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Muscle mass is associated with incident fracture in postmenopausal women: The OFELY study

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ABSTRACT

The relationships between body composition and bone mineral density are well established but the contribution of body composition to the risk of fracture (Fx) has rarely been evaluated prospectively. We analyzed the risk of Fx by body composition in 595 postmenopausal women (mean age 66 ± 8 years) from a longitudinal cohort study (Os des Femmes de Lyon). We assessed the risk of the first incident fragility Fx according to body composition obtained from whole-body DXA: abdominal visceral (VFAT) and subcutaneous fat mass (SFAT), total body fat mass (FM), lean mass index (LMI) and appendicular skeletal muscle mass index (ASMI).

During a median [IQ] follow-up of 13.1 years [1.9], 138 women sustained a first incident Fx, including 85 women with a major osteoporotic Fx (MOP Fx: hip, clinical spine, humerus or wrist). After adjustment for age, women who sustained Fx had lower BMI (−4%, $p = 0.01$), LMI (−6%, $p = 0.002$) and ASMI (−3%, $p = 0.003$), compared with women without Fx. After adjustment for age, prevalent Fx, physical activity, incident falls and FN BMD, each SD increase of baseline values of LMI and ASMI was associated with decreased Fx risk with adjusted hazard ratios of 0.76 for both of $p \leq 0.02$. Those associations were similar after accounting for the competing risk of death. VFAT and SFAT were associated with Fx risk in the multivariate model only for MOP Fx and the association did not persist after consideration of competing mortality.

We conclude that lean mass and appendicular muscle mass indexes are associated with the risk of fracture in postmenopausal women independently of BMD and clinical risk factors.

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1. Introduction

The relationships between body composition and bone mineral density (BMD) have been widely analyzed [1–5]. Both lean mass and fat mass increase mechanical load on weight-bearing bones [4,6–8]. Additional positive effects of lean mass on the skeleton include loads coming from muscle contraction and non-mechanical factors such as genetic, hormonal and growth factors [6,9–11]. For fat mass, the secretion of bone-active hormones from the pancreatic β cell (insulin, amylin) and factors from the adipocytes (estrogens, adipokines such as leptin, adiponectin) have either positive or negative effects on bone formation whereas production of inflammatory cytokines promotes bone resorption [1,12–15].

Nevertheless, the independent contribution of body composition to the risk of fracture has rarely been evaluated prospectively. Some studies have shown an increased risk of hip and major osteoporotic fractures in postmenopausal women with lower lean mass or fat mass but those associations were no more significant after taking BMD [16] or FRAX [17] into account. In the Study of Osteoporotic Fractures, lean and fat masses, assessed by bioelectrical impedance, contributed equally to the risk of hip fracture [16] whereas in French women from the EPIDOS prospective study, where fat and lean masses were measured with DXA, fat mass alone was found to be a significant risk factor for hip fractures [18]. Nevertheless, no specific analyses of appendicular muscle mass and abdominal fat mass were performed in those studies. In some reports, the relationships between fat mass and bone are different according to the distribution of fat mass [19,20]. In a case-control study in the elderly, Nguyen et al. showed a 50% higher hip fracture risk for a 10% abdominal fat mass decrease [21]. Similarly, Yang et al. showed in a recent prospective study, an increased risk of vertebral fracture associated with a decrease of abdominal fat in postmenopausal women, contrasting with no association with total body fat mass [22]. Despite being widely believed that the decline in muscle mass and function with age is concurrent with a decline in BMD, followed by increased fragility fractures, only one prospective study has reported an inverse association between muscle mass and hip fractures [23].

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The aim of this study was to prospectively investigate in the same study the risk of fragility Fx by fat mass (total body and abdominal including visceral and subcutaneous fat), lean mass and appendicular muscle mass in postmenopausal women. We hypothesized that greater abdominal fat mass and lean mass would be associated with a lower risk for fracture.

2. Material and methods

2.1. Population

We studied the 595 postmenopausal women from the OFELY (Os des FEmmes de LYon) cohort who had a first evaluation of body composition on a HOLOGIC QDR 4500 device between years 2000 and 2001 (i.e., at their ninth annual follow-up, called baseline for the current analysis). The OFELY cohort was described elsewhere [24,25]. Briefly, OFELY is an ongoing prospective study of the determinants of bone loss in 1039 volunteer women, recruited between February 1992 and December 1993, 31–89 years of age, randomly selected from the affiliates of a large health insurance company (Mutuelle Générale de l'Education Nationale) from the Rhône district (i.e., Lyon and its surroundings in France), with an annual follow-up. Written informed consent was obtained from each participant and the study was approved by the local ethics committee.

2.2. Body composition assessment

Whole-body DXA (QDR4500, APEX V8.26a, HOLOGIC Inc., Bedford, MA) exams were analyzed to obtain total body fat mass (FM) and lean mass (LM). Abdominal fat mass, including visceral (VFAT) and subcutaneous fat mass (SFAT) was obtained using a different APEX version (4.0.2). Abdominal fat mass was measured in a 5-cm-wide region placed across the entire abdomen just above the iliac crest at a level that approximately coincided with the 4th lumbar vertebrae on the whole-body DXA scan [26]. Since DXA is a two-dimensional projection method, both visceral and subcutaneous fat are measured in the abdominal cavity. Thus, using appropriate modeling, the amount of subcutaneous fat over the visceral cavity is estimated from the DXA measurement of the subcutaneous fat on each side of the abdominal cavity. This estimate of the subcutaneous fat overlying the abdominal cavity added to the subcutaneous fat measured by DXA, are subtracted from the total abdominal fat DXA to obtain VFAT. With that method, DXA performs as well as computed tomography to estimate visceral fat [26]. Appendicular skeletal muscle mass (ASM) was calculated as the sum of lean mass (non-fat, non-bone) in the arms and legs. The indexes (LMI and ASMI) were obtained by dividing LM and ASM by height squared. The in vivo reproducibility, expressed as the root mean square coefficient of variation (rms CV) and calculated from 2 repeated measurements in 26 women aged 48–83 years was 1.4% for FM, 0.8% for LM, 1.7% for VFAT and 0.5% for SFAT.

Areal BMD (aBMD) was measured at the same visit at the femoral neck (FN BMD) on the same densitometer. Height and weight were measured and body mass index (BMI) was calculated (kg/m^2).

Clinical assessment. All women completed a written health questionnaire at baseline (described previously), including medical history, tobacco use, medication use, physical activity (expressed by a score calculated from sport or recreational activity, job and home activities), fall(s) during the past 12 months and occurrence of radiologically confirmed low-trauma fractures [27]. Incident falls were reported at each annual follow-up in addition with incident fragility fractures. Incident fallers were women who fell 1 or more times per year during the whole follow-up in absence of incident Fx or until the first incident Fx.

2.3. Fracture evaluation

For the present analysis, prevalent fragility fractures were all those that occurred since the inclusion in the study, in addition to the fragility fractures of the wrist, humerus, vertebrae, or hip that occurred before the inclusion in the study and after the age of 40 years. Incident non-vertebral and clinical vertebral fractures were reported during each annual follow-up after the 9th visit (baseline visit of the current analysis) until February 2015 (i.e., at their 22nd or 23rd annual follow-up). For women who did not come to the clinical center, a letter was sent every year to identify the occurrence of fractures. All fractures were confirmed by radiographs or by a surgical report. Only low-trauma fractures (i.e., those occurring as a result of falls from standing height or less) were taken into account in this analysis, and we excluded fractures of the fingers, toes, skull and face. Morphometric vertebral fractures were also assessed, using the semiquantitative method of Genant, at baseline and during the follow-up after 4 years and 9 years on lateral X-ray films of the thoracic and lumbar spine and after 11 years on DXA (Hologic Discovery, HOLOGIC Inc., Bedford, MA) using Vertebral Fracture Assessment software (VFA). Spine radiographs were obtained at baseline in 534 (90%) women, including 99% ($n = 484$) of women aged 60 years or more. The information about incident morphometric vertebral fractures was available for 506 (85%) women, including 415 women aged 60 years or more at baseline. Both clinical and morphometric incident vertebral fractures were taken into account except for the analysis of major fractures that included clinical spine, hip, humerus or wrist fractures. For the present study, the first incident fragility fracture was analyzed according to the time since baseline.

3. Statistical analysis

Chi-square tests, Wilcoxon rank-sum tests and logistic regression were used to compare women with and without incident fracture, before and after adjusting for age. Correlation analyses were performed with the test of Spearman, because most variables were not normally distributed. Cox proportional hazards models based on time to the first fragility fracture (or to the first radiograph showing morphometric incident vertebral fracture) were used to calculate hazard ratios with their 95% confidence interval (HR, 95% CI), to estimate the fracture risk prediction for a SD change of body composition parameter. All models were first adjusted for age and multivariable models included confounders of the fracture risk prediction by body composition, that were significant in the univariate analysis. Body weight and BMI were not used in these models because of their high correlation ($r > 0.7$) with body composition variables to avoid multicolinearity among covariates. Thus, FN BMD, prior Fx and physical activity were entered simultaneously into the second model and incident falls were further added in the third model. Cox regression models were repeated accounting for the competing risk of death according to the Fine and Gray model [28]. Finally, a stepwise regression was used with a 0.10 significance level for addition to the model to analyze the respective role of fat and lean mass on the risk of fracture. All statistical analyses were performed using Stata 12 (StataCorp LP, College Station, Texas, USA).

4. Results

During a median [IQ] 13.1 [1.9] years of follow-up, 138 women sustained a first incident fragility Fx, including 85 women with a major osteoporotic (MOP) Fx: clinical spine ($n = 20$), distal forearm ($n = 42$), hip ($n = 14$), humerus ($n = 9$) and 53 women with other Fx: morphometric vertebral Fx ($n = 6$), clavicle ($n = 1$), humerus diaphysis ($n = 2$), elbow ($n = 2$), rib ($n = 9$), scapula ($n = 2$), pelvis ($n = 3$), ankle ($n = 16$), femoral diaphysis ($n = 1$), lower leg ($n = 8$), patella ($n = 3$). Fifty-two non-fractured women (mean age 72 ± 10 years) died during the follow-up. Compared with women without incident Fx ($n = 457$), women with incident Fx were significantly

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