Bone Health in Adult Men and Women with a History of Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** Our aim was to determine areal bone mineral density (BMD_a) and disease-related factors linked with BMD_a in adults with a history of juvenile idiopathic arthritis (JIA).

Methods. Men and women with a history of JIA attending a young adult rheumatology clinic in Newcastle, UK, underwent dual energy x-ray absorptiometry (DEXA) of the lumbar spine and total hip. Information was obtained about disease duration and subtype, previous treatment including corticosteroid and methotrexate therapy, and large-joint replacement. Subjects completed the modified Health Assessment Questionnaire (HAQ). Blood was taken for assessment of C-reactive protein, erythrocyte sedimentation rate, and rheumatoid factor (RF).

Results. Seventy-one women and 16 men, mean age 28.7 and 31.4 years, and mean disease duration 20.6 and 24.0 years, respectively, were studied. Mean BMD_a was 0.982 (Z-score = –0.328; 95% CI –0.657, 0.001) and 1.028 g/cm^2 (Z-score = –0.251; 95% CI –1.266, 0.764) in women and men, respectively, at the spine and 0.817 (Z-score = –0.542; 95% CI –0.975, –0.109) and 0.857 g/cm^2 (Z-score = –0.176; 95% CI –2.323, 1.971) at the hip. After adjusting for age and sex, increasing HAQ score was associated with both lower spine BMD_a and hip BMD_a. Compared with patients with oligoarticular disease, those with enthesitis-related arthritis had higher BMD_a at the spine, while those with extended oligoarticular and polyarticular RF-negative disease had lower hip BMD_a. Oral corticosteroids and the presence of a large-joint replacement were associated with lower BMD_a at both the spine and hip.

Conclusion. There was a trend toward low BMD_a in women with a history of JIA. These patients may be at risk of the complications of osteoporosis including fragility fractures and should be considered for targeted preventive measures. (First Release June 15 2011; J Rheumatol 2011;38:1689–93; doi:10.3899/jrheum.101232)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS   AREAL BONE MINERAL DENSITY
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Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease of childhood. It is associated with decreased areal bone mineral density (BMD_a)[1,2,3,4,5,6]. Known risk factors for low BMD_a and fragility fractures in children with JIA include the inflammatory process[7], nutrition[8], growth impairment[9], reduced physical activity[8], and treatment, especially corticosteroids[5,10]. Children with a mean duration of systemic onset JIA of 10.2 years attending Great Ormond Street Hospital, London, UK, had lumbar spine BMD_a assessments that were on average 2 SD lower than expected[11]. Reduced BMD_a is associated with an increased risk of fractures. Data from the UK General Practice Research Database showed that a higher proportion of children with arthritis experienced fractures compared with a control group during a median followup of 3.9 years (6.7% vs 3.3%)[12].

JIA can persist into adulthood, but few studies have followed bone health beyond childhood[7,13,14,15]. An understanding of bone health and factors influencing bone health in

adults with a history of JIA is important, as reduced bone mass may lead to an increased risk of fracture in later life. Further, a knowledge of factors influencing bone mass is an important first step in developing strategies to optimize bone.

We examined a series of UK patients with a history of JIA who attended a young adult rheumatology clinic. Our aims were to determine the BMD_a in affected individuals and to assess disease-related factors linked with BMD_a.

MATERIALS AND METHODS

Patients. Consecutive men and women with a history of JIA attending a young adult rheumatology clinic in Newcastle upon Tyne, UK, between 1996 and 2002, were included in the analysis. All patients were seen by the same rheumatologist and assigned a JIA subtype according to the International League of Associations for Rheumatology classification[16]. The patient group and the JIA young adult clinic have been described[17].

Data collection. Dual energy x-ray absorptiometry (DEXA) of the lumbar spine (L1–L4) and hip was performed as part of routine clinical assessment. All scans were done between 1996 and 2002 on either a Hologic 4500A or Hologic QDR 2000 scanner (Bedford, Massachusetts, USA). Each machine was subject to maintenance and regular quality assurance and testing in accordance with the manufacturer's recommendations. Results were recorded as BMD_a (g/cm^2) and as an age-standardized or Z-score (the number of SD an observed measurement is from the mean value for an individual of the same age and sex, calculated using the manufacturer's normative data).

As part of routine clinical practice at the time, all clinic attendees completed a modified Health Assessment Questionnaire (HAQ) and had blood taken for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF) estimation. Height and weight were recorded at the time of the scan. Clinical records were reviewed within 6 months of the DEXA scan date and often involved retrieval of case notes from many years previously. Information was obtained about disease subtype, disease duration, and current and previous treatment with oral corticosteroids (ever/never). In addition, data were recorded on duration of treatment (months), treatment with methotrexate (yes/no), and large-joint replacement (hip or knee, yes/no). Because this was an audit of clinical practice, all data were anonymous and informed consent was not required.

Analysis. Body mass index was calculated [weight (kg)/height (m)^2]. The associations between putative disease-related risk factors and BMD_a at both the spine and hip were examined using linear regression, with adjustments made for age and sex. The results were expressed as ß coefficients and 95% CI. Analysis was undertaken using STATA version 9.2 (http://stata.com).

RESULTS

Subjects. Of the 130 patients with a history of JIA who attended the young adult rheumatology clinic, 98 had bone densitometry done of the spine and hip. Eleven of them (3 men and 8 women) were excluded from our study because of missing DEXA data. That left 87 patients for our analysis. The characteristics of these patients are summarized in Table 1. There were 71 women and 16 men; mean age at scan was 28.7 (SD 10.1) and 31.4 (SD 13.8) years, respectively, and mean disease duration was 20.6 (SD 11.0) and 24.0 (SD 13.6) years, respectively. Fifty-one percent of the patients had ever received oral corticosteroids and 29% had taken methotrexate. Some patients had a history of polyarticular RF-negative disease (26%); 21% had polyarticular RF-positive disease, 17% oligoarticular disease, 14% systemic disease, 9% extended oligoarticular disease, 6% psoriasis, 5% enthesitis-related dis-

ease, and 2% other. One in 4 had had either hip or knee arthroplasty. The mean ESR at the time of assessment was 23 mm/h, and CRP was 19.2 mg/l.

Bone mineral density. Mean (95% CI) BMD_a was 0.982 (0.947, 1.018) and 1.028 (0.910, 1.146) g/cm^2 in women and men, respectively, at the lumbar spine and 0.817 (0.761, 0.874) and 0.857 (0.665, 1.050) g/cm^2 at the hip (Table 2). In women, the mean Z-score at the spine was –0.328, and at the hip, –0.542, a value significantly lower than would be expected in a normal population (p < 0.02). In men, mean Z-scores were –0.251 at the spine and –0.176 at the hip. Increasing age was significantly associated with BMD_a at the spine. BMD_a was lower in women compared to men at both spine and hip, although CI embraced unity. After adjusting for age and sex, increasing weight and height were associated with a higher BMD_a at both the spine and hip (Table 3). Increasing physical disability (HAQ score) was associated with both a lower spine and hip BMD_a. Compared with oligoarticular disease, those with enthesitis-related arthritis had a higher lumbar spine BMD_a, while those with extended oligoarticular disease and polyarticular RF-negative disease had lower hip BMD_a. Treatment with oral corticosteroids was associated with a lower lumbar spine and hip BMD_a, as was having a large-joint arthroplasty (hip or knee).

DISCUSSION

In our study, there was a trend toward a low BMD_a, particularly at the hip, in women with a history of JIA. BMD_a was reduced particularly among patients with more severe disease as determined by disease subtype and level of function.

Ours is the first UK study to examine the effect of disease-related factors on bone health in adults with a history of JIA. It was a retrospective review of clinical practice at the time and accordingly, as with many such clinical outcome studies reliant on retrospective case note analysis, there are a number of limitations to consider. While all patients attending the clinic were offered a bone density scan, about 25% did not subsequently keep the appointment. It is possible that these patients may have differed with respect to bone mass levels from those who had a scan. Their omission may have resulted in an overestimate or underestimate of bone mass levels in the group, and the data need to be interpreted with some caution. It should not have influenced, however, the analysis of disease factors influencing bone mass that was based on an internal analysis of responders. The data concerning disease characteristics, including treatment, were obtained from clinical records and therefore subject to recording errors. Because little information on dose or duration of corticosteroid treatment was available, the analysis of corticosteroid use was restricted to comparison of patients who had ever received or never received corticosteroids. Recording was incomplete for other risk factors for osteoporosis, for example, smoking and drinking habits. The DEXA scans were performed as part of routine clinical practice and on a separate date (invariably within 6

Table 1. Demographic and disease-related characteristics. All data are mean (SD) or n (%).

Characteristics	Women, n = 71	Men, n = 16	Overall, n = 87
Age, yrs	28.7 (10.1)	31.4 (13.8)	29.2 (10.8)
Height, m	1.6 (0.1)	1.7 (0.1)	1.6 (0.9)
Weight, kg	60.2 (16.0)	67.6 (18.6)	61.5 (16.7)
Body mass index, kg/m^2	23.4 (5.3)	24.1 (6.2)	23.5 (5.5)
Disease duration, yrs	20.6 (11.0)	24.0 (13.6)	21.2 (11.5)
Current smoker	16 (22.5)	2 (22.2)	18 (22.5)
Disease characteristics and treatment			
Disease subtype (ILAR)			
Systemic	7 (9.9)	5 (1.3)	12 (13.8)
Oligoarticular	12 (16.9)	3 (18.8)	15 (17.2)
Extended oligoarticular	8 (11.3)	0	8 (9.2)
Polyarticular RF-positive	17 (23.9)	1 (6.3)	18 (20.7)
Polyarticular RF-negative	21 (29.6)	2 (12.5)	23 (26.4)
Psoriasis	3 (4.2)	2 (12.5)	5 (5.8)
Enthesitis-related	2 (2.8)	2 (12.5)	4 (4.6)
Other	1 (1.41)	1 (6.3)	2 (2.3)
RF-positive	21 (29.6)	1 (6.3)	22 (25.3)
HAQ score (0–3)	1.3 (0.8)	1.5 (0.8)	1.3 (0.8)
ESR, mm/h	23.2 (20.0)	21.0 (26.3)	23.0 (20.5)
CRP, mg/l	17.8 (20.9)	26.3 (29.2)	19.2 (22.3)
Large-joint arthroplasty (yes vs no)	16 (22.5)	4 (66.7)	20 (26.0)
Hip arthroplasty (yes vs no)	15 (21.1)	4 (66.7)	19 (24.7)
Knee arthroplasty (yes vs no)	12 (16.9)	4 (66.7)	16 (20.8)
Methotrexate (ever, yes vs no)	20 (29.0)	2 (25.0)	22 (28.6)
Other DMARD (ever, yes vs no)	33 (46.5)	6 (37.5)	39 (44.8)
Oral steroids (ever, yes vs no)	34 (49.3)	5 (62.5)	39 (50.7)
Duration of oral steroids, mo	76.3 (90.1)	19.0 (24.0)	72.9 (88.5)

ILAR: International League of Associations for Rheumatology; RF: rheumatoid factor; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug.

Table 2. Areal bone mineral density (BMD$_a$) and Z-score at the lumbar spine and total hip. Data are mean (95% CI).

	Women	Men
BMD$_a$		
Lumbar spine, g/cm^2	0.982 (0.947, 1.018)	1.028 (0.910, 1.146)
Total hip, g/cm^2	0.817 (0.761, 0.874)	0.857 (0.665, 1.050)
Z-score		
Lumbar spine	–0.328 (–0.657, 0.001)	–0.251 (–1.266, 0.764)
Total hip	–0.542 (–0.975, –0.109)	–0.176 (–2.323, 1.971)

months of the clinical notes reviews and clinic assessment). Finally, the subjects included in the analysis were those who were attending an adult continuity rheumatology clinic and who were therefore likely to have had more severe disease; results should be extrapolated beyond this group with caution.

Our data are consistent with previous studies that reported that BMD$_a$ was low in adults with JIA[7,13,14,15]. A cohort of 32 adults with JIA was followed retrospectively for a mean of 27.1 years; a greater proportion were osteopenic at the femoral neck than would have been expected[14]. In a case–control study, 65 adult patients (mean age 32.2 years) with a history of JIA were compared with healthy control subjects matched for age, sex, height, and weight. BMD$_a$ at the hip and lumbar spine were significantly lower in both men and women with JIA compared with matched healthy control subjects[13]. Subsequent linear regression with group (JIA or control) as the only predictor confirmed that JIA was strongly associated with hip or spine BMD$_a$ (p < 0.001), explaining about 20% of the variation in outcome[13]. Haugen, *et al* followed 229 adults with JIA[7]. The mean followup since diagnosis was 15.6 years in women and 14.9 years in men. Men and women with persistent JIA had significantly reduced BMD$_a$ at the femoral neck, total body, and radius and lumbar spine compared with healthy subjects[7]. In 26 young women with JIA, BMD$_a$ (measured using dual photon absorptiometry) was lower than expected in 23% of patients[15].

There is some evidence in the literature that disease activity is associated with reduced bone mass in adults with JIA. Zak, *et al* noted that active disease and spine erosions at baseline were associated with significantly reduced spine BMD$_a$ at followup[13]. In contrast, French, *et al*, found no association with disease activity as measured by joint count[14]. Haugen, *et al* differentiated subjects with active disease and those in remission[7]. Men and women with persistent disease activity had reduced BMD$_a$, while men in remission had BMD$_a$ similar to controls and women had a similar BMD$_a$ to controls at the spine, although BMD$_a$ was significantly reduced at the

Table 3. Influence of disease-related factors on areal bone mineral density (BMD_a) at the lumbar spine and total hip. Results are expressed as ß-coefficient (95% CI) adjusted for age and sex.

	Lumbar Spine BMD_a (g/cm^2)	Total Hip BMD_a (g/cm^2)
Weight, kg	0.005 (0.003, 0.007)*	0.006 (0.003, 0.009)*
Height, cm	0.007 (0.004, 0.011)*	0.012 (0.005, 0.019)*
Age at scan, yrs	0.004 (0.001, 0.007)*	0.000 (–0.006, 0.006)
Sex (F vs M)	–0.046 (–0.136, 0.045)	–0.040 (–0.195, 0.114)
Disease duration, yrs	–0.005 (–0.011, 0.001)	–0.004 (–0.015, 0.006)
HAQ score (0–3)	–0.099 (–0.148, – 0.051)*	–0.122 (–0.217, –0.026)*
ESR, mm/h	0.000 (–0.002, 0.003)	0.002 (–0.004, 0.007)
ESR, mm/h		
< 20	Referent	Referent
≥ 20	–0.007 (–0.110, 0.097)	0.057 (–0.142, 0.255)
CRP, mg/l	–0.001 (–0.004, 0.001)	–0.001 (–0.005, 0.003)
RF-positive (yes vs no)	0.023 (–0.058, 0.103)	0.057 (–0.065, 0.178)
Disease subtype		
Oligoarticular	Referent	Referent
Systemic	–0.108 (–0.222, 0.007)	–0.180 (–0.382, 0.022)
Extended oligoarticular	–0.034 (–0.167, 0.098)	–0.280 (–0.496, –0.064)*
Polyarticular RF-positive	–0.101 (–0.205, 0.003)	–0.098 (–0.266, 0.070)
Polyarticular RF-negative	–0.090 (–0.190, 0.009)	–0.184 (–0.343, – 0.025)*
Psoriasis	0.036 (–0.116, 0.188)	0.074 (–0.154, 0.302)
Enthesitis-related	0.212 (0.044, 0.379)*	0.053 (–0.226, 0.333)
Other	–0.062 (–0.287, 0.163)	0.072 (–0.267, 0.411)
Oral corticosteroids (yes vs no)	–0.143 (–0.211, –0.075)*	–0.136 (–0.248, –0.024)*
Methotrexate (yes vs no)	–0.071 (–0.154, 0.013)	0.015 (–0.112, 0.143)
Large-joint replacement (yes vs no)	–0.101 (–0.188, – 0.013)*	–0.194 (–0.343, –0.046)*

* $p < 0.05$. RF: rheumatoid factor; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

femoral neck and total body[7]. Our study included patients with active disease and also those in remission; who are only seen infrequently. Overall, there was no association with current disease activity as assessed by ESR and CRP at the time of our study.

Previous studies suggested a greater degree of bone loss among those with functional impairment. Thus, higher Steinbrocker functional class in adolescence was associated with reduced adult BMD_a at the femoral neck or lumbar spine[14] and hip[13]. Our data support these findings, demonstrating lower bone mass in those with higher HAQ scores. Our data are consistent also with previous studies that suggest that polyarticular disease is associated with a greater degree of bone loss than other disease subtypes[13,14]. We found also that those with extended oligoarticular disease had reduced bone mass at the hip[13]. The higher spine bone mass in those with enthesitis-related disease may perhaps reflect the presence of abnormal bone formation related to spondylitis.

Longterm oral corticosteroid treatment is known to be associated with low BMD_a and fractures in patients with chronic diseases[18,19]. Some studies support an association between corticosteroid therapy and bone mass in JIA. Haugen, *et al* found duration of corticosteroid treatment was associated with low BMD_a[7] and comparing T-scores, while Zak, *et al* found corticosteroid treatment for > 1 year was associated with reduced BMD_a[13]. In contrast, French, *et al* found no association of reduced BMD_a with corticosteroid treatment, although the number of patients treated with corticosteroids was low[14]. We found that those with a history of corticosteroid therapy had lower bone mass than those without, although there was no apparent association with duration of therapy. It is possible this may have been due to a lack of accurate recording of therapy in the medical record. Evidence of an association, however, does not imply causality and it is possible that the apparent association may have been confounded by disease severity.

Our results suggest that there is a reduction in bone mass in adults with a history of JIA and they are therefore likely to be at increased risk of fracture in later life. A metaanalysis of 11 prospective cohort studies (90,000 patient-years and 2000 fractures of any type) demonstrated that the risk of fracture in otherwise healthy adults appears to double for each 1 SD decrease in BMD_a[20]. Thus, measures to optimize bone health in patients with JIA need to be considered, including modification of reversible risk factors and also optimizing function. In those with severe disease or those on longterm corticosteroids, bone densitometry should be considered an important component of routine clinical practice.

BMD_a is reduced in some adults with JIA, particularly among those with more severe disease. These patients are at risk of the complications of osteoporosis in the future, including fragility fractures, and should be considered for preventive therapy.

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