Radiographic Damage Associated With Low Bone Mineral Density and Vertebral Deformities in Rheumatoid Arthritis: The Oslo-Truro-Amsterdam (OSTRA) Collaborative Study

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Objective. To examine variables associated with bone mineral density (BMD) and vertebral deformities in women with rheumatoid arthritis (RA) from 3 northwest European countries.

Methods. Female patients were recruited from rheumatology clinics in Oslo, Norway; Truro, UK; and Amsterdam, The Netherlands (150 total, 50 per center, age 50–70 years, disease duration >5 years). Demographic and clinical data were collected and BMD was measured by means of dual energy x-ray absorptiometry. Associations between demographic and clinical measures on the one hand and BMD and vertebral deformities on the other were investigated by single and multiple regression analyses.

Results. Body mass index (BMI), medication use, RA damage measures, and BMD differed significantly between the 3 centers. Overall, Norwegian patients had the lowest BMI, used more corticosteroids and antiosteoporotic drugs, had lower joint damage measured by Larsen score, and lower BMD at both spine and hip. High age, low BMI, and high cumulative dose of corticosteroids (last 2 years) are related to low BMD. A high Larsen score was associated with low BMD at the hip. Larsen score was the independent determinant of vertebral deformities after correction for center, age, BMI, and BMD.

Conclusion. Data from 3 countries on BMD and vertebral deformities in female patients aged 50–70 years with long-standing RA are presented, demonstrating an association between radiographic RA damage and low BMD and between radiographic RA damage and vertebral deformities.

KEY WORDS. Rheumatoid arthritis; Postmenopausal women; Bone density; Vertebral deformities; Radiography.

INTRODUCTION

Generalized low bone mass is considered a complication of rheumatoid arthritis (RA) (1). Over the past few years, generalized bone loss was largely thought to be 1 of 3 separate types of bone involvement in RA, the other 2 being juxtaarticular osteoporosis and bone erosions of individual joints. Recently, however, it was suggested that some of the pathophysiologic mechanisms involved in generalized osteoporosis are common to those for local bone involvement (2). The osteoclast plays a central role in these processes, and the biology of this cell depends on the balance between receptor activator of nuclear factor κB ligand and osteoprotegerin (3,4).

During the last few years, the extent of osteoporosis in RA became more clear. A 2-fold higher frequency of osteoporosis was shown in 394 female RA patients recruited from a patient register, representative of the underlying patient population in Oslo, as compared with a healthy reference population (5). A similar increased occurrence of reduced bone mass has been reported in male RA patients (6).

In an attempt to unravel the pathogenesis of bone loss and to identify patients at high risk of osteoporosis, the
relation between demographic and disease-related variables on the one hand and bone mass on the other was studied in RA patients (7–9). The demographic variables high age and low body mass index (BMI) were found to be related to low bone mass (10). Moreover, disease-related variables are reported as determinants of low bone mineral density (BMD) (11,12). Despite the overall results mentioned, studies on osteoporosis in RA show conflicting results with regard to many possible risk factors for low bone mass or osteoporosis (13–15). This lack of unanimity might be ascribed to the complex interaction between inflammation and corticosteroid use. Moreover, these discrepancies might be attributed to differences in methodologic aspects, such as sample size and patient selection, or local customs in lifestyle and treatment in the various studies.

Symptomatic fractures are the relevant clinical outcome of low bone mass. The increased risk of both hip and vertebral fractures in people with RA compared with those without RA underlines the significance of osteoporosis as a complication in RA (16–18). However, the contributions of the different risk factors could not be assessed in the mentioned studies on fracture risk in RA.

The present cross-sectional study addresses these issues by identifying factors associated with BMD and vertebral deformities in postmenopausal women with longstanding RA from 3 northwest European countries.

PATIENTS AND METHODS

Patients. In each of 3 centers, general rheumatology clinics in Oslo (Norway), Truro (UK), and Amsterdam (The Netherlands), 50 female patients were consecutively enrolled. The patients included were 50–70 years old and fulfilled the American College of Rheumatology (formerly American Rheumatism Association) 1987 revised classification criteria for RA (19). The disease duration of all patients was 5 or more years. At the time of clinical examination, the 150 patients underwent a BMD measurement unless they had a BMD measurement within the previous 3 months.

Demographic and clinical variables. The demographic and clinical variables of the patients were retrieved by interview and clinical examination. The interviews and examinations were carried out by trained research nurses in Oslo and Truro in cooperation with a local rheumatologist; in Amsterdam the examination was performed by 1 physician (MCL). The demographic variables collected were age, disease duration, body weight, and height. Other data collected concerned menopause status, previous and current use of antioestoporetic and disease-modifying antirheumatic drugs (DMARDs), history of corticosteroid use (never/previous/current use, cumulative amount over the past 2 years, use of ≥7.5 mg for >6 months, and number of months of corticosteroid use), and smoking status (never/previous/current smoker). RA disease activity core measures were collected: pain and patient’s and investigator’s global disease activity assessment as measured on a visual analog scale (0–100 mm), physical disability by means of the Health Assessment Questionnaire (HAQ; 20 items, score range 0–3, with higher scores indicating worse disability) (20), 28 tender joint count, 28 swollen joint count, and acute phase reactants (the erythrocyte sedimentation rate [ESR; mm/hour] and C-reactive protein [CRP; g/dl]) measured with local measurement techniques. The modified disease activity score (DAS) was calculated according to published guidelines (21). Serum rheumatoid factor (RF) status was defined as positive if it ever was positive according to locally applied measurement techniques and local cut-off points.

Joint damage was assessed by an 18 deformed joint count (5) and by radiographs. Hand radiographs were read by a trained rheumatologist according to the modified Larsen method (range 0–120) (22). Intraobserver variability was calculated by means of intraclass correlation coefficient (ICC) on a sample of 30 radiographs reflecting the distribution of damage status at first reading (ICC = 0.96, confidence interval 0.92–0.98) and by means of Bland and Altman’s 95% limits of agreement method (23). This method yielded a smallest detectable difference of ±16.9 modified Larsen score units.

Lateral radiographs of thoracic and lumbar spine were read as proposed by Genant et al (24) by 1 observer (MCL). This semiquantitative method grades vertebral T4–L4 on visual inspection into grades 0 (normal), 1 (20–25% reduction in anterior, middle, and/or posterior height), 2 (25–40% height reduction), and 3 (40% height reduction). A vertebral scoring of grade 1 or higher was considered a deformed vertebra. Vertebral deformities in patients were categorized as mild (≥1 vertebral deformity grade 1, without grade 2 or 3 deformities), moderate (≥1 vertebral deformity grade 2, without a grade 3 deformity), or severe (≥1 vertebral deformity grade 3). Intraobserver variability was calculated on a sample of 40 radiographs, half of which were judged as having vertebral deformities on first reading. The kappa score for presence versus absence of ≥1 vertebral deformity grade ≥1 was 0.80. The weighted kappa scores with quadratic weights for severity and number of deformities were 0.90 and 0.78, respectively.

BMD measurements. BMD measurements of the hip, total hip and femoral neck, and lumbar spine L2–4 anteroposterior view were carried out by a trained technician at each site. Several quality aspects of the BMD data collected on 3 different dual energy x-ray absorptiometry (DEXA) machines (Lunar Expert [Lunar, Madison, WI] in Oslo, Lunar DPX [Lunar] in Amsterdam, and Hologic [Hologic, Waltham, MA] QDR 4500 in Truro) were examined. In vitro reproducibility, calculated from measurements of the local spine phantom and expressed as a coefficient of variation (CV), were 0.8%, 0.6%, and 0.4% for the complete study period in Oslo, Truro, and Amsterdam, respectively. In vivo reproducibility of BMD measurements was investigated by means of duplicate DEXA measurements in 10 healthy volunteers recruited per center (mean age ± SD: Norway 55.1 ± 4.5, UK 54.7 ± 5.4, the Netherlands 59 ± 4.1). The CVs were 1.6%, 1.3%, and 1.2% at the femoral neck; 1.3%, 1.0%, and 1.1% at the total hip; and 2.5%, 0.8%, and 0.7% at the lumbar spine L2–4 in Oslo,
Truro, and Amsterdam, respectively. Crosscalibration of the 3 DEXA machines was carried out by means of a Bona Fide Phantom (Bio-Imaging Technologies Inc., Newton, PA), a calcium hydroxyapatite spine (L1–4) phantom (range of density 0.7–1.5 g/cm²), that traveled between the 3 centers. At each center, the crosscalibration phantom was measured 5 times on 5 consecutive days. The phantom was not repositioned between the measurements within 1 day. A linear regression model was used to adjust the BMD values from Amsterdam and Truro to the Oslo BMD data. The use of a linear model was justified by the highly significant correlations found between the phantom BMD measured in Oslo and Amsterdam (r = 0.99), and Oslo and Truro (r = 0.99).

The raw Oslo BMD and the adjusted Amsterdam and Truro BMD values were compared with a pooled European/US reference database for T and Z score estimation. Details on the database for T and Z score estimation are extensively described elsewhere (5). To ensure the validity of the data from the pooled European/US reference population, we compared the data of this reference population with data (all obtained with Lunar machines) from populations in Norway, the UK, and The Netherlands (25–27). No substantial difference was found between the pooled European/US reference population and the Scandinavian, British, and Dutch reference populations for the femoral neck and spine L2–4, because the 95% confidence interval of the mean BMD values were overlapping in each age decade or were close to the BMD values for the pooled European/US reference population.

Ethics. The study protocol was approved by the local medical ethical committees of the 3 centers.

Statistical analysis. Data on all 150 patients collectively were analyzed, as were the data separated by center. Bone mass was expressed as BMD (g/cm²) and also presented as T and Z scores. Osteoporosis was defined as a T score of ≤ −2.5 SD (28). Reduced bone mass was defined as a Z score of ≤ −1 SD. The Z score was calculated by adjustment for both age and weight. Regarding continuous variables, groups were compared by means of 2-sided t-tests or analysis of variance with Bonferroni correction for multiple comparisons. The chi-square test (categorical variables) or the Kruskal-Wallis test was performed where appropriate. In the single analysis (1 independent variable), relations between demographic and clinical variables listed in Table 1 on the one hand and BMD and vertebral deformities on the other hand were investigated. Based on the results of the corresponding single analysis (P < 0.20) and supposed clinical relevance, variables were added to the respective multiple regression models. In all multiple regression models, we adjusted for age, BMI, and center, which was added as a dummy variable in the linear regression models. The multiple regression analyses were performed as backward and forward procedures. The models were then further refined by tentatively adding first-order interactions, square terms investigating curving of the regression, and single variables initially not included in the model. By means of linear regression, the independent variables associated with BMD at different measurement sites were investigated. Logistic regression was used to examine the determinants of the dichotomous dependent variable, at least 1 vertebral deformity grade ≥ 1. A 2-sided P ≤ 0.05 was considered statistically significant. The software used was SPSS for Windows (Chicago, IL), version 9.0.

RESULTS

Patient characteristics. The demographic and clinical characteristics of the 150 patients included in the study are shown in Table 1. The most striking differences between the centers, occurring for some of the demographic and disease-related variables, exist between Truro and Oslo. Patients in Truro had the highest BMI, and patients in Oslo more frequently used corticosteroids and drugs for the prevention and treatment of osteoporosis. However, the Oslo patients had the lowest BMD values and the lowest radiographic damage scores. The Larsen score of the hands was almost twice as high in Amsterdam patients as compared with the patients from Oslo. The patients’ self-reported perception of pain and physical disability was worst in Truro.

BMD, frequency of osteoporosis, and reduced bone mass. In 6 patients, no hip measurement was performed due to bilateral hip replacement. The BMD and the derived T and Z scores differed between the 3 centers, with a tendency of the values of Oslo patients to be lowest and of Truro patients to be highest. At the total hip and spine, these differences reached statistical significance (Table 1). The frequency of osteoporosis (T score ≤ −2.5 SD) and reduced bone mass (Z score ≤ −1 SD) per BMD measurement site are presented in Table 2. Both osteoporosis and reduced bone mass most frequently occurred in Oslo as compared with Truro and Amsterdam. This applies to all BMD measurement sites. Regarding the total group, reduced bone mass, expressed as the Z score, occurred more frequently in the hip than in the spine.

Variables associated with BMD. The demographic and disease-related variables listed in Table 1 were investigated in a single regression analysis with BMD. The variables investigated as independent variables associated with BMD are shown in Table 3. Higher age, lower BMI, and higher cumulative dose of corticosteroids used during the last 2 years were independent factors associated with low BMD at all measurement sites. At the hip, total Larsen score was associated with low BMD. The final model for hip BMD explained 54% of the variation in BMD; for the spine model this percentage was 37%. A number of other variables, including smoking status, disease duration, RF status, HAQ, DAS, (mean) ESR, and (mean) CRP, did not show an independent association with BMD in the multivariate analysis. Although none of the interaction terms contributed significantly to the models, one square term (for BMI) did in the models determining hip BMD. Because the negative effect of this square term only had a small influence on the slope of the regression line (figures not shown), we neglected the effect, giving preference to the more comprehensible linear model.
Frequency of vertebral deformities. Spine radiographs of 142 women were included in the analysis. The spine radiographs of 8 patients were not read because of insufficient quality. Of the 142 women whose spine radiograph was read, 20 (14%) had at least 1 vertebral deformity grade 1 or higher; 9 (18%) in Oslo, 6 (14%) in Truro, and 5 (10%) in Amsterdam. Of the 142 patients, 11 (8%) had at least 1 vertebral deformity grade 2 or higher.

Variables associated with vertebral deformities. Three separate models, including the 3 different BMD measurement sites as 1 of the independent variables, investigated the associations with vertebral deformities. Lower femoral neck BMD, after adjustment for age, BMI, and center, was associated with vertebral deformity. Higher total Larsen score was independently associated with vertebral deformity after correction for center, age, and BMI, both for the
model including total hip BMD and for the model including spine BMD. Thus, femoral neck and not total hip and spine BMD were independently associated with vertebral deformities. The variables on the use of corticosteroids (never/ever use, not current/current use, cumulative amount over the past 2 years, never/ever use of ≥7.5 mg for >6 months, and number of months of corticosteroid use) were consecutively investigated in these models; none of these variables showed a significant contribution to any of the models. None of the added first-order interaction terms and square terms demonstrated a significant result.

**DISCUSSION**

The main conclusion from this study in postmenopausal women with longstanding RA is the association between joint damage measured by the Larsen score and low BMD measured by DEXA and the association between joint damage and vertebral deformities, or in other words a relation between radiographic damage and osteoporosis in RA patients.

In line with previous studies in RA, high age and low BMI were independent variables associated with low BMD at all measurement sites (5). The RA-specific marker for BMD found in this study was high total Larsen score. This variable was associated with low BMD at the hip. Total Larsen score represents cumulative joint damage and could be considered a measure that reflects cumulative disease activity. Therefore, this variable seems an appropriate measure of past fluctuating disease activity, which can be used in cross-sectional studies on BMD in RA. Moreover, a recent study by Sinigaglia et al (29) showed the presence of erosions associated with a higher prevalence of osteoporosis at both the spine and the hip. These findings suggest that some of the disease mechanisms for generalized osteoporosis may be common to those of local bone involvement. Even more in line with our results are data presented by Sambrook et al (30) showing an inverse association between Larsen score of the feet and both age-adjusted BMD and ultrasound measures.

In our population of 50–70 year olds, there was no significant association between Larsen score and BMD of the spine. The absence of this significant association might be ascribed to osteoarthritis of the spine, atherosclerosis of the aorta, and vertebral deformities, increasing measured BMD and thus obscuring a possible relation between potential predictors and true BMD. The same mechanism probably explains the lower $R^2$ of the final model for spine BMD as compared with the final model for hip BMD. The

### Table 3. Multiple linear regression analysis of BMD (g/cm²) at different sites of measurement (dependent variable), demographic variables, and disease variables (independent variables)*

<table>
<thead>
<tr>
<th>Center (dummy)</th>
<th>Femoral neck</th>
<th>Beta</th>
<th>SE</th>
<th>95% CI</th>
<th>Total hip</th>
<th>Beta</th>
<th>SE</th>
<th>95% CI</th>
<th>Spine L2–4</th>
<th>Beta</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oslo-Amsterdam</td>
<td>0.022</td>
<td>0.029</td>
<td>-0.036 to 0.080</td>
<td>-0.008</td>
<td>0.033</td>
<td>-0.074 to 0.058</td>
<td>0.040</td>
<td>0.042</td>
<td>-0.042 to 0.123</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oslo-Truro</td>
<td>0.010</td>
<td>0.030</td>
<td>-0.050 to 0.071</td>
<td>0.10</td>
<td>0.034</td>
<td>0.028 to 0.165†</td>
<td>0.045</td>
<td>0.044</td>
<td>-0.042 to 0.132</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>-0.006</td>
<td>0.002</td>
<td>-0.01 to -0.003†</td>
<td>-0.008</td>
<td>0.002</td>
<td>-0.012 to -0.003†</td>
<td>-0.0056</td>
<td>0.003</td>
<td>-0.011 to -0.0003‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.016</td>
<td>0.002</td>
<td>0.011 to 0.021†</td>
<td>0.018</td>
<td>0.003</td>
<td>0.013 to 0.024†</td>
<td>0.022</td>
<td>0.004</td>
<td>0.014 to 0.029†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative steroids last 2 years, grams</td>
<td>-0.007</td>
<td>0.002</td>
<td>-0.012 to -0.003†</td>
<td>-0.010</td>
<td>0.003</td>
<td>-0.015 to -0.005†</td>
<td>-0.013</td>
<td>0.003</td>
<td>-0.019 to -0.006†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Larsen score hands</td>
<td>-0.0014</td>
<td>0.0004</td>
<td>-0.002 to -0.001†</td>
<td>-0.0016</td>
<td>0.0004</td>
<td>-0.002 to -0.001†</td>
<td>-0.0009</td>
<td>0.0005</td>
<td>-0.002 to 0.0002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R^2$</td>
<td></td>
<td>45</td>
<td></td>
<td></td>
<td>54</td>
<td></td>
<td></td>
<td></td>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* BMD = bone mineral density; SE = standard error; 95% CI = 95% confidence interval; BMI = body mass index; $R^2$ = percentage of total variance explained in the model. Dummy variables for center Oslo is reference category.
† $P < 0.01$.
‡ $P < 0.05$. 

### Table 2. Frequency of osteoporosis and reduced bone mass in hip (femoral neck and total hip) and spine L2–4 among RA patients from Oslo, Truro, and Amsterdam

<table>
<thead>
<tr>
<th></th>
<th>Femoral neck</th>
<th>Total hip</th>
<th>Spine L2–4</th>
<th>Femoral neck</th>
<th>Total hip</th>
<th>Spine L2–4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 150)</td>
<td>18</td>
<td>13</td>
<td>16</td>
<td>27</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Oslo (n = 50)</td>
<td>21</td>
<td>17</td>
<td>32</td>
<td>32</td>
<td>38</td>
<td>28</td>
</tr>
<tr>
<td>Amsterdam (n = 50)</td>
<td>18</td>
<td>18</td>
<td>10</td>
<td>27</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>Truro (n = 50)</td>
<td>15</td>
<td>2</td>
<td>6</td>
<td>23</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

* Data presented as percentages. RA = rheumatoid arthritis.
difficulties in interpreting findings on spine BMD are reflected in recent recommendations preferring the measurement of BMD in the hip to other sites (31). In accordance with previous reports, cumulative corticosteroid dose during the 2 years before BMD measurement was independently associated with low hip and spine BMD (1,32). RF status, disease duration, and HAQ score, variables related to BMD in other studies (5,12,13), did not independently predict low BMD in this study. An explanation for this may be that these variables are incorporated in the total Larsen score.

The multiple regression analyses investigating vertebral deformities showed age and total Larsen score as independent variables associated with this endpoint. In contrast with findings of other studies showing relations between corticosteroid use and vertebral deformities (33–35), none of the variables related to corticosteroid use was significantly associated with vertebral deformities in the current study. The reason for the discrepancy between the data from literature and our findings could be a lack of statistical power in the detection of a relation between corticosteroid use and vertebral deformities; only 20 of the 142 women who had their spine radiographs assessed had vertebral deformities, and 65% of the patients were classified as ever using corticosteroids. Besides, the mean dose of corticosteroids used was relatively low in our patients. The effects of corticosteroids on bone are complex (36). The value of glucocorticoids in reducing the rate of radiographic progression in RA was elegantly proven by Kirwan (37). The beneficial effect on suppression of disease activity, radiographic progression, and the potential reversibility of corticosteroid effects after tapering and stabilization of continued therapy should be weighed against the induction of osteoporosis. The significance of negative influence of RA on bone is underlined by the current finding of the Larsen score as independent predictor of vertebral deformities. Previous studies also found an effect of disease-related variables with vertebral deformities in RA (29,38).

Despite the fact that this study on osteoporosis in RA contains data from 3 geographically closely related European countries, remarkable differences in treatment of RA and osteoporosis, joint damage, and BMD are shown. The most striking findings were the frequent use of corticosteroids and the low mean Larsen score in the Norwegian patients as compared with the other centers. The difference in BMI between patients from the 3 centers could reflect a different lifestyle regarding diet and physical activity. The variation in joint damage and BMD between the centers suggests an effect of the differences in antirheumatic treatment in these patient groups of similar age, RF status, disease duration, and menopausal age.

The difference in RA treatment regarding corticosteroid use might originate from local clinical preference. The frequent use of antioestoprotic drugs in Oslo can be explained by recent local research on osteoporosis in RA, resulting in the start of antioestoprotic treatment in some patients.

All patients were consecutively recruited from eligible patients attending the outpatient clinic. Therefore, we consider these patient samples representative of the respective clinic population. The sample size of 50 patients per center was chosen for practical reasons. The adjustment for center in the multiple regression analysis controls for the heterogeneity between the respective centers regarding, for instance, BMI and corticosteroid use. Despite the cross-sectional design of the study, the relation between disease activity and BMD could be investigated by the use of total Larsen score as a representative of cumulative disease activity. Potential bias is introduced in multicenter studies by different assessors and, here, DEXA machines. However, the radiographs were scored by one assessor whose reproducibility was tested and found adequate. The reproducibility of DEXA measurements was acceptable. The BMD data were cross-calibrated and no difference was found between BMD data of national reference populations and the pooled European/US database, allowing for the use of this pooled database for T and Z score calculations.

At first sight, there is a discrepancy between the findings for the total group and the subgroup of Oslo patients regarding the association between radiographic joint damage and BMD. The patients from Oslo have the lowest total Larsen score but also the lowest BMD as compared with the other 2 subgroups. However, when the final multiple regression model (BMD as dependent variable) constructed for the total group is applied to the subgroup from Oslo, total Larsen score of the hands is independently associated with low BMD.

The current data were obtained from women with longstanding RA, therefore, they cannot be generalized to other patient groups such as men and women with early RA. Yet, osteoporosis is mainly a problem of postmenopausal women who sustained the various deleterious RA-related effects on bone for a prolonged period of time. Consequently, the presented data concern a patient group of particular interest. Considering the median disease duration of the patients, radiographic damage in the majority of patients may have in part developed prior to the availability of DMARDs, which prevent radiographic damage. Future investigations will examine radiographic damage and its relation to bone status in patients of similar disease duration who have been exposed to newer and more effective drugs with known effects on bone destruction.

In summary, the new findings on the relation between radiographic joint damage and BMD and vertebral deformities further support the suggestion of some common pathogenetic mechanisms for generalized osteoporosis and local bone involvement (2). The results highlight that the future research agenda should focus on possible associations between the aggressive suppression of disease activity in RA patients and the prevention of joint damage, BMD loss, and the resulting vertebral deformities.

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