Osteopenia in Adults with a History of Juvenile Rheumatoid Arthritis. A Population Based Study

ANTHONY R. FRENCH, TOM MASON, AUDREY M. NELSON, CYNTHIA S. CROWSON, W. MICHAEL O’FALLON, SUNDEEP KHOSLA, and SHERINE E. GABRIEL

ABSTRACT. Objective. To determine the extent of osteopenia in a population based cohort of adults with a history of juvenile rheumatoid arthritis (JRA).

Methods. The Rochester Epidemiology Project database was used to identify all cases of JRA diagnosed among Rochester, Minnesota residents under the age of 16 years between January 1, 1960, and December 31, 1993. Thirty-two of the 57 adult patients in this population based cohort (ages 19–53 years, mean 35) participated in this study. Average length of followup from the time of diagnosis was 27.1 years (median 26.9, range 7.7–39.1). Dual energy x-ray absorptiometry scans were used to assess bone density of the lumbar spine, hip, distal one-third radius, and whole body. In addition, a number of variables that influence bone mass were analyzed.

Results. Although many participants had T scores within the normal range (T score > –1) at all measured sites, 41% (n = 13) were osteopenic (T score ≤ –1) at either the lumbar spine or femoral neck. Twenty-eight percent (n = 9) had T scores ≤ –1 in the lumbar spine (p = 0.058 relative to expected). Thirty-two percent (n = 10) had T scores ≤ –1 in the femoral neck (p = 0.012 relative to expected). Several variables were significantly (p < 0.05) associated with low bone density in this cohort of adults with a history of JRA, including: (1) revised Steinbrocker functional class ≥ 2 during adolescence, indicating poorer physical functioning; (2) lack of participation in organized sports during adolescence (a surrogate measure of physical activity); (3) tobacco use during adolescence; and (4) lower calcium intake during adolescence.

Conclusion. Although many adults with a history of JRA have normal bone density, a substantial subset are osteopenic, placing them at increased risk of fractures later in life. This observation is particularly striking given the predominance of patients with pauciarticular JRA in this population based group. We identified several variables associated with osteopenia in this cohort. Further work is needed to identify those patients with JRA who may benefit from aggressive therapy targeted at preventing the longterm morbidity associated with osteopenia. (J Rheumatol 2002;29:1065–70)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS

OSTEOPENIA
OSTEOPOROSIS

Osteopenia is a serious potential longterm complication of juvenile rheumatoid arthritis (JRA)1. Studies have documented significantly decreased bone mineral density (BMD) in children and adolescents with JRA compared to controls2–15. Most reports focused primarily on patients with polyarticular or systemic JRA treated with corticosteroids, but several studies have described decreased BMD in noncorticosteroid treated JRA patients16–19.

Although many studies have found osteopenia in chil-
density of adults who developed JRA living in Rochester, Minnesota, during a 33 year period.

MATERIALS AND METHODS

Study cohort. The Rochester Epidemiology Project database was used to identify all cases of JRA (American College of Rheumatology criteria) diagnosed among Rochester, Minnesota, residents under the age of 16 between January 1, 1960, and December 31, 1993. The Rochester Epidemiology Project provides the unique capability to perform population based epidemiological research in Olmsted County, Minnesota, due to several factors, including: (1) the relative isolation of the county from other urban areas; (2) the longstanding centralization of health care to a handful of providers including a major tertiary care center; and (3) centralized records accumulated in a single dossier with a master list of diagnoses. Adult members of this cohort with birth dates prior to December 31, 1980, were eligible for the study. The study was approved by the Institutional Review Board and the Radiation Safety Committee. All eligible participants were sent a letter describing the rationale, methods, and goals of the study, a consent form, and a survey. A second mailing was sent to those individuals who did not reply within one month. If there still was no response, telephone contact was attempted.

Determination of bone density. All dual energy x-ray absorptiometry (DEXA) scans were performed on Hologic DXA scanners (Hologic, Waltham, MA, USA). All participants were asked to return to the Mayo Clinic General Clinical Research Center in Rochester to have their BMD measured on a single Hologic QDR4500 scanner. If a participant was unwilling or unable to return to the Mayo Clinic, arrangements were made to have DEXA scans done on Hologic scanners at other regional institutions. DEXA scans were performed of the patient’s lumbar spine, hip, distal one-third radius, and whole body. Hologic QDR4500 scanners have a coefficient of variation of 0.4% for replicate same-day measurements at the lumbar spine. All female participants were provided the opportunity to have a pregnancy test prior to the BMD measurements.

Survey. Pertinent information (such as JRA subtype, age at diagnosis, and history of corticosteroid treatment) was abstracted from each participant’s complete medical record (including inpatient and outpatient care by all local providers). In addition, participants were surveyed to assess historical and current information that could affect bone density including: demographic data, age at menarche and menopause (if applicable), medication use including estrogens and corticosteroids, history of prior fractures, family history of osteoporosis, calcium intake, tobacco and alcohol use, and physical activity. Participants were questioned about ongoing swelling or pain with movement in joints previously affected by JRA. Limitation in physical functioning during adolescence (age 12–16) and over the last month was assessed with a revised Steinbrocker score that assesses the ability to perform vocational, leisure, and self-care activities. Longterm outcomes were also assessed with a Health Assessment Questionnaire (HAQ) score. Participants were surveyed regarding prior fractures and any family history of osteoporosis in first or second-degree relatives. Calcium intake during adolescence (ages 12–16 years) was assessed by surveying the frequency of milk or cheese intake with meals (specifically with every meal or less frequently). Current calcium intake was estimated with an abbreviated food frequency questionnaire focused primarily on intake of dairy products (300 mg per each 8 oz glass of milk/day or 8 oz of yogurt/day, 150 mg for each 1 oz serving of cheese/day or 8 oz serving of cottage cheese/day or cup of dark green leafy vegetables/day, plus an additional 300 mg per day to account for nondairy product associated calcium intake). Physical activity during adolescence (ages 12–16 years) was assessed by questioning whether participants were more active, as active, or less active than their peers as well as surveying the frequency of participation in organized sports. Current physical activity was assessed through questions about whether participants were more active, as active, or less active than their peers, and whether participants would classify themselves as sedentary, moderately active, or active over the last 4 weeks. Alcohol intake was assessed as positive if a participant had drunk more than 12 alcoholic drinks of any type over their lifetime. If participants responded positively, they were questioned further whether they had consumed more than one drink per week during adolescence and over the last 12 months. Tobacco use was assessed as positive if a participant had smoked more than 100 cigarettes over their lifetime. If participants responded positively, they were queried further concerning whether they had smoked more than 100 cigarettes during adolescence (ages 12–16 years) and whether they were currently smoking more than 1 cigarette/day.

Statistical analysis. Participant’s BMD were converted to T scores [(participant’s BMD – young adult normal BMD)/SD of young adult normals] using well established age and sex matched young adult normals provided by Hologic. Chi-square statistics were used to compare the observed number of patients with low BMD (T score ≤ –1) to the expected number in the general population based on a normal distribution. Pearson correlations were used to analyze the association of a variety of variables affecting BMD and individual participants’ T scores.

RESULTS

Sixty-five patients were diagnosed with JRA while living in Rochester during the 33 year period between January 1, 1960, and December 31, 1993. Fifty-nine of these 65 patients had birth dates prior to December 31, 1980, and were eligible for inclusion in the study. Two of the 59 patients (one male, one female, both with pauciarticular JRA) had previously refused research authorization to their medical records and were not included as potential participants. Four patients were deceased at the time of the study. The remaining 53 patients were invited to participate in the study. Seventeen patients declined to participate. Five patients could not be located or did not respond. Thirty-two participants participated in the study, and 30 had DEXA scans performed from August 1999 to December 1999. DEXA scans of one participant performed 8 months prior to initiation of the study and of one deceased patient performed at the Mayo Clinic in January 1994 were included. The demographic characteristics of the 32 participants are compared with the entire cohort and the 25 nonparticipants in Table 1. All 32 participants had lumbar spine DEXA scans. Thirty-one participants also had hip DEXA scans. Twenty-eight participants had distal one-third radius DEXA scans. Due primarily to technical problems, only 20 of the participants had whole body DEXA scans. Figure 1 is a scatterplot of the individual participants’ T scores at the lumbar spine, femoral neck, total hip, distal one-third radius, and whole body. Although the majority of participants had T scores in the normal range at each of these sites (T scores > –1), a substantial subset of participants were osteopenic (T scores ≤ –1). Figure 2 illustrates the individual femoral neck T scores versus age of the participants and shows that the osteopenic participants are widely distributed in age. The distribution of lumbar spine T scores versus age also revealed that the osteopenic participants showed a similar pattern (data not shown). As noted above, a substantial number of the participants had T scores < –1 at the various sites. A T score of –1 is the World Health Organization’s threshold for defining low.
bone mass or osteopenia and has been associated with an increased fracture risk in postmenopausal women.\textsuperscript{31-33} When compared to the expected normal distribution in the general population, a significantly larger than expected proportion of the JRA patients had T scores < –1 (Table 2). Twenty-eight percent (n = 9) of the participants had T scores < –1 in the lumbar spine (p = 0.058 relative to expected). Thirty-two percent (n = 10) had T scores < –1 in the femoral neck (p = 0.012 relative to expected). Although both the distal one-third radius and the femoral neck are made up primarily of cortical bone, no increased proportion of the participants were osteopenic at the distal one-third radius. This was a slightly surprising finding, given previous reports of significant osteopenia associated with the appendicular skeleton of children with JRA.\textsuperscript{1} Overall, 14 of the 32 participants (44%) were osteopenic in at least one measured site. One patient was osteopenic only in the trochanter region of the hip although his lumbar spine T score was –0.9. Thirteen of the participants (41%) were osteopenic at either the lumbar spine or femoral neck, which represent the 2 most common clinically studied sites.

We then examined characteristics of participants that could be used to identify patients with JRA at greatest risk of osteopenia persisting into adulthood. Since the majority of peak bone mass is acquired during the pubertal growth spurt when bone mass nearly doubles,\textsuperscript{34,35} efforts were focused on identifying variables affecting bone mass during the critical period of adolescence defined here as ages 12–16. Pearson correlations were used to analyze the association of a variety of factors affecting BMD and individual participants’ T scores at various scan sites. Four variables found to significantly correlate with low bone density at either the femoral neck or lumbar spine were: (1) calcium intake during adolescence as assessed by milk or cheese intake less frequently than with every meal (p = 0.047 at the femoral neck and p = 0.022 at the lumbar spine); (2) lower levels of physical activity during adolescence as assessed by lack of participation in organized sports (p = 0.043 at the femoral neck and p = 0.14 at the lumbar spine); (3) smoking during adolescence (p = 0.018 at the femoral neck and p = 0.54 at the lumbar spine); and (4) revised Steinbrocker functional class ≥ 2 during adolescence (p = 0.086 at the femoral neck and p = 0.016 at the lumbar spine). No association was observed between individuals’ T scores and JRA subtype or ongoing disease activity assessed as current joint pain or swelling in joints previously affected by JRA. In addition, eight percent (n = 9) of the participants had T scores < –1 in the lumbar spine (p = 0.058 relative to expected). Thirty-two percent (n = 10) had T scores < –1 in the femoral neck (p = 0.012 relative to expected). Although both the distal one-third radius and the femoral neck are made up primarily of cortical bone, no increased proportion of the participants were osteopenic at the distal one-third radius. This was a slightly surprising finding, given previous reports of significant osteopenia associated with the appendicular skeleton of children with JRA.\textsuperscript{1} Overall, 14 of the 32 participants (44%) were osteopenic in at least one measured site. One patient was osteopenic only in the trochanter region of the hip although his lumbar spine T score was –0.9. Thirteen of the participants (41%) were osteopenic at either the lumbar spine or femoral neck, which represent the 2 most common clinically studied sites.

We then examined characteristics of participants that could be used to identify patients with JRA at greatest risk of osteopenia persisting into adulthood. Since the majority of peak bone mass is acquired during the pubertal growth spurt when bone mass nearly doubles,\textsuperscript{34,35} efforts were focused on identifying variables affecting bone mass during the critical period of adolescence defined here as ages 12–16. Pearson correlations were used to analyze the association of a variety of factors affecting BMD and individual participants’ T scores at various scan sites. Four variables found to significantly correlate with low bone density at either the femoral neck or lumbar spine were: (1) calcium intake during adolescence as assessed by milk or cheese intake less frequently than with every meal (p = 0.047 at the femoral neck and p = 0.022 at the lumbar spine); (2) lower levels of physical activity during adolescence as assessed by lack of participation in organized sports (p = 0.043 at the femoral neck and p = 0.14 at the lumbar spine); (3) smoking during adolescence (p = 0.018 at the femoral neck and p = 0.54 at the lumbar spine); and (4) revised Steinbrocker functional class ≥ 2 during adolescence (p = 0.086 at the femoral neck and p = 0.016 at the lumbar spine). No association was observed between individuals’ T scores and JRA subtype or ongoing disease activity assessed as current joint pain or swelling in joints previously affected by JRA. In addition, eight percent (n = 9) of the participants had T scores < –1 in the lumbar spine (p = 0.058 relative to expected). Thirty-two percent (n = 10) had T scores < –1 in the femoral neck (p = 0.012 relative to expected). Although both the distal one-third radius and the femoral neck are made up primarily of cortical bone, no increased proportion of the participants were osteopenic at the distal one-third radius. This was a slightly surprising finding, given previous reports of significant osteopenia associated with the appendicular skeleton of children with JRA.\textsuperscript{1} Overall, 14 of the 32 participants (44%) were osteopenic in at least one measured site. One patient was osteopenic only in the trochanter region of the hip although his lumbar spine T score was –0.9. Thirteen of the participants (41%) were osteopenic at either the lumbar spine or femoral neck, which represent the 2 most common clinically studied sites.

We then examined characteristics of participants that could be used to identify patients with JRA at greatest risk of osteopenia persisting into adulthood. Since the majority of peak bone mass is acquired during the pubertal growth spurt when bone mass nearly doubles,\textsuperscript{34,35} efforts were focused on identifying variables affecting bone mass during the critical period of adolescence defined here as ages 12–16. Pearson correlations were used to analyze the association of a variety of factors affecting BMD and individual participants’ T scores at various scan sites. Four variables found to significantly correlate with low bone density at either the femoral neck or lumbar spine were: (1) calcium intake during adolescence as assessed by milk or cheese intake less frequently than with every meal (p = 0.047 at the femoral neck and p = 0.022 at the lumbar spine); (2) lower levels of physical activity during adolescence as assessed by lack of participation in organized sports (p = 0.043 at the femoral neck and p = 0.14 at the lumbar spine); (3) smoking during adolescence (p = 0.018 at the femoral neck and p = 0.54 at the lumbar spine); and (4) revised Steinbrocker functional class ≥ 2 during adolescence (p = 0.086 at the femoral neck and p = 0.016 at the lumbar spine). No association was observed between individuals’ T scores and JRA subtype or ongoing disease activity assessed as current joint pain or swelling in joints previously affected by JRA. In addition,

---

Table 1. Demographic characteristics of this population based cohort of adults with a history of JRA.

<table>
<thead>
<tr>
<th></th>
<th>Cohort, n = 57 (%)</th>
<th>Participants, n = 32 (%)</th>
<th>Nonparticipants, n = 25 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. female, %</td>
<td>42 (72)</td>
<td>27 (84)</td>
<td>15 (60)</td>
</tr>
<tr>
<td>No. pauciarticular, %</td>
<td>39 (68)</td>
<td>25 (78)</td>
<td>14 (56)</td>
</tr>
<tr>
<td>No. polyarticular, %</td>
<td>11 (19)</td>
<td>6 (19)</td>
<td>5 (20)</td>
</tr>
<tr>
<td>No. systemic, %</td>
<td>7 (12)</td>
<td>1 (3)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Mean age at diagnosis, yrs, ± SD</td>
<td>8.7 ± 4.8</td>
<td>8.6 ± 4.8</td>
<td>8.8 ± 4.9</td>
</tr>
<tr>
<td>Mean age at followup or death, yrs (minimum, maximum)</td>
<td>34.3 (18,53)</td>
<td>35.7 (19,53)</td>
<td>32.4 (18,48)</td>
</tr>
<tr>
<td>Average years of followup, yrs, ± SD</td>
<td>25.6 ± 9</td>
<td>27.1 ± 9.1</td>
<td>23.6 ± 8.6</td>
</tr>
</tbody>
</table>

---

Figure 1. Scatterplot of participants’ T scores at measured sites.

Figure 2. Participants’ femoral neck T scores versus ages.
no association with steroid use was observed; however, the number of patients treated with steroids in this cohort was very small (< 13%).

DISCUSSION

This population based study demonstrates that a significant subset of adults with a history of JRA is osteopenic. Although the majority of participants in our cohort had T scores in the normal range, over 40% of our population based cohort are osteopenic at either the lumbar spine or femoral neck (T score ≤ –1), placing them at increased future fracture risk. This observation is surprising given the predominance of pauciarticular patients with JRA in this population based cohort and the lack of significant corticosteroid use. We observed lower percentages of patients with osteopenia/osteoporosis in our study than previously reported in adults with a history of JCA. Twenty-eight percent of our patients had T scores < –1 in the lumbar spine compared to nearly 50% in Havelka, et al20, 43% in Zak, et al21, and 49% in Bartram, et al22. Thirty-two percent of our patients had T scores < –1 in the femoral neck compared to 53% with low BMD in the hip in Zak, et al21 and 40% in Bartram, et al22. In addition, all 3 of these studies reported substantially more patients with osteoporosis (T score ≤ –2.5) than we observed. These differences likely reflect both the higher proportion of patients with polyarticular and systemic JCA and higher use of corticosteroids in these referral based studies compared to our population based cohort. However, like these 3 studies, our results confirm that a significant fraction of patients with JRA have low BMD in adulthood.

Haugen and co-workers recently reported finding less osteopenia and osteoporosis than reported in previous studies in a large Norwegian cohort of young adults with a history of JCA23. They concluded that the majority of young adults with a history of JCA attained normal BMD, although patients with persistent disease activity did have significantly lower BMD than healthy controls. Patients with arthritis in remission were found to have normal BMD at the lumbar spine and distal radius, but women with JCA in remission had significantly lower BMD at the femoral neck and total body than controls. This study showed the negative effect of persistent disease activity on BMD; however, the results were presented in a dichotomized format (JCA patients with active versus inactive disease), making direct comparisons of the whole cohort with our study or previous reports difficult.

Corticosteroid use varied widely in these reports and likely accounts for some of the observed differences in BMD. In the initial study of Havelka and co-workers, 42% of the participants had been treated with longterm corticosteroids, including all 6 patients with BMD > 2 standard deviations below the mean value20. Forty-three percent of participants in the study by Zak and colleagues had been treated with corticosteroids21. Bartram and co-workers noted significantly lower BMD in patients who had been treated with corticosteroids (47% of the cohort)22. In contrast, only 12.5% of the patients in our cohort and 26% of the patients in Haugen’s study23 had been treated with corticosteroids. Although our results support the conclusion of Haugen and co-workers23 that the majority of adults with a history of JCA will have normal BMD, we found a larger subset of

Table 2. Distribution of low BMD (T score ≤ 1) and normal BMD (T score > –1) at various sites in adults with a history of JRA compared to expected values.

<table>
<thead>
<tr>
<th>Site</th>
<th>Observed (%)</th>
<th>Expected (%)</th>
<th>Chi-square p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (n = 32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23 (72)</td>
<td>26.9 (84.1)</td>
<td>0.058</td>
</tr>
<tr>
<td>Low</td>
<td>9 (28)</td>
<td>5.1 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Femoral neck (n = 31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>21 (68)</td>
<td>26.1 (84.1)</td>
<td>0.012</td>
</tr>
<tr>
<td>Low</td>
<td>10 (32)</td>
<td>4.9 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Ward’s triangle, Total Hip (n = 31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>24 (77)</td>
<td>26.1 (84.1)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7 (23)</td>
<td>4.9 (15.9)</td>
<td>0.31</td>
</tr>
<tr>
<td>Trochanter, intertrochanter (n = 31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23 (74)</td>
<td>26.1 (84.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Low</td>
<td>8 (26)</td>
<td>4.9 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Distal 1/3 radius (n = 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>25 (89)</td>
<td>23.6 (84.1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Low</td>
<td>3 (11)</td>
<td>4.4 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Whole body (n = 16)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>14 (88)</td>
<td>13.5 (84.1)</td>
<td>0.71</td>
</tr>
<tr>
<td>Low</td>
<td>2 (13)</td>
<td>2.5 (15.9)</td>
<td></td>
</tr>
</tbody>
</table>

*Expected populations based on Gaussian distribution of T scores. † Whole body T scores are shown for 16 female participants and exclude data on 4 men because there are no standardized normal values available for men.
patients were osteopenic in adulthood. The reasons for this relative difference are not entirely clear. It is not explained by corticosteroid use or by differences in disease subtype, since pauciarticular patients make up a larger proportion of our cohort (78% vs 44%). Although our cohort was older (average age 35.7 years compared to 25 years), with significantly longer average followup (27.1 compared to 15.3 years), this is unlikely to account for the observed differences because in our study osteopenic participants were well distributed throughout the age spectrum. One explanation of this relative difference may lie in potential differences in genetic predisposition to osteopenia between the Norwegian and Midwestern American cohorts. Other potential explanations of this discrepancy could include differences in various variables affecting bone mass such as control of disease activity, diet including calcium intake, and exercise during the critical period of adolescence.

Our observation that a substantial subset of adults with a history of JRA are osteopenic correlates well with the work of Henderson and co-workers, who identified a significant history of JRA are osteopenic correlates well with the work during the critical period of adolescence. Other potential explanations of this discrepancy could include differences in the reduced statistical power of our analysis, several statistical significant associations emerged. Our study is also limited by the fact that the population of Rochester is primarily Caucasian, which may decrease the generalizability of our data.

Our results indicate that the majority of patients with JRA will enter adulthood with normal bone mass; however, osteopenia associated with childhood JRA may persist into adulthood, particularly in corticosteroid treated patients with polyarticular and systemic JRA. Our population based study suggests that a subset of noncorticosteroid treated patients with pauciarticular JRA are also at risk of osteopenia in adulthood. Our results suggest that every effort should be made to control disease activity and allow normal physical activity during the critical period of adolescence to allow achievement of maximal peak bone mass. In addition, all patients with JRA should be encouraged not to smoke and to optimize their calcium intake during adolescence to minimize their risk of osteopenia. Additional longitudinal studies are needed to further identify which subset of patients with JRA will benefit from aggressive, targeted therapy to avoid or mitigate the longterm morbidity associated with osteopenia.

ACKNOWLEDGMENT
We gratefully acknowledge the participation of the Mayo Clinic General Clinical Research Center in this project.

REFERENCES
12. Kotaniemi A. Growth retardation and bone loss as determinants of