Individuals with Primary Osteoarthritis Have Different Phenotypes Depending on the Affected Joint - A Case Control Study from Southern Sweden Including 514 Participants

Magnus K. Karlsson*, Caroline Karlsson, Håkan Magnusson, Maria Cöster, Tord von Schewelov, Jan Åke Nilsson, Lars Brudin and Björn E. Rosengren

Clinical and Molecular Osteoporosis Research Unit, Departments of Orthopedics and Clinical Sciences, Lund University, Skåne University Hospital, Malmö and Department of Clinical Physiology, Kalmar Hospital, Kalmar, Sweden

Abstract: *Objective:* The aim of this study was to evaluate whether primary osteoarthritis (OA), independent of affected joint, is associated with a phenotype that is different from the phenotype in a normative cohort.

Material and Methods: We included 274 patients with primary OA, 30 women and 32 men (mean age 66 years, range 42-84) with primary hip OA, 38 women and 74 men (mean age 61 years; range 34-85) with primary knee OA, 42 women and 19 men (men age 64 years, range 42-87) with primary ankle or foot OA and 20 women and 19 men (mean age 66 years, range 47-88) with primary hand or finger OA. Of all patients included with OA, 23% had hip OA, 41% knee OA, 22% ankle or foot OA and 14% hand or finger OA. Serving as references were 122 women and 118 men of the same ages who were population-based, included as a control cohort. We measured total body BMD (g/cm^2) and proportion of fat and lean mass (%) with dual energy X-ray absorptiometry. Height, weight and BMI (kg/m^2) were also assessed. We then calculated Z-scores (number of standard deviations difference from the mean value of the control cohort) in the OA patients and compared these between the groups.

Results: Individuals with hand OA and controls had similar phenotype. Individuals with lower extremity OA, irrespective of the affected joint, had similar weight, BMI and BMD, but higher than in individuals with hand OA and controls (all $p<0.05$). Individuals with lower extremity OA had higher fat and lower lean mass than individuals with hand OA and controls (all $p<0.001$).

Conclusion: Individuals with primary OA in the lower extremity have a phenotype with higher BMD, higher BMI, proportionally higher fat content and lower lean body mass content. The different skeletal phenotypes in our patients with OA in the lower extremity and patients with hand OA indicate that separate pathophysiologic pathways may be responsible for primary OA in different joints

Keywords: Ankle, anthropometry, body mass index, bone mineral density, fat, fingers, foot, hand, hip, knee, lean, primary osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) affects joint cartilage, adjacent skeleton, and surrounding soft tissue [1-5] and may affect most joints [1, 3, 4, 6]. General risk factors for primary OA include heredity, old age, female gender, ethnicity, and (at least in the hip and knee) a high body mass index (BMI) [1, 7]. Moderate chronic repeated load are also mandatory for cartilage integrity [8]. But local factors such as loads with high magnitude, ligament instability, neuromuscular impairment, and joint deformity may accelerate the degenerative process [9]. A high prevalence of OA has been reported in the hip and knee in obese patients [9, 10], and has been partly referred to the high joint surface load [11]. It is unclear whether the same applies to all patients with OA in the lower extremity. But since primary OA is also found in non-weight-bearing joints, such as the carpometacarpal I joint and the finger joints [12, 13], in non-obese individuals [12, 13], and as there are gender differences in the prevalence of primary OA [9, 10], there is reason to believe that different pathophysiologic etiologies may be responsible for primary OA in different joints and therefore possible to approach by different preventive strategies [7].

Primary OA results in local effects on the skeleton, with cysts, subchondral sclerosis, and osteophytes [14]. But OA in the hip and knee is also associated with a high bone mineral density (BMD) [7, 10, 15-20]. OA in these joints is also associated with high weight and high BMI [15, 16, 18-20]. It is unclear whether this phenotype is associated with OA in all joints in the lower extremity or in all joints with primary OA also in the upper extremity. The literature suggests that high BMI is associated with knee OA but not hip OA and with progression of knee OA but not hip OA [15, 16]. Body fat has been found to be more strongly

*Address correspondence to this author at the Department of Orthopaedics, Skåne University Hospital, SE - 205 02 Malmö, Sweden; Tel: +46 40 331000; Fax: +46 40 336200; E-mail: magnus.karlsson@med.lu.se

1874-3250/14

associated with knee OA than with hip OA [21]. These reports also indicate that there could be different anthropometric and musculoskeletal characteristics in patients with primary OA depending on the affected joint, and thus maybe also different pathophysiological pathways.

We therefore conducted this study to evaluate whether individuals with primary hip, knee, ankle or foot (referred to as foot OA) or carpometacarpal I (CMC I) or distal interphalangeal (DIP) finger joint OA (referred to as hand OA) have a similar phenotype with (1) higher BMD, (2) higher BMI, (3) proportionally higher fat mass and (4) proportionally lower lean (muscle) mass.

MATERIAL AND METHODS

All included patients were white and residents of Malmö, Sweden, consecutively collected from the only hospital in the city during a four-year period, when the patients were referred to the orthopedic clinic for a decision as to whether treatment should include OA surgery or not. All had disabling pain from the affected joint, both at rest and during activity, and typical clinical and radiographic features of primary joint OA, with the radiographic severity classified as grade 3 or 4 according to Kellgren and Lawrence [22]. We did not include patients with inflammatory joint disease or previous joint fractures; no other exclusion criteria were used. There were 30 women and 32 men (mean age 66 years, range 42-84) with primary hip OA. There were 38 women and 74 men (mean age 61 years, range 34-85) with primary knee OA. There were 42 women and 19 men (mean age 64 years, range 42-87) with primary ankle and/or foot OA. Thirteen patients had ankle osteoarthritis, 8 arthritis in the hind foot, 3 in the mid-foot and 37 in the forefoot, the patients referred to in this manuscript as having foot OA. There were 20 women and 19 men (mean age 66 years, range 47-88) with DIP finger joint and/or CMC I joint OA. Twenty-eight patients had DIP finger joint OA, 6 CMC I joint OA and 5 both DIP finger joint and CMC I joint OA, the patients in this manuscript referred to as having hand OA. Of all those included with OA, 23% had hip OA, 41% knee OA, 22% ankle or foot OA and 14% hand or finger OA

A group of 122 women (mean age 64 years, range 40-87) and 118 men (mean age 61, range 34-85) served as controls [23]. The attendance rate in the control cohort was 50% and the control population was included separately from the cases, the control population previously reported as a normative sample consisting of community-based individuals randomly selected from the Statistics Sweden, a central government register including all Swedes; the sample is described in detail in previous publication [23]. No radiographs were taken of the different joints in the control cohort and there was no specific matching to each patient with OA. The patients and controls underwent the same study protocol and had measurements with the same dual energy X-ray absorptiometry (DXA) apparatus.

All participants answered the same questionnaire about lifestyle including questions on occupation (blue-collar or white-collar worker), recreational exercise (yes/no), smoking, alcohol and coffee consumption, food restrictions, diabetes or other diseases, use of any medication (yes/no), and for women childbirths, menopause and birth control pills. Gender-specific age and lifestyle factors for patients and controls are reported in Table **1**.

Body weight and body height were measured by standard equipment and BMI was calculated as weight/height squared (kg/m^2). Bone mineral density (BMD; g/cm^2) was measured by dual energy X-ray absorptiometry (DXA) (Lunar DPX-L® 1.3z, Lunar Corporation, Madison, WI, USA) in total body and spine with a total body scan. Total body lean mass and fat mass were evaluated from the same total body scan. Daily calibration of the apparatus was done with a Lunar® phantom. The coefficient of variation (CV) after repositioning 14 individuals was 0.4% for total body BMD 1.0% for lumbar spine BMD, 3.7% for fat mass and 1.5% for lean mass.

Statistical calculations were done with Statistica®, 7.1 (StatSoft, Tulsa, OK, USA). Data were first analyzed separately for men and women. Descriptive data are presented as numbers with proportions (%), means ± standard deviations (SD), or as means with 95% confidence intervals (95% CI). Individual Z-scores (the number of SDs above or below the age-predicted mean) were derived by linear regression using the control cohort as reference population. Group differences were evaluated by Student's t-test as a parametric test, Fisher's exact and chi-square tests as nonparametric tests, and analysis of covariance (ANCOVA) when adjusting for the covariates age and body mass index (BMI), both traits known to be associated with the anthropometry. Odds ratios (ORs) with 95% CI were calculated by logistic regression to estimate the probability of having OA with each SD higher height, weight, BMI, total body BMD and spine BMD and with each SD lower proportion of lean body mass.

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

Descriptive data in respect of age, life style, anthropometric and musculoskeletal characteristics are presented in Tables **1** and **2**.

Patients with OA in the lower extremity had higher BMD than the control cohort (Table **3**). Patients with hip OA had a total body BMD Z-score of 0.5 (95% CI 0.5, 0.8), patients with knee OA 0.5 (95% CI 0.4, 0.7) and patients with foot OA 0.8 (95% CI 0.5, 1.1). There were no differences in BMD in patients with OA in the lower extremities. Patients with hand OA had similar BMD to the control cohort (Table **3**). Patients with hand OA had a total body BMD Z-score of 0.2 (95% CI -0.2, 0.6).

Patients with OA in the lower extremity had higher weight and higher BMI than the control cohort (Table **3**). Patients with hip OA had a weight Z-score of 0.7 (95% CI 0.4, 1.0) and a BMI Z-score of 0.7 (95% CI 0.4, 1.1), patients with knee OA had a weight Z-score of 1.1 (95% CI 0.8, 1.3) and a BMI Z-score of 1.1 (95% CI 0.9, 1.3) and patients with foot OA a weight Z-score of 0.8 (95% CI 0.5, 1.1) and a BMI Z-score of 0.8 (95% CI 0.5, 1.0). There were no differences in weight or BMI in patients with OA in the lower extremities. Patients with hand OA had similar weight

Table 1. Age and lifestyle in women and men. Data presented as mean values ± SD for age and as numbers with proportion (%). Evaluations of group differences were done by Student´s t-test between means, Chi-square test and Fisher´s exact test. Statistically significant differences are highlighted in bold text.

Women						
Parameter	**Hip OA**	**Knee OA**	**Ankle/Foot OA**	**Hand/Finger OA**	**Controls**	**p-Value**
Numbers	(n=30)	(n=38)	(n=42)	(n=20)	(n=122)	
Age (years)	67.9 ± 8.8	63.3 ± 11.9	61.5 ± 8.9	63.7 ± 8.2	63.9 ± 14.4	0.29
Blue-collar worker	13/27 (48 %)	16/36 (44%)	20/42 (48%)	8/20 (40%)	45/107 (42%)	0.95
Recreational exercise	13/26 (50%)	6/17 (35%)	30/42 (71%)	13/20 (65%)	35/107 (33%)	**<0.001**
Smoker	6/29 (21%)	9/37 (24%)	10/41 (37%)	3/20 (15%)	18/106 (17%)	**<0.001**
Uses alcohol	22/24 (92%)	19/29 (66%)	38/41 (93%)	18/20 (90%)	75/94 (80%)	**0.02**
Drinks coffee	27/29 (93%)	31/35 (89%)	33/42 (79%)	20/20 (100%)	6/100 (94%)	0.20
Any food restrictions	0/8 (0%)	0/24 (0%)	5/42 (12%)	808 (0%)	2/105 (2%)	0.06
Has given childbirth	25/28 (89%)	33/37 (89%)	38/40 (95%)	18/20 (90%)	91/102 (89%)	0.93
Menopause	22/30 (73%)	29/38 (76%)	28/42 (66%)	17/20 (85%)	83/122 (68%)	0.45
Diabetes	1/30 (3%)	3/38 (8%)	5/42 (12%)	1/20 (5%)	1/122 (1%)	**0.03**
Other diseases	15/30 (50%)	22/38 (58%)	34/42 (81%)	10/20 (50%)	57/122 (47%)	**<0.01**
Current medication	15/29 (52%)	30/35 (86%)	29/41 (71%)	13/20 (65%)	55/107 (51%)	**<0.01**

Men						
Parameter	**Hip OA**	**Knee OA**	**Ankle/Foot OA**	**Hand/Finger OA**	**Controls**	**p-Value**
Numbers	(n=32)	(n=74)	(n=19)	(n=19)	(n=118)	
Age (years)	65.0 ± 9.5	61.2 ± 10.6	66.2 ± 9.5	68.5 ± 11.5	61.2 ± 15.8	0.14
Blue-collar worker	17/30 (57%)	44/67 (66%)	11/19 /58%)	8/18 (44%)	45/99 (45%)	0.11
Recreational exercise	17/31 (55%)	4/16 (25%)	15/19 (79%)	14/18 (78%)	45/99 (45%)	**<0.01**
Smoker	8/32 (25%)	18/69 (26%)	3/19 (16%)	8/18 (44%)	26/98 (27%)	**<0.001**
Uses alcohol	26/28 (93%)	54/67 (81%)	17/19 (89%)	14/16 (88%)	90/96 (94%)	0.11
Drinks coffee	27/30 (90%)	44/51 (86%)	16/19 (84%)	17/18 (94%)	77/80 (96%)	0.11
Any food restrictions	1/6 (17%)	0/56 (0%)	0/19 (0%)	0/3 (0%)	2/99 (2%)	0.23
Diabetes	1/32 (3%)	4/71 (6%)	2/19 (11%)	1/19 (5%)	4/118 (3%)	0.75
Other diseases	16/32 (50%)	30/71 (42%)	11/19 (58%)	12/19 (63%)	57/118 (48%)	0.48
Current medication	15/32 (47%)	40/68 (59%)	9/16 (56%)	10/18 (56%)	47/99 (47%)	0.62

and BMI to the control cohort (Table **3**). Patients with hand OA had a weight Z-score of 0.1 (95% CI -0.4, 0.9) and a BMI Z-score of 0.1 (95% CI -0.3, 0.5).

Patients with OA in the lower extremity had higher proportional fat content than the control cohort (Table **3**). Patients with hip OA had a fat content Z-score of 0.7 (95% CI 0.4, 0.9), patients with knee OA 0.9 (95% CI 0.7, 1.1) and patients with foot OA 0.5 (95% CI 0.2, 0.7). There were no differences in the proportion of fat content in patients with OA in the lower extremities. Patients with hand OA had similar fat content to the control cohort (Table **3**). Patients with hand OA had a fat content Z-score of 0.0 (95% CI -0.4, 0.3).

Patients with OA in the lower extremity had lower proportional lean mass content than the control cohort (Table **3**). Patients with hip OA had a lean mass content Z-score of -0.7 (95% CI -0.9, -0.4), patients with knee OA -0.9 (95% CI -1.1, -0.7) and patients with foot OA -0.5 (95% CI -0.7, -0.2). There were no differences in the proportion of lean mass in patients with OA in the lower extremities. Patients with hand OA had similar lean mass to the control cohort (Table **3**). Patients with hand OA had a lean mass content Z-score of 0.0 (95% CI -0.3, 0.4).).

In patients with OA in the lower extremity, each SD higher weight and BMI was associated with roughly a doubled probability of having OA, each SD higher BMD a 2 to 3 times higher probability, each SD higher proportion of fat mass a 1.5 to 3 times higher probability and each SD

Table 2. Anthropometry, bone mineral density (BMD) and soft tissue composition soft in women and men. Data are shown as unadjusted means with 95% CI within brackets. Group comparison were made by ANCOVA adjusted for age[1] or for age and body size (BMI)[2]. Statistically significant differences are highlighted in bold.

	Women with Different Types of OA and Controls					Group Comparisons	
	Hip OA	**Knee OA**	**Ankle/Foot OA**	**Hand/Finger OA**	**Controls**	**p-Value[1]**	**p-Value[2]**
Anthropometry	(n=30)	(n=38)	(n=42)	(n=20)	(n=122)		
Height (cm)	163.4 (161.1, 165.7)	163.6 (161.2, 166.1)	162.8 (161.1, 164.6)	165.1 (162.0, 168.1)	163.3 (162.4, 164.3)	0.50	---
Weight (kg)	70.5 (65.9, 75.1)	80.2 (75.3, 85.1)	74.0 (69.5, 78.6)	67.5 (60.6, 74.4)	63.9 (62.0, 65.8)	**<0.001**	---
BMI (kg/m^2)	26.4 (24.8, 28.0)	29.9 (28.3, 31.5)	27.8 (26.4, 29.2)	24.7 (22.6, 26.8)	23.9 (23.3, 24.6)	**<0.001**	---
DXA-measurements	(n=25)	(n=26)	(n=42)	(n=20)	(n=115)		
Total body BMD (g/cm^2)	1.08 (1.04, 1.13)	1.14 (1.10, 1.18)	1.14 (1.11, 1.17)	1.09 (1.03, 1.14)	1.03 (1.01, 1.05)	**<0.001**	**<0.001**
Spine BMD (g/cm^2)	1.06 (1.00, 1.12)	1.17 (1.09, 1.24)	1.11 (1.07, 1.15)	1.04 (0.98, 1.11)	1.00 (0.97, 1.02)	**<0.001**	**0.02**
Proportion body fat (%)	40.2 (37.4, 42.9)	43.0 (40.0, 46.0)	39.8 (37.2, 42.4)	36.4 (33.0, 39.7)	36.4 (35.0, 37.8)	**<0.001**	**<0.001**
Proportion lean mass (%)	55.0 (52.3, 57.7)	54.7 (51.5, 57.9)	60.2 (57.6, 62.8)	63.6 (60.3, 67.0)	63.5 (62.2, 65.0)	**<0.001**	**0.01**

	Men with Different Types of OA and Controls					Group Comparisons	
	Hip OA	**Knee OA**	**Ankle/Foot OA**	**Hand/Finger OA**	**Controls**	**p-Value[1]**	**p-Value[2]**
Antropometry	(n=32)	(n=70)	(n=19)	(n=19)	(n=118)		
Height (cm)	175.9 (173.5, 178.3)	177.5 (176.0, 178.9)	175.4 (172.1, 178.8)	173.4 (169.2, 177.6)	176.8 (175.5, 177.8)	0.48	---
Weight (kg)	86.8 (81.9, 91.6)	87.8 (85.1, 90.5)	83.4 (76.9, 89.8)	75.9 (69.6, 82.2)	79.1 (77.1, 81.1)	**<0.001**	---
BMI (kg/m^2)	28.0 (26.6, 29.5)	27.9 (27.1, 28.7)	27.0 (25.3, 28.8)	25.2 (23.3, 27.2)	25.3 (24.8, 25.9)	**<0.001**	---
DXA Measurements	(n=26)	(n=58)	(n=19)	(n=18)	(n=109)		
Total body BMD (g/cm^2)	1.22 (1.17, 1.27)	1.22 (1.20, 1.25)	1.23 (1.18, 1.27)	1.15 (1.09, 1.22)	1.17 (1.15, 1.19)	**0.003**	0.21
Spine BMD (g/cm^2)	1.16 (1.10, 1.22)	1.18 (1.14, 1.21)	1.19 (1.11, 1.27)	1.07 (0.99, 1.14)	1.11 (1.08, 1.14)	**0.004**	0.17
Proportion body fat (%)	28.3 (25.9, 30.7)	28.7 (27.4, 29.9)	27.2 (23.9, 30.5)	24.6 (20.6, 28.5)	23.9 (22.6, 25.2)	**<0.001**	**0.01**
Proportion lean mass (%)	71.7 (69.3, 74.1)	71.3 (70.1, 72.6)	72.8 (69.5, 76.1)	53.7 (49.9, 57.5)	76.1 (74.8, 77.4)	**<0.001**	**0.01**

lower proportion of lean mass a 1.5 to 3 times higher probability (Table **4**). No such association was found in patients with hand OA (Table **4**).

DISCUSSION

Individuals with primary OA in the lower extremity have a phenotype with higher BMD, higher BMI, proportionally

Table 3. Z-score data shown as means with 95% confidence interval within brackets in individuals with osteoarthritis (OA). Statistically significant differences are highlighted in bold. The p-value in the column all OA is referred to when we compared all groups with OA irrespectively of affected joint and the p-value in the column lower extremity when we compared the groups with OA only in the lower extremity.

Parameter	All Individuals				Group Comparisons	
	Hip OA	**Knee OA**	**Ankle/Foot OA**	**Hand/Finger OA**	**All p-Value**	**Lower Extremity p-Value**
Anthropometry	N=62	N=108	N=61	N=39		
Height	0.0 (-0.3, 0.3)	0.1 (-0.1, 0.3)	-0.1 (-0.4, 0.1)	0.0 (-0.4, 0.4)	0.66	0.43
Weight	**0.7 (0.4, 1.0)**	**1.1 (0.8, 1.3)**	**0.8 (0.5, 1.1)**	0.1 (-0.4, 0.9)	**<0.001**	0.14
Body mass index	**0.7 (0.4, 1.1)**	**1.1 (0.9, 1.3)**	**0.8 (0.5, 1.0)**	0.1 (-0.3, 0.5)	**<0.001**	0.19
DXA measurements	N=51	N=84	N=61	N=38		
Total body BMD	**0.5 (0.2, 0.8)**	**0.5 (0.4, 0.7)**	**0.8 (0.5, 1.0)**	0.2 (-0.2, 0.6)	**0.03**	0.32
Spine BMD	**0.5 (0.2, 0.7)**	**0.6 (0.4, 0.8)**	**0.7 (0.4, 0.9)**	0.0 (-0.3, 0.4)	**0.006**	0.46
Proportion body fat	**0.7 (0.4, 0.9)**	**0.9 (0.7, 1.1)**	**0.5 (0.2, 0.7)**	0.0 (-0.4, 0.3)	**<0.001**	**0.04**
Proportion lean mass	**-0.7 (-0.9, -0.4)**	**-0.9 (-1.1, -0.7)**	**-0.5 (-0.7, -0.2)**	0.0 (-0.3, 0.4)	**<0.001**	**0.04**

Table 4. Odds ratio for having osteoarthritis (OA) in different joints. Data are shown as means with 95% CI within brackets. Statistically significant differences are highlighted in bold.

All Individuals				
Parameter	**Hip OA**	**Knee OA**	**Ankle/Foot OA**	**Hand/Finger OA**
For Each SD Higher				
Height	1.0 (0.8, 1.4)	1.1 (0.9, 1.4)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)
Weight	**1.8 (1.4, 2.4)**	**2.4 (1.9, 3.1)**	**1.8 (1.4, 2.4)**	1.1 (0.8, 1.5)
BMI	**1.8 (1.4, 2.4)**	**2.4 (1.9, 3.1)**	**2.1 (1.6, 2.7)**	1.1 (0.8, 1.5)
Total body BMD	**2.0 (1.4, 2.9)**	**2.3 (1.7, 3.3)**	**2.9 (2.0, 4.2)**	1.3 (0.9, 1.9)
Spine BMD	**1.6 (1.2, 2.3)**	**2.0 (1.5, 2.7)**	**1.6 (1.2, 2.3)**	1.0 (0.7, 1.5)
Proportion body fat	**2.2 (1.5, 3.2)**	**2.9 (2.0, 4.0)**	**1.6 (1.2, 2.3)**	1.0 (0.7, 1.4)
For Each SD Lower				
Proportion lean body mass	**2.2 (1.5, 3.2)**	**2.9 (2.0, 4.0)**	**1.6 (1.2, 2.3)**	1.0 (0.7, 1.4)

higher fat content and lower lean body mass content. The different skeletal phenotypes in our patients with OA in the lower extremity, in comparison with patients with hand OA and controls, indicate that separate pathophysiologic pathways may be responsible for primary OA in different joints.

Studies suggest an inverse relationship between OA and osteoporosis [7, 10, 15-20, 24], and associations between OA in the hip and knee and a high BMD have been reported in some but not all studies [10, 19, 20, 25-29]. It is unclear whether the same phenotype can be found in patients with OA in other lower extremity joints and in patients with OA in non-weight-loaded joints [18]. Previous studies, however, have raised the hypothesis that 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 [30]. In our study we found that individuals with lower extremity OA had a higher BMD, in women independently of the high BMI but not in men. Furthermore, the association between high BMD and primary lower extremity OA was strong, each SD higher BMD being associated with a 2 to 3 times higher risk of having OA. In contrast, hand OA was not associated with a higher BMD. This opposes the view that primary OA is associated with a higher BMD, independent of affected joint, but supports the view that BMD may play a role in the development of OA in the lower extremities.

However, as this is a cross-sectional study we cannot state that a higher BMD results in a higher risk of lower extremity OA, but only that a higher BMD was associated with a higher risk of having lower extremity OA. This is unexpected, as most studies suggest that high BMD is the result of strong muscle forces acting on the bone [31], whereas we found low lean (muscle) mass in individuals with lower extremity OA. We therefore speculate that individuals with OA in the lower extremity may have a specific phenotype with higher BMD, unrelated to muscle forces acting on the bone. In the clinical setting a normal or high BMD is probably beneficial for prosthesis fixation in joint replacement surgery [32]. Since OA in the lower extremity is associated with this phenotype, routine preoperative BMD assessment before joint replacement surgery, as proposed by some [33], seems of little use.

High BMI is a well-known risk factor for knee OA [15, 16, 19, 20, 34] and overweight has been found to precede the disease in the knee [35]. However, a high BMI is difficult to interpret since a high BMI could be the result of totally different anthropometric phenotypes in different individuals. The higher BMI in the patients with OA in the lower extremity in our study was the result of a high fat mass, not a high 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 OA in the lower extremity by most physicians, may still be good advice, but attention should probably also be paid to gaining muscle mass by exercise. However, even if there is evidence in the literature that overweight precedes the development of OA [35], the study design means that we cannot state that the deficit we found in muscle mass preceded the development of OA.

Clinically it is also important to note that high BMI may be a risk factor for peri- and post-operative complications [11]. It is also important to emphasize that a high BMI, high fat content and low lean mass are not a general characteristic of all patients with primary OA, as we found normal BMI in patients with hand OA. These findings once more indicate that the pathogenesis of primary OA may be different in different joints.

The low lean mass in patients with OA in the lower extremity is of clinical interest. Inferior neuromuscular function has been identified as a risk factor for knee OA [15, 16, 19, 20, 34, 35], as joint protection from trauma then may be inadequate [36, 37]. Our data support this view, and increase the knowledge when inferring that the same probably also accounts for patients with hip or foot OA, as each SD deficit in proportion of lean mass was associated with 2 to 3 times higher risk of OA in lower extremity joints. The findings of higher BMD and lower proportion of lean mass in patients with primary OA in the lower extremity joints indicate that these patients may have a specific phenotype unrelated to the forces exerted on the skeleton by muscles [19, 20, 31]. The muscle mass deficit we found may

hence be involved in the development of OA, as the muscle mass deficit may provide inadequate joint protection and thereby also indirectly be harmful to the joint. The higher weight found in our patients may amplify this local unfavorable condition by causing a higher than normal joint load.

The limitations of this study include the cross-sectional design and the study should consequently be regarded as hypothesis-generating. We included only patients with generalized OA, and it is not known whether the same phenotype is found in patients with early OA. If this is true it would strengthen the view that the phenotype may be associated with the pathogenesis of OA. However, as the data indicate a specific phenotype in individuals with OA in the lower extremity, large prospective observational studies should be conducted, following individuals longitudinally from young years to old age, with DXA to evaluate if the phenotype precedes the disease. The approach used in our study is however often advocated in research. First a cross-sectional study is done, and if the proposed hypothesis is verified, future more resource-demanding prospective studies are done to verify or refute the hypothesis. In the current study it would have been beneficial to have a larger sample size to facilitate sub-group analysis of premenopausal and postmenopausal women, individuals with only foot and only ankle OA and individuals with only CMC I joint and DIA finger joint OA. It would also have been advantageous to have data about joint symptoms in the control group, as we could not exclude that there are also individuals with joint degeneration in the control group since this was collected as a normative cohort without specific joint evaluations. The cases could also have degeneration in other than the index joint, but without clinical symptoms, not possible to exclude since we only performed radiographic examinations of the index joint. This is another flaw that could influence our data. A more thorough evaluation of current and previous lifestyle in all groups would also have been preferable and it would have been advantageous to compare patients with OA and the controls with validated clinical scores such as the PASE-score, SF-36 or EQ5D, but such data were not collected at baseline.

CONCLUSION

Individuals with primary OA in the lower extremity have a phenotype with higher BMD, higher BMI, proportionally higher fat content and lower lean body mass content. Even though 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 peri- and post-operative complications and the lower muscle mass in a low capacity to withstand joint trauma. The different skeletal phenotypes in our patients with OA in the lower extremity and patients with hand OA indicate that separate pathophysiologic pathways may be responsible for primary OA in different joints. Future prospective studies must be done to evaluate whether the group differences are due to participant selection or if OA in the lower extremities occurs as a result of high BMD or BMI.

ABBREVIATIONS

ANCOVA = Analysis of covariance

BMD = Bone mineral density

BMI = Body mass index

CI = Confidence interval

CV = Coefficient of variation

DXA = Dual energy X-ray absorptiometry

OA = Osteoarthritis

OR = Odds ratios

SD = Standard deviation

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Financial support was received from the Region Skåne, Skåne University Hospital, Österlund and Herman Järnhardt Foundation.

REFERENCES

[1] Akune T. Epidemiology of bone and joint disease - the present and future-Genetic epidemiology on osteoarthritis. Clin Calcium 2014; 24(5): 695-701.

[2] Arden N, Nevitt MC. Osteoarthritis: epidemiology. Best Pract Res Clin Rheumatol 2006; 20(1): 3-25.

[3] Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med 2010; 26(3): 355-69.

[4] Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am 2013; 39(1): 1-19.

[5] Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005; 365(9463): 965-73.

[6] Pereira D, Peleteiro B, Araújo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. Osteoarthritis Cartil 2011; 19(11): 1270-85.

[7] Felson DT, Lawrence RC, Dieppe PA, *et al*. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000; 133(8): 635-46.

[8] Tiderius CJ, Svensson J, Leander P, Ola T, Dahlberg L. dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) indicates adaptive capacity of human knee cartilage. Magn Reson Med 2004; 51(2): 286-90.

[9] Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. Clin Orthop Relat Res 2004; (427 Suppl): S6-15.

[10] Bergink AP, Uitterlinden AG, Van Leeuwen JP, Hofman A, Verhaar JA, Pols HA. Bone mineral density and vertebral fracture history are associated with incident and progressive radiographic knee osteoarthritis in elderly men and women: the Rotterdam Study. Bone 2005; 37(4): 446-56.

[11] Sridhar MS, Jarrett CD, Xerogeanes JW, Labib SA. Obesity and symptomatic osteoarthritis of the knee. J Bone Joint Surg Br 2012; 94(4): 433-40.

[12] Wilder FV, Barrett JP, Farina EJ. The association of radiographic foot osteoarthritis and radiographic osteoarthritis at other sites. Osteoarthritis Cartil 2005; 13(3): 211-5.

[13] van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989; 48(4): 271-80.

[14] Gupta KB, Duryea J, Weissman BN. Radiographic evaluation of osteoarthritis. Radiol Clin North Am 2004; 42(1): 11-41, v.

[15] Reijman M, Pols HA, Bergink AP, *et al*. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis 2007; 66(2): 158-62.

[16] Järvholm B, Lewold S, Malchau H, Vingård E. Age, body weight, smoking habits and the risk of severe osteoarthritis in the hip and knee in men. Eur J Epidemiol 2005; 20(6): 537-42.
[17] Sowers M. Epidemiology of risk factors for osteoarthritis: systemic factors. Curr Opin Rheumatol 2001; 13(5): 447-51.
[18] Cöster MC, Rosengren BE, Karlsson C, *et al*. Bone mass and anthropometry in patients with osteoarthritis of the foot and ankle. Foot Ankle Surg 2014; 20: 52-56.
[19] Karlsson MK, Magnusson H, von Schewelov T, Cöster M, Karlsson C, Rosengren BE. Patients with knee osteoarthritis have a phenotype with higher bone mass, higher fat mass, and lower lean body mass. Clin Orthop Relat Res 2014; [Epub ahead of print].
[20] Karlsson MK, Magnusson H, von Schewelov T, Cöster M, Karlsson C, Rosengren BE. Patients with hip osteoarthritis have a phenotype with high bone mass and low lean body mass. Clin Orthop Relat Res 2014; 8: 390-6.
[21] Lohmander LS, Gerhardsson de Verdier M, Rollof J, Nilsson PM, Engström G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis 2009; 68(4): 490-6.
[22] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16(4): 494-502.
[23] Karlsson MK, Gärdsell P, Johnell O, Nilsson BE, Akesson K, Obrant KJ. Bone mineral normative data in Malmo, Sweden. Comparison with reference data and hip fracture incidence in other ethnic groups. Acta Orthop Scand 1993; 64(2): 168-72.
[24] Dequeker J, Johnell O. Osteoarthritis protects against femoral neck fracture: the MEDOS study experience. Bone 1993; 14 (Suppl 1): S51-6.
[25] Lingard EA, Mitchell SY, Francis RM, *et al*. The prevalence of osteoporosis in patients with severe hip and knee osteoarthritis awaiting joint arthroplasty. Age Ageing 2010; 39(2): 234-9.
[26] Chaganti RK, Parimi N, Lang T, *et al*. Bone mineral density and prevalent osteoarthritis of the hip in older men for the Osteoporotic Fractures in Men (MrOS) Study Group. Osteoporos Int 2010; 21(8): 1307-16.
[27] Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartil 2010; 18(1): 24-33.
[28] Haugen IK, Slatkowsky-Christensen B, Orstavik R, Kvien TK. Bone mineral density in patients with hand osteoarthritis compared to population controls and patients with rheumatoid arthritis. Ann Rheum Dis 2007; 66(12): 1594-8.
[29] Nevitt MC, Zhang Y, Javaid MK, *et al*. High systemic bone mineral density increases the risk of incident knee OA and joint space narrowing, but not radiographic progression of existing knee OA: the MOST study. Ann Rheum Dis 2010; 69(1): 163-8.
[30] Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relat Res 1986; (213): 34-40.
[31] Lang TF. The bone-muscle relationship in men and women. J Osteoporosis 2011; 2011: 702735.
[32] Hilding M, Aspenberg P. Local peroperative treatment with a bisphosphonate improves the fixation of total knee prostheses: a randomized, double-blind radiostereometric study of 50 patients. Acta Orthop 2007; 78(6): 795-9.
[33] Lee JH, Park JW, Shin YH. The insertional torque of a pedicle screw has a positive correlation with bone mineral density in posterior lumbar pedicle screw fixation. J Bone Joint Surg Br 2012; 94(1): 93-7.
[34] van Saase JL, Vandenbroucke JP, van Romunde LK, Valkenburg HA. Osteoarthritis and obesity in the general population. A relationship calling for an explanation. J Rheumatol 1988; 15(7): 1152-8.
[35] Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. J Rheumatol 1996; 23(7): 1221-6.
[36] Montgomery MM, Shultz SJ, Schmitz RJ, Wideman L, Henson RA. Influence of Lean Body Mass and Strength on Landing Energetics. Med Sci Sports Exerc 2012 2012; 44(12): 2376-83.
[37] Thorlund JB, Aagaard P, Roos EM. Muscle strength and functional performance in patients at high risk of knee osteoarthritis: a follow-up study. Knee Surg Sports Traumatol Arthrosc 2012; 20(6): 1110-7.

Received: July 16, 2014 Revised: November 6, 2014 Accepted: November 13, 2014