± 0.09[b,d]	0.59 ± 0.08[c,e]
TH BMD (g/cm^2)	0.95 ± 0.08	0.95 ± 0.09	0.76 ± 0.09[b,d]	0.74 ± 0.09[c,e,f]

$P < 0.05$, considered significant difference by ANOVA and Chi-square tests comparing parameters among obesity groups in women

[a]O versus SO; [b]O versus OO; [c]O versus OSO; [d]SO versus OO; [e]SO versus OSO; [f]OO versus OSO are marked with significant differences among the groups by post hoc analysis using Tukey's HSD. Values are shown in mean ± SD or *n* and percentage (%) within each obesity group in women

Sex-Specific Comparison of Prevalent Diseases among Obesity Groups

Table 4 shows a comparison of prevalent diseases among the obesity groups stratified by sex. In men, the prevalence of MetS was similarly high in the O, SO, and OSO groups. The prevalence of T2D and HTN was higher in the SO and OSO groups than that in the other obesity groups. The prevalence of HL was the lowest in the OSO group while that of MI/angina was higher in the SO, OO, and OSO groups than that in the O group. The prevalence of CVA was higher in the SO and OSO groups than that in the other obesity groups while that of OA was similar among all the obesity groups. In women, the prevalence of MetS, T2D, HTN, and OA was the highest in the OSO group while that of HL was similar among all the obesity groups. No significant findings were noted for the prevalence of MI/angina except that it tended to be higher in the OSO group than that in the OO group. The prevalence of CVA did not differ among all the obesity groups. For both sexes, vitamin D deficiency was the most prevalent in the OSO group, while the prevalence of fracture did not differ among all the obesity groups (Table 4).

Table 4 Comparison of prevalent diseases among obesity groups stratified by sex

	Men (n = 1080)				Women (n = 2187)			
	O (n = 229)	SO (n = 287)	OO (n = 261)	OSO (n = 303)	O (n = 204)	SO (n = 179)	OO (n = 926)	OSO (n = 878)
MetS (*n*, %)	165 (75.7)	222 (83.1)	151 (60.9)[b,d]	210 (77.8)[f]	91 (46.9)	86 (50.6)	405 (47.6)	448 (58.3)[c,e,f]
T2D (*n*, %)	41 (18.4)	73 (26.8)[a]	32 (12.8)[d]	77 (27.1)[c,f]	21 (10.7)	24 (14.0)	125 (14.3)	162 (20.1)[c,e,f]
HTN (*n*, %)	92 (40.4)	176 (61.5)[a]	101 (39.3)[d]	164 (54.5)[c,f]	73 (36.0)	68 (38.0)	402 (43.6)[b]	482 (55.3)[c,e,f]
HL (*n*, %)	40 (17.5)	56 (19.6)	37 (14.4)	33 (11.0)[c,e]	47 (23.2)	42 (23.5)	185 (20.0)	173 (19.8)
MI, angina (*n*, %)	6 (2.6)	28 (9.8)[a]	20 (7.8)[b]	29 (9.6)[c]	5 (2.5)	8 (4.5)	29 (3.2)	47 (5.4)[f]
CVA (*n*, %)	8 (3.5)	21 (7.3)[a]	8 (3.1)[d]	26 (8.6)[c,f]	6 (3.0)	7 (3.9)	31 (3.4)	36 (4.1)
OA (*n*, %)	20 (8.8)	31 (10.8)	19 (7.4)	26 (8.6)	48 (23.6)	54 (30.2)	311 (33.7)[b]	374 (42.9)[c,e,f]
Vitamin D deficiency (*n*, %)	117 (52.7)	149 (54.6)	131 (52.2)	180 (64.1)[c,e,f]	128 (65.0)	120 (69.8)	570 (65.2)	563 (70.4)[f]
Fracture (*n*, %)	15 (6.6)	15 (5.2)	20 (7.7)	19 (6.3)	13 (6.4)	12 (6.7)	83 (9.0)	84 (9.6)

$P < 0.05$, considered significant difference by ANOVA and Chi-square tests comparing parameters among obesity groups

[a]O versus SO; [b]O versus OO; [c]O versus OSO; [d]SO versus OO; [e]SO versus OSO; [f]OO versus OSO are marked with significant differences among the groups. Values are shown in *n* and percentage (%) within each obesity group, men and women separately

Association between Laboratory Parameters and Regional Body Composition Factors with Bone and Muscle Losses in Men and Women with Obesity

Table 5 presents the results of multivariate linear regression analyses conducted to determine whether laboratory parameters and regional body composition factors were associated with ASM and BMD of LS, FN, and TH. Accordingly, glucose was positively associated with BMD in men but not in women. Insulin level and HOMA-IR were negatively associated with FN and TH BMD in women but not in men. TG level was negatively associated with ASM only in men, and no significant associations were observed for ALT level in both sexes. Level of iPTH was negatively associated with BMD only in women, and 25OHD level was positively associated with FN and TH BMD in both sexes and with ASM and LS BMD in women. In terms of regional body composition factors, BF % was negatively associated with ASM and FN and TH BMD, and TF % was negatively associated with ASM in both sexes and with FN BMD in women. LF % was positively associated with ASM in both sexes and with FN BMD in women. ASM and BMD were positively associated with each other even after adjusting for baseline characteristics, HOMA-IR, and 25OHD level.

Discussion

The present large-scale, cross-sectional, observational study showed that men comprised a higher proportion of the O and SO groups, whereas women comprised a higher proportion of the OO and OSO groups. Moreover, an increasing trend of OSO prevalence with age was observed in both sexes, although it was more prominent in women. Compared with the other obesity groups, cardiometabolic diseases were mostly higher among men in the SO and OSO groups and women in the OSO group than those in men and women in other groups, respectively. Similarly, metabolic markers were mostly higher in men in the SO group and women in the OSO than those in men and women in the other obesity groups, respectively. After analyzing regional body composition differences, we found that BF % and TF % were negatively associated with ASM and/or femur BMD, while LF % was positively associated with them in both sexes.

To overcome the limitation associated with defining obesity using BMI in elderly individuals, obesity was classified using BF % cutoff points modified from those reported in clinical trials in other Asian countries. Accordingly, we found that in this study, OSO population was higher than that included in previous trials given the differences in the enrolled population and diagnostic criteria [16, 21]. Currently, there are no clear estimates for the prevalence of patients with OSO. However, the prevalence of its components, individually or in combination, has been roughly estimated. Some estimates revealed that 25% of overweight/obese women over a wide age range suffered from OSO, whereas only 12% of overweight/obese postmenopausal women had OSO [22, 23]. Based on our data, the present study found that OO and OSO were more prevalent among women, whereas O and SO were more prevalent among men with obesity. Furthermore, the proportion of OSO with age profoundly increased in women but only steadily in men. This may suggest that after early appendicular muscle loss in both sexes, muscle loss exacerbates with the occurrence of steep bone loss, especially among women.

OSO syndrome or unhealthy body composition changes in elderly individuals can be a considerable cause of concern, given the possible consequences of clinical morbidity.

Table 5 Multiple regression coefficients (β) determining the association between laboratory parameters and regional body composition factors with appendicular muscle mass or bone mass in men and women with obesity

	Men				Women			
	ASM (kg)	LS BMD (g/cm^2)	FN BMD (g/cm^2)	TH BMD (g/cm^2)	ASM (kg)	LS BMD (g/cm^2)	FN BMD (g/cm^2)	TH BMD (g/cm^2)
Laboratory parameters								
Glucose (mg/dL)	−0.031 (0.508)	0.078 (0.075)*	0.057 (0.230)*	0.064 (0.255)*	−0.004 (0.466)	0.006 (0.184)	−0.021 (0.365)	−0.013 (0.353)
Insulin (μIU/mL)	0.035 (0.518)	−0.021(0.074)	−0.047 (0.230)	−0.057 (0.249)	−0.017 (0.463)	−0.037 (0.183)	−0.064 (0.373)†	−0.061 (0.356)†
HOMA-IR	0.022 (0.516)	0.033 (0.075)	−0.007 (0.229)	−0.013 (0.248)	−0.022 (0.464)	−0.022 (0.183)	−0.062 (0.373)†	−0.060 (0.355)†
TG (mg/dL)	−0.052 (0.510)*	−0.013 (0.069)	−0.001 (0.226)	−0.006 (0.250)	−0.020 (0.466)	0.000 (0.183)	−0.018 (0.366)	0.014 (0.355)
ALT (IU/L)	−0.030 (0.508)	0.006 (0.069)	0.010 (0.226)	0.021 (0.250)	−0.007 (0.466)	0.022 (0.184)	−0.004 (0.354)	0.034 (0.356)
iPTH (pg/mL)	0.000 (0.506)	−0.044 (0.070)	−0.046 (0.228)	−0.043 (0.252)	−0.022 (0.466)	−0.048 (0.186)*	−0.091 (0.374)†	−0.104 (0.365)†
25OHD (ng/mL)	0.017 (0.508)	0.046 (0.071)	0.058 (0.229)*	0.061 (0.254)*	0.035 (0.467)*	0.041 (0.185)*	0.052 (0.368)†	0.054 (0.358)†
Regional body composition factors								
BF %	−0.329 (0.611)†	−0.042 (0.079)	−0.079 (0.237)*	−0.112 (0.262)†	−0.411 (0.607)†	−0.030 (0.185)	−0.063 (0.378)†	−0.110 (0.367)†
TF %	−0.115 (0.529)†	0.027 (0.078)	0.019 (0.232)	0.047 (0.253)	−0.110 (0.477)†	−0.014 (0.184)	−0.071 (0.379)†	−0.027 (0.358)
LF %	0.113 (0.529)†	−0.018 (0.078)	−0.018 (0.232)	−0.049 (0.254)	0.114 (0.478)†	0.020 (0.184)	0.073 (0.380)†	0.026 (0.358)
ASM (kg)	–	0.156 (0.090)†	0.220 (0.255)†	0.202 (0.271)†	–	0.116 (0.191)†	0.177 (0.392)†	0.162 (0.371)†
LS BMD (g/cm^2)	0.083 (0.515)†	–	0.577 (0.533)†	0.590 (0.568)†	0.076 (0.469)†	–	0.485 (0.567)†	0.512 (0.573)†
FN BMD (g/cm^2)	0.139 (0.529)†	0.687 (0.444)†	–	0.839 (0.792)†	0.151 (0.480)†	0.634 (0.434)†	–	0.839 (0.797)†
TH BMD (g/cm^2)	0.131 (0.527)†	0.722 (0.471)†	0.861 (0.787)†	–	0.135 (0.478)†	0.652 (0.456)†	0.815 (0.802)†	–

*$P < 0.05$; †$P < 0.01$, considered significant parameters by multivariate regression analysis with ASM, LS BMD, FN BMD, or TH BMD as a dependent variable. Regression coefficients, β (R^2) of laboratory and regional body composition factors to ASM and BMD were analyzed individually after adjusting age, BMI, smoking, alcohol, and exercise habit for all variables, and included HOMA-IR and 25OHD for regional body composition factors

Thus, the prevalence of cardiometabolic diseases, vitamin D deficiency, and fractures were compared among the obesity groups. These diseases are caused by complex mechanisms primarily due to increased impaired metabolism and atherosclerotic changes. Accordingly, such diseases had been mostly prevalent in men with SO and OSO and women with OSO. These results suggest that although impaired metabolism may be aggravated by appendicular muscle loss in men with obesity, the same may be aggravated by both appendicular muscle and bone losses in women with obesity. Age-related fat redistribution or infiltration of fat into the bone or muscle may lead to accelerated and deleterious body composition changes [24]. Other possible explanations include the various effects of TF and LF. From our results, BF and TF were negatively associated with ASM and/or femur BMD, while LF was positively associated with them. Despite the similarly high percentage of BF among the individuals enrolled herein, increased TF and decreased LF contributed to appendicular muscle and femur bone losses. We previously showed that LF may be an independent predictive factor for MetS in individuals with obesity [25]. Moreover, reports have shown that leg fat confers favorable effects on cardiovascular risk and was positively associated with adiponectin levels, which may support the protective effects of LF against muscle and bone losses via anti-inflammatory effects on the cross-talk between muscle and bone [26–28].

Both the SO and OSO groups displayed the sarcopenia phenotype, which has been defined by various diagnostic criteria as appendicular muscle loss and decreased muscle function [10, 18, 29]. Our data showed that appendicular

muscle loss is of considerable metabolic importance in both sexes, particularly in men. Numerous reports have shown that sarcopenia is associated with functional ability, morbidity, or mortality in elderly individuals, particularly among those with comorbid obesity or osteoporosis [9, 18, 30, 31]. The present study found that appendicular muscle loss increases cardiometabolic diseases to a greater extent than bone loss in both sexes, with the latter being more frequent among women with obesity than men. Moreover, the presence of both muscle and bone losses resulted in more cardiometabolic diseases in women. Although our data showed no significant differences in the prevalence of fractures, the incidence thereof may theoretically increase if muscle and bone masses simultaneously decrease. As only individuals with obesity were included in this study, the relatively low number of fractures may have been due to the mechanical loading effects of obesity. However, there have been positive reports regarding sarcopenia and fractures in the general population, and marked obesity may not be able to protect against the development of fractures. Thus, more clinical studies are required to verify the incidence of OSO and fractures.

In the present study, insulin resistance profiles showed sex-specific associations with bone mass but not muscle mass, partly because only individuals with obesity who were already insulin resistant were enrolled. Among other laboratory parameters, iPTH level was negatively associated with BMD at all sites in women only, whereas 25OHD level was positively associated with femur BMD in men and ASM and BMD at all sites in women. Vitamin D plays a potential role in individual bone, muscle, and fat physiologies and recent studies have also suggested its favorable effects on cross-talk between bones and muscles [28, 32]. Moreover, a recent study showed that vitamin D level was associated with an increased number of body composition changes with age [21]. The present study found a significantly higher proportion of both men and women with vitamin D deficiency in the OSO group, which may support the possible protective role of adequate vitamin D levels on both appendicular muscle and bone losses in elderly individuals.

The possible protective mechanisms of vitamin D on bone, muscle, and fat tissues include the inhibition of myokine production such as myostatin, and the stimulation of growth factors production such as vascular endothelial growth factor, insulin-like growth factor-1, and osteoglycin in the muscles, which are beneficial to bones [32]. Moreover, in bones, vitamin D may increase the production of sclerostin and osteokines, similar to that of osteocalcin and fibroblast growth factor-23, which are beneficial for muscles [28]. Adipose tissues may also be involved in the cross-talk between bones and muscles through adipokines [28]. Vitamin D also potentially modulates adipogenesis and preadipocyte differentiation and has been shown to have potential anti-inflammatory effects [33, 34]. The present study showed that low vitamin D levels and vitamin D deficiency play a role in the development of unfavorable body composition changes associated with OSO, particularly in women. Nonetheless, more prospective clinical trials are still required to clarify the possible protective effects of dietary or supplemental vitamin D intake and to determine the adequate range of vitamin D level that may protect or treat OSO in elderly individuals.

Several limitations and strengths of the present study should be noted. First, given that this was a cross-sectional, observational study from the KNHANES survey, possible information and selection bias may have existed because of the self-report method employed for data collection regarding lifestyle and prevalent diseases from a relatively healthy population. Second, using BF % to determine obesity may lead to overestimations therein, which should be considered when comparing with those obtained from other ethnicities or non-obese populations. Third, sarcopenia was defined using only muscle mass and appropriate evaluation of muscle strength was not conducted for its diagnosis. Lastly, hidden confounders other than the covariates used in the present study may have affected the results of multivariate regression analyses. However, the strength of our study is the inclusion of a large number of individuals from a nationwide survey with detailed data regarding prevalent diseases and body composition analyses for FM and LM as well as BMD.

In conclusion, OSO increases with age in both men and women with obesity. Appendicular muscle loss was metabolically significant regardless of bone loss in men with obesity, whereas appendicular muscle loss with bone loss resulted in worse metabolic markers among women. Appendicular muscle and bone mass were positively associated with each other in both sexes. In terms of fat distribution, BF % and TF % were positively and LF % was negatively related to appendicular muscle and bone loss, especially in women. Moreover, vitamin D deficiency was most prevalent with the OSO phenotype in both sexes. Thus, treatment measures that maintain appendicular muscle mass, bone mass, favorable fat distribution, and optimal vitamin D levels while aging may reduce the risk of OSO, even in individuals with obesity.

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Compliance with Ethical Standards

Conflict of interest Yoo Mee Kim, Sunghoon Kim, Young Jun Won, and Se Hwa Kim confirm that they have no conflict of interest related to this study.

Human and Animal Rights and Informed Consent All procedures on participants were performed in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Each participant gave written informed consent.

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