Patients With Knee Osteoarthritis Have a Phenotype With Higher Bone Mass, Higher Fat Mass, and Lower Lean Body Mass

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Abstract

Background Although knee osteoarthritis (OA) is common, its etiology is poorly understood. Specifically, it is not known whether knee OA is associated with abnormal anthropometric and musculoskeletal characteristics known to be associated with OA in general. We recently studied this topic for patients with hip arthritis; however, it is important to evaluate it for knee OA separately, because there are reports indicating that patients with primary OA in different joints may have a different phenotype.

Questions/purposes Do patients with primary knee OA have a phenotype with higher bone mineral density (BMD), higher body mass index (BMI), larger skeletal size, lower lean body mass, and higher fat content?

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Methods We included 38 women and 74 men (mean age, 61 years; range, 34–85 years) with primary knee OA and 122 women and 121 men as control subjects. We used dual-energy x-ray absorptiometry to measure total body BMD (g/cm^2), femoral neck width (cm), fat and lean mass (%), and BMI (kg/m^2). Z scores were calculated for each individual. Data are presented as means with 95% confidence intervals.

Results Women with knee OA had the following Z scores: total body BMD 0.8 (0.5–1.0); BMI 1.6 (1.1–2.0); femoral neck width 0.1 (–0.3 to 0.4); proportion of lean mass –1.0 (–1.5 to –0.6); and proportion of fat mass 1.0 (0.6–1.4). Men with knee OA had the following Z scores: total body BMD 0.5 (0.3–0.7); BMI 0.9 (0.6–1.1); femoral neck width 0.3 (0.1–0.7); proportion of lean mass –0.9 (–1.1 to –0.8); and proportion of fat mass 0.7 (0.5–0.9).

Conclusions Women and men with idiopathic knee OA have a phenotype with higher BMD, higher BMI, proportionally higher fat mass, and proportionally lower lean body mass. Men also have a larger skeletal size.

Clinical Relevance A higher BMD may lead to stiffer bone, a higher BMI to a greater joint load, and a proportionally lower lean body (muscle) mass to lower joint-protective ability, and all trait deviations probably predispose for knee OA.

Introduction

Primary osteoarthritis (OA) can affect joint cartilage, adjacent skeleton, and surrounding soft tissue [10] in most joints [24, 30]. General risk factors for OA include heredity, older age, female gender, ethnicity, and high body mass index (BMI) [11]. The variety of risk factors suggests that different pathophysiologic etiologies may cause primary OA, and identification of these different etiologies

may help direct us toward different treatment approaches. Local factors such as chronic repeated loads, loads with high magnitude, ligament instability, neuromuscular impairment, and joint deformity may accelerate the degenerative process [5]. A high prevalence of OA has been reported in obese patients and in weightbearing joints [3, 5], often referred to as high joint surface load [28]. Primary OA can also be found in nonweightbearing joints such as the base of the thumb and the fingers [30, 32], and there are also differences in prevalence of primary OA in men and women [3, 5]. Thus, primary OA may be the result of more generalized pathophysiologic etiologies [11].

Primary OA leads to local effects on the skeleton, including cysts, subchondral sclerosis, and osteophytes [12]; however, OA is also associated with high bone mineral density (BMD) [3, 8, 11, 17, 26, 27], high BMI [15, 26], and small bone size [8]. It is unclear whether this phenotype is found in all patients with OA, irrespective of the affected joint. Previous studies have suggested that high BMI is associated with knee OA but not hip OA and with progression of knee OA but not of hip OA [15, 26]. We recently studied this topic for patients with hip arthritis [17]; however, it is important to evaluate it for knee OA separately, because primary OA in different joints may have a different phenotype and thus have different pathophysiological pathways. For example, high body fat is more strongly associated with knee OA than with hip OA [21]. Furthermore, different anthropometry may confer different pre-, peri-, and postoperative clinical implications. These aspects should therefore be evaluated separately for each large joint affected by OA.

We therefore conducted our study to determine whether individuals, based on sex, with primary knee OA have a phenotype with (1) higher BMD; (2) higher BMI; (3) smaller bone size; and (4) proportionally lower lean (muscle) mass and higher fat mass compared with patients without knee OA and if any such phenotype is related or not to body size (BMI).

Patients and Methods

We included 112 patients in our study: 38 women, aged 63 ± 12 (mean $\pm$ SD) years (range, 46–85 years), and 74 men, aged 60 ± 12 years (range, 34–85 years), with radiographically verified end-stage OA of the knee referred to our hospital during 2 consecutive years for a decision on surgery. All patients were white and residents of Malmö, Sweden. All had disabling pain from the affected joint, both at rest and during activity, and typical clinical and radiographic features of knee OA. No exclusion criteria were used. Control subjects were selected randomly from the

population register and were described in a report as having normative BMD and body composition data in our region [16]. From the normative sample, we included all individuals within the same age ranges as our patient groups, without any matching to specific patients, resulting in 122 women, aged 64 ± 14 years old (range, 40–87 years), and 121 men, aged 61 ± 15 years (range, 34–85 years), as a control cohort in our study [16]. The patients and control subjects received the same protocol and had measurements with the same dual-energy x-ray absorptiometry (DEXA) apparatus. All participants answered the same questionnaire on lifestyle, including questions on occupation (blue-collar or white-collar worker), number of children, recreational exercise (yes/no), smoking, alcohol and coffee consumption, dietary limitations, diabetes or other diseases, use of any medication (yes/no), and for women, menopause and birth control pills. Age and lifestyle factors for patients and control subjects are presented separately for men and women (Table 1).

Body weight and height of study subjects were measured by standard equipment and BMI was calculated as weight/height squared (kg/m^2). BMD (g/cm^2) was measured by DEXA (Lunar DPX-L[®] 1.3z; Lunar Corporation, Madison, WI, USA) in total body, spine, leg, and arm with a whole body scan. Femoral neck, Ward triangle, and trochanter region BMD were measured in a hip scan as was the femoral neck width, a measurement often used to estimate bone size [1, 2]. Femoral neck width was calculated from the AP hip scan as the femoral neck area divided by the scan length. Total body lean mass and fat mass were evaluated from the total body scan. Daily calibration of the apparatus was done with a Lunar[®] phantom (Lunar Corporation). The coefficient of variation after repositioning 14 individuals was 0.4% for total body BMD, 1.6% for femoral neck BMD, 1.0% for lumbar spine BMD, 3.0% for arm and leg BMDs, 1.5% for femoral neck width, 1.5% for total body lean mass, and 3.7% for total body fat mass.

Statistical calculations were done with Statistica[®], 7.1 (StatSoft, Tulsa, OK, USA). Data were analyzed separately for men and women. Descriptive data are presented as numbers with proportions (%), means $\pm$ SD, or as means with 95% confidence intervals (CIs). Individual Z scores (the number of SDs above or below the age-predicted mean) were derived by linear regression using the control cohort as the reference population. Group differences were evaluated using the t-test as a parametric test, Fisher's exact and chi-square tests as nonparametric tests and analysis of covariance when adjusting for covariates. Odds ratios (ORs) with 95% CI were calculated by logistic regression to estimate the risk of having OA with each SD higher total body BMD, higher BMI, higher proportion of fat mass, and each SD lower proportion of lean body mass.

Table 1. Age and lifestyle factors

Parameter	Women			Men		
	Patients with OA (n = 38)	Control subjects (n = 122)	p value	Patients with OA (n = 74)	Control subjects (n = 121)	p value
Age (years)	63.3 ± 11.9	63.9 ± 14.4	0.82	59.8 ± 11.9	60.6 ± 15.4	0.71
Height (cm)	163.6 ± 7.5	163.3 ± 5.2	0.80	177.5 ± 5.8	176.9 ± 6.5	0.49
Weight (kg)	80.2 ± 0.9*	63.9 ± 10.5*	<0.001*	88.4 ± 11.8*	79.4 ± 10.5*	<0.001*
BMI (kg/m ²)	29.9 ± 4.9*	23.9 ± 3.8*	<0.001*	28.1 ± 3.7*	25.4 ± 3.0*	<0.001*
Blue-collar worker	16/36 (44%)	45/107 (42%)	0.80	48/70 (69%)	48/102 (47%)	<0.01*
Recreational exercise	6/17 (35%)	35/107 (33%)	0.83	4/15 (27%)	47/102 (46%)	0.16
Smoker	9/37 (24%)	18/106 (17%)	0.33	20/72 (29%)	28/101 (28%)	0.99
Uses alcohol	19/29 (66%)	75/94 (80%)	0.11	57/70 (81%)	92/99 (92%)	0.02*
Drinks coffee	33/37 (89%)	99/105 (94%)	0.30	63/70 (90%)	85/88 (97%)	0.09
Any dietary restriction	0/24 (0%)	2/105 (2%)	0.50	0/60 (0%)	2/102 (2%)	0.28
Has birthed children	33/37 (89%)	91/102 (89%)	0.99	—	—	—
Menopause	29/38 (76%)	83/122 (68%)	0.33	—	—	—
Diabetes	3/38 (8%)*	1/122 (1%)*	0.04*	4/74 (5%)	4/121 (3%)	0.47
Concomitant disease	22/38 (58%)	57/122 (47%)	0.23	30/74 (41%)	58/121 (48%)	0.31
Taking medication	30/35 (86%)*	55/107 (45%)*	<0.001*	44/71 (62%)	46/102 (45%)	0.03*

Data are presented as mean (± SD) for continuous parameters and numbers with proportions (%) for categorical parameters; evaluations of group differences were performed using t-test between means, chi square test, or Fisher' exact test; *statistically significant difference ($p < 0.05$); OA = osteoarthritis; BMI = body mass index.

The study was approved by the Ethics Committee of Lund University (LU 267-00) and conducted in accordance with the Helsinki Declaration. Informed written consent was obtained from all participants before the start of the study.

Results

Individuals with knee OA had a phenotype with higher BMD (Table 2). In women, the mean total body BMD Z score was 0.8 (odds/hazard ratio for each higher SD 4.2; 95% CI, 2.1–8.1), and in men it was 0.5 (odds/hazard ratio, 1.9; 95% CI, 1.3–2.7). Thus, for women, each increase in SD represented a fourfold increase in the risk of having OA, whereas for men, each increase nearly doubled the risk (Table 3). After adjustment for body size (BMI) in women, the group difference in BMD remained (Table 2). After adjustment for body size (BMI) in men, no group differences remained in BMD (Table 2).

Individuals with knee OA had a phenotype with higher BMI (Table 2): in women, a Z score of 1.6 (odds/hazard ratio for each higher SD 3.2; 95% CI, 2.1–4.8) and in men, 0.9 (odds/hazard ratio, 2.1; 95% CI, 1.6–2.9). That is, for women, each increase in SD for BMI was associated with a three times higher risk of OA, and for men, each increase doubled the risk of OA.

Women with knee OA had normal bone size with a femoral neck width Z score of 0.1 (odds/hazard ratio, 1.1; 95% CI, 0.8–1.5), whereas men with knee OA had a phenotype with larger bone size with a femoral neck width Z score of 0.3 (odds/hazard ratio for each higher SD 1.4; 95% CI, 1.04–1.9) (Table 2). Larger bone size in women was not associated with a higher risk of having knee OA. Conversely, for men, larger bone size represented a risk for having OA.

Individuals with knee OA had a phenotype with proportionally lower total body lean mass: in women, a Z score of −1.0 (odds/hazard ratio for each lower SD 3.2; 95% CI, 1.8–5.7) and in men, −0.9 (odds/hazard ratio, 4.1; 95% CI, 2.4–6.9) (Table 2). That is, each SD lower proportion of lean (muscle) mass in women was associated with a three times higher risk and in men a four times higher risk of having knee OA (Table 3). Individuals with knee OA had a phenotype with proportionally higher fat mass (Table 2): in women, a Z-score of 1.0 (odds/hazard ratio for each higher SD 3.3; 95% CI, 1.8–5.8) and in men, 0.7 (odds/hazard ratio, 2.5; 95% CI, 1.6–3.7). That is, each SD higher proportion of fat mass in women was associated with a three times higher risk and in men a 2.5 times higher risk of having knee OA (Table 3). In addition, when we adjusted for group differences in body size (BMI), the proportion of lean and fat mass was no longer higher in the female patients with knee OA, whereas the group differences remained in the men (Table 2).

Table 2. Anthropometry and BMD

Parameter	Women				Men			
	Patients with osteoarthritis (n = 38)	Control subjects (n = 122)	p value	p-adjust	Patients with osteoarthritis (n = 74)	Control subjects (n = 121)	p value	p-adjust
Anthropometry								
Proportion body fat (%)	43.0 (40.0–46.0)	35.5 (34.1–36.9)	<0.001*	0.39	27.5 (26.2–28.7)	23.4 (22.2–24.6)	<0.001*	0.03*
Proportion lean mass (%)	54.7 (51.5–57.9)	61.9 (60.6–63.3)	<0.001*	0.59	68.1 (66.9–69.2)	74.3 (73.0–75.5)	<0.001*	<0.001*
Bone mineral density (g/cm²)								
Total body	1.14 (1.10–1.18)	1.03 (1.01–1.05)	<0.001*	0.01*	1.23 (1.20–1.25)	1.17 (1.15–1.19)	<0.001*	0.06
Spine	1.17 (1.09–1.24)	1.00 (0.97–1.02)	<0.001*	<0.01*	1.17 (1.13–1.21)	1.11 (1.08–1.14)	0.02*	0.17
Leg	1.14 (1.09–1.19)	1.06 (1.03–1.09)	<0.001*	0.42	1.34 (1.31–1.37)	1.29 (1.27–1.31)	0.02*	0.30
Arm	0.85 (0.81–0.90)	0.76 (0.74–0.78)	<0.001*	0.02*	0.97 (0.95–1.00)	0.95 (0.93–0.97)	0.07	0.33
Hip femoral neck	0.87 (0.82–0.91)	0.83 (0.80–0.86)	0.28	0.51	0.99 (0.95–1.03)	0.96 (0.92–0.99)	0.25	0.63
Hip Ward triangle	0.75 (0.69–0.80)	0.72 (0.69–0.76)	0.46	0.60	0.88 (0.83–0.93)	0.82 (0.78–0.85)	0.02*	0.70
Hip trochanter	0.81 (0.77–0.86)	0.74 (0.71–0.76)	<0.01*	0.59	0.97 (0.93–1.01)	0.91 (0.88–0.95)	0.06	0.93
Bone size (cm)								
Femoral neck width	3.47 (3.37–3.58)	3.45 (3.40–3.51)	0.72	0.17	4.04 (3.96–4.12)	3.93 (3.87–3.99)	0.03*	0.21

Data are presented as unadjusted group means with 95% confidence interval within parentheses; group comparison were made adjusted for body size (BMI) (ANCOVA); *statistically significant difference ($p < 0.05$); BMD = bone mineral density; BMI = body mass index; ANCOVA = analysis of covariance.

Table 3. Sex-specific odds ratio (OR) for knee OA

Parameter	Women (n = 160)	Men (n = 195)
For each SD higher		
BMI	3.21 (2.14–4.80)	2.14 (1.57–2.93)
Total body BMD	4.14 (2.12–8.08)	1.87 (1.28–2.72)
Femoral neck bone size	1.07 (0.75–1.53)	1.41 (1.04–1.90)
Proportion body fat	3.26 (1.83–5.83)	2.45 (1.62–3.72)
For each SD lower		
Proportion lean body mass	3.23 (1.84–5.67)	4.10 (2.43–6.91)

Data presented as means with 95% confidence interval (CI) within parentheses; 95% CIs for odds ratio were calculated by logistic regression; OA = osteoarthritis; BMD = bone mineral density.

Discussion

It is unclear whether knee OA is associated with a specific musculoskeletal and anthropometric phenotype. If so, the phenotype could be involved in the pathogenesis of the disorder or could represent the sequelae of disease. We previously examined this question in patients with hip OA [17], but felt it important also to analyze it in patients with knee OA because primary OA in different joints may have a different phenotype, indicating a different pathophysiological background and different pre-, peri-, and postoperative

clinical implications. We therefore wished to examine differences in BMD, BMI, skeletal size, lean mass, and fat mass between patients with knee OA and individuals without knee OA.

Limitations of our study include the cross-sectional design and the study should consequently be regarded only as hypothesis-generating with no inferences regarding causality. That is, we cannot conclude if arthritic people are heavy because they are inactive or if heavy patients get arthritis. We included only patients with end-stage knee OA. We thus cannot say whether the same phenotype would be found in patients with early knee OA. If this is the case, it would strengthen the view that the phenotype may be associated with the pathogenesis of OA. The use of femoral neck width as an estimate of general bone and joint size has been used by others [1, 2] but should be regarded as a weakness, because it does not directly correlate with skeletal size. Further prospective studies that follow bone size from before the development of OA with CT measurements of bone size and cartilage surface in the evaluated joint should be done. We also had no access to radiographs from our study population before the development of OA; with these, we could have evaluated if the reported differences exist early in the disease. Another limitation is that we had no knee radiographs conducted in the control cohort. Hypothetically there could be

individuals in this group with knee OA with minor symptoms, a fact that if anything would conceal the actual group differences. Our sample size was limited, with only 38 women. A larger group would allow subgroup analysis of premenopausal or postmenopausal women. We also cannot comment on racial or ethnic differences. More thorough evaluation of current and previous lifestyles would have been helpful to address the possible confounding effects of differing life experiences. Finding similar levels of activity in individuals with and without knee OA was unexpected. However, all patients in our region with knee OA are referred for physical training before a definitive decision on surgical treatment, and the data probably reflect this treatment strategy. Our patients volunteered for this study and may not reflect the general OA population, either physically or socially. Finally, it must be emphasized that there are many other factors involved in idiopathic OA such as weight in young adulthood, prior injury, and prior and current level of physical activity. Again, this study can only show an association between knee OA and the studied variables, does not imply causation, and should therefore be regarded as hypothesis-generating.

Studies suggest that OA and osteoporosis are distinct different diseases [9] and an association between OA in the hip, knee, ankle, and feet and a high BMD has also been found [3, 4, 6, 8, 13, 17, 20, 23]. It has been speculated that a high BMD may result in a denser and stiffer skeleton with less load absorptive ability, a phenotype that may be involved in the pathogenesis of primary OA [25]. In our study, women and men with knee OA had a higher total body BMD, in women, independent of their high BMI, but not in men. Furthermore, the association between high BMD and primary knee OA was strong—each SD higher BMD was associated with a more than quadrupled risk of OA in women and a close to doubled risk in men. This is unexpected, because some studies suggest that high BMD is the result of strong muscle forces acting on the bone [18], whereas we found low lean mass in individuals with knee OA. In the clinical setting, a normal or high BMD is probably beneficial for prosthesis fixation in joint replacement surgery [14]. Because knee OA is associated with this phenotype, routine preoperative BMD assessment before joint replacement surgery, as proposed by some [19], seems of little use.

High BMI is a well-known risk factor for knee OA [15, 26, 31], and overweight has been found to precede the disease [7]; however, a high BMI is difficult to interpret because a high BMI could be the result of totally different anthropometric phenotypes in different individuals. The higher BMI in patients with OA in our study was the result of a large proportion of fat mass, not a large proportion of lean (muscle) mass or short stature (Table 2). The low proportion of muscle could indicate a lower capacity to

withstand joint trauma. Weight loss, recommended to patients with knee OA by most physicians, may still be good advice, but attention should probably also be paid to gain muscle mass by exercise. However, even if there is evidence in the literature that overweight precedes the development of OA [7], we cannot state that the deficit we found in muscle mass preceded the development of OA.

We found a larger femoral neck width in men but not in women with OA, indicating that different pathogenic pathways could underlie the development of primary knee OA in women and men. However, after adjustment for body size (BMI), the femoral neck width was similar in women and men with knee OA compared with control subjects. This is in contrast to previous reports on primary OA in other joints (ankle and foot) where OA was associated with small skeletal size [8]. Primary OA in different joints may therefore be associated with different anthropometric and musculoskeletal phenotypes.

Inferior neuromuscular function has also been identified as a risk factor for knee OA [7, 15, 26, 31], because joint protection from trauma may be inadequate [22, 29]. Our data support this, because each SD deficit in proportion of lean mass was associated with four times higher risk in women and three times higher risk in men of having knee OA. The findings of higher BMD and lower proportion of lean mass in patients with primary knee OA indicate that these patients may have a specific phenotype unrelated to the forces exerted on the skeleton by muscles [18]. The muscle mass deficit we found may therefore be involved in the development of the disease in that the muscle mass deficit may provide inadequate protection of the joint and also be harmful to the joint. The higher weight found in our patients may amplify such a local unfavorable condition by causing a higher joint load than usual.

Our findings should lead to clinical implications. Because normal or high BMD is beneficial for prosthesis fixation, some clinicians perform routinely preoperative BMD measurements. Our data indicate that there is no need for general preoperative screening of low BMD when planning for knee arthroplasty. High BMI is known as a risk factor for peri- and postoperative complications [28], and this group of patients should then be regarded as a risk cohort in this aspect. Furthermore, weight loss should be encouraged in this group of patients to reduce the mechanical load over the joint, and the proportionally low muscle mass indicates that these patients both pre- and postoperatively should be subjected to intense physical training as to improve the muscle protective ability.

Women and men with idiopathic knee OA have a phenotype with higher BMD, higher BMI, proportionally lower lean body mass, and proportionally higher fat mass. Men also have a larger skeletal size. Although the higher BMD may provide a solid base for prosthesis fixation, the

higher BMI may result in a higher joint load and an elevated risk of perioperative and postoperative complications and the lower muscle mass in a depleted capacity to withstand joint trauma. The different skeletal phenotypes in our patients with knee OA and patients with OA in other joints indicate that separate pathophysiologic pathways may be responsible for the development of primary OA in different joints. However, because the data indicate a specific phenotype in individuals with OA, large prospective observational studies should be conducted, longitudinally following individuals from younger years to older age, with DEXA used to evaluate if the phenotype precedes the disease. These resource-demanding prospective studies would thus verify or refute our hypothesis that high BMD, high BMI, smaller bone size, and a combination of proportionally lower lean (muscle) mass and higher fat mass contribute to development of knee OA.

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