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Serum irisin concentrations and osteoporotic vertebral fractures in women with rheumatoid arthritis

A cross-sectional study

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Abstract

Irisin stimulates osteoblast differentiation increasing bone mass a decreasing in irisin levels might contribute to osteoporotic fractures in inflammatory diseases. To date, there is controverted whether irisin levels are associated with osteoporotic fractures in rheumatoid arthritis (RA). Therefore, we evaluate the association of serum irisin with osteoporotic Vertebral Fractures (VFs) in women with RA.

A total of 148 women with RA was included in the study.

Clinical characteristics and risk factors of VFs was evaluated. For measurement of bone mineral density we included the assessment of lumbar spine (AP L1-L4) and Femoral Neck by dual-energy X-ray absorptiometry (DXA). VFs were evaluated by lateral vertebral assessment (LVA) of the dorsal and lumbar regions using X-ray and digital vertebral morphometry by DXA, using the Genant scale. Serum irisin levels were measured by ELISA. A reference group of 97 women with non-rheumatic diseases were included to compare irisin levels.

RA patients had a median age of 59 years and 41% had osteoporosis. Seventy three (49%) had VFs. Lower irisin levels were observed in RA patients compared to controls (94 ± 74 vs 135 ± 103, $P < .001$). Irisin concentrations were lower in RA + VFs than RA non-VFs (74 ± 42 vs 113 ± 92 ng/mL, $P = .001$). In the multivariable logistic regression analysis the low 50 percentile irisin levels < 73 ng/mL (OR:3.1, 95% CI:1.55–6.2, $P = .001$), and disease duration of RA (OR:1.04, 95% CI:1.001–1.08, $P = .04$) were associated with an increase in the risk of VFs.

A decrease of irisin levels is associated to VFs in RA. These results are valuable to consider that RA patients with low levels of irisin are in a potential risk of VFs.

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JIG-N and MRV contributed equally to this work.

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The data used to support the findings of this study available on request through the authors for correspondence.

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Abbreviations: BMD = bone mineral density, BMI = Body mass Index, CG = control group, DAS28 = disease activity score for 28 joints, DXA = dual-energy X-ray absorptiometry, RA = rheumatoid arthritis, VFs = osteoporotic vertebral fractures, WHO = World Health Organization.

Keywords: irisin, markers, osteoporosis, osteoporotic vertebral fractures, rheumatoid arthritis

1. Introduction

Osteoporosis is a well-recognized manifestation associated to rheumatoid arthritis (RA). In several studies included our own findings the prevalence of osteoporosis in RA patients is from 19% to 29.9%.[1–3] Being the osteoporosis one of the major factors associated with osteoporotic fractures is not surprise that RA patients had an increase in the risk of osteoporotic fractures.[4]

Several studies have demonstrated that the most prevalent sites of osteoporotic vertebral fractures in RA patients are the dorsal and lumbar spine regions.[4,5] Prevalence of osteoporotic vertebral fractures (VFs), has been reported from 13% to 40% in RA patients.[4–6]

On the other side, there are a number of factors in the general population that are protective for osteoporosis and VFs.[7] A regular practice of exercise is considered a relevant stimulus for maintain a healthy rate of bone formation.[7] The practice of physical exercise can release the irisin a new myokine with anabolic actions on the bone remodeling.[8,9] Irisin is encoded by the fibronectin-type III domain containing 5 gene (FNDC5) secreted by skeletal muscle in contraction, and is induced by exercise and cold exposure.[9,10] Likewise irisin is considered an adipokine implicated in the regulation of a variety of endocrine and metabolic diseases.[10,11] Several studies described an association between irisin with bone mineral density (BMD) and strength in athletes.[12,13]

In postmenopausal women some reports have associated low levels of irisin with osteoporotic fractures.[14–16] In RA patients, Lavrova et al observed an association of lower concentrations of Irisin with the presence of low-grade fractures, higher degree of inflammatory activity, disease duration, and presence of extra-articular manifestations.[17]

The aim of this study is to evaluate the association of serum levels of irisin with the presence of VFs in women with RA. New studies are needed to determine if irisin would be a useful diagnostic marker and a therapeutic target for clinical use.

2. Materials and methods

Study design: cross-sectional study

2.1. Subjects

We included 148 women with RA matched with 97 women without rheumatic inflammatory disorders for the control group (CG) who underwent BMD measurement by dual energy X-ray absorptiometry (DXA) recruited in an out-patient Rheumatology clinic of a secondary-care hospital (Hospital General Regional 110, del Instituto Mexicano del Seguro Social, IMSS (Mexican Institute of Social Security) in Guadalajara, Mexico.

2.2. Characteristics of the RA group

Women with RA were eligible if they were aged ≥45 years, met 1987 American College of Rheumatology criteria for RA[18] and if they signed a voluntary consent form for the study. We included patients with or without menopause independently of the history of previous fractures. We excluded RA patients with overlapping syndrome, infections (including hepatitis B or C, human immunodeficiency virus, or tuberculosis). We also excluded pregnant or breastfeeding patients, and also patients with malignancy, hypothyroidism, hypogonadism, and chronic renal failure.

2.3. Characteristics of the control group

We invited to participate as controls 97 women of similar age and race to the patients with RA, who were being attended by the outpatient clinic of the preventive medicine department at the same hospital. This outpatient clinic assessed any chronic disease in these patients mainly hypertension, obesity, diabetes mellitus, dyslipidemia, osteoporosis, and metabolic syndrome. We excluded from the controls those that had antecedents of any inflammatory autoimmune disorders, cancer, chronic kidney diseases, endocrinopathies, and active infections or if they had any of the exclusion criteria described above for RA patients. All the patients invited to participate in the study including RA and controls signed a voluntary informed consent form.

2.4. Study protocol

Patients with RA and controls were assessed using a structured interview and chart review seeking information on the demographic and clinical characteristics of the disease's comorbidities. Body Mass Index (BMI) was classified according to the World Health Organization (WHO) as follows: normal weight (range from 18.5–24.9 kg/m^2); overweight (ranging from 25–29.9 kg/m^2), and obesity (≥30 kg/m^2).[19]

In the clinical evaluation of patients with RA, the activity of the disease was evaluated by trained researchers using the disease activity score for 28 joints (DAS28) and classified according to the EULAR criteria.[20] Physical functioning was assessed using the validated Spanish version of the Health Assessment Questionnaire-Disability index (HAQ-Di).[21] In this index, the score ranges from 0 to 3 points, and a higher score is associated with greater severe functional impairment.

2.5. Bone mineral density measurements

In patients with RA and controls, BMD was measured by DXA using a General Electric Lunar Prodigy Advance scanner with a software Encore 16.0 version (Madison, WI). Regions assessed were lumbar spine (L1-L4) and hip.[22,23] All scans were performed by bone densitometry trained technician certified by ISCD (International Society for Clinical Densitometry). According to BMD results, patients were classified as normal, osteopenic or osteoporotic using the 1994 WHO criteria.

2.6. Vertebral fracture assessment

To perform vertebral fracture assessment (VFA), we obtain in RA patients lateral view radiographs of the thoracic and lumbar

spine, using standardized acquisition procedures. We also evaluate VFA using DXA images obtained during bone scan procedure using the VFA application of the Encore software. VFs were defined using the Genant scale (Semiquantitative method).[24] RA patients were classified into 2 groups: RA with VFs [RA-VFs (+) and RA with non-VFs (RA-VFs(-)]. The severity and type of the osteoporotic vertebral fractures were classified into grades 1-3, which represent a reduction in the anterior, middle and / or posterior vertebral heights of 20% to 25%, 25% to 40%, and more than 40%, respectively.[24] All the scans by DXA and radiographs of the thoracic and lumbar spine were analyzed independently by 2 readers (EG and GR) and discrepancies for both the diagnosis of fracture and the grades were adjudicated in the presence of a third experienced researcher (GL). For the diagnosis VFs, concordance between X-rays and DXA was a kappa of 0.89.

2.7. Laboratory determinations

After 8-hour fasting, a venous sample was obtained from the patient's (RA and control group). Rheumatoid Factor (RF) and erythrocyte sedimentation rate were determined by nephelometry and Wintrobe, respectively

Serum levels of irisin were determined by Enzyme-Linked ImmunoSorbent Assay (ELISA) using a commercial kit (MyBioSource , San Diego, California). The detection range of irisin is 15.6 to 500 ng/mL with a sensitivity of <2.0 ng/mL and a precision inter-assay of CV < 10%.

2.8. Statistical analysis

Quantitative variables were expressed as means and standard deviations (SD) and qualitative variables as frequencies and percentages (%). Comparisons of proportions between groups [RA-VFs(+) and RA-VFs(-)] were computed using Chi-Squared test (or when required Fisher exact test). Comparisons between means were computed using independent-sample Student *t*-tests. We performed logistic regression analyses in order to identify variables associated with the presence of VFs (dependent variable) adjusting for potential confounders. Covariates included in this model were those with a P value $\leq .20$ in the univariate analyses, or those with biological plausibility for influencing VFs. The model was adjusted for age and disease duration (years). We utilized the forward stepwise method for the multivariate analyses. Statistical significance was set at $P \leq .05$ level. SPSS statistical software version 21.0 was employed for these analyses.

2.9. Ethics

Institution's ethics board approval number: **R-2016-1303-41** of Instituto Mexicano del Seguro Social). The study protocol complied with the lineaments described in the Declaration of Helsinki. The study complied with the research Ethics standard of the hospital and the official normativity of Mexico for research studies (Norma Oficial Mexicana en materia de Investigación). Previous to the study onset all the participants signed a voluntary informed consent letter.

3. Results

We included 148 patients with RA. Sixty four percentage of the RA patients had functional disability and 77% an active disease.

Table 1

Clinical and laboratory variables and characteristics of vertebral fractures in Rheumatoid Arthritis.

Variable	n = 148
Female gender, n (%)	148 (100)
Age (years), mean ± SD	59 ± 10
Disease duration of RA (years), mean ± SD	13.6 ± 9
Vertebral fractures, n (%)	73 (49.3)
Non-VFs or grade 1, n (%)	99 (66.9)
VFs grade 2 or 3, n (%)	49 (33.1)
Lumbar spine fractures, n (%)	25 (17)
Grade 1, n (%)	6 (4.1)
Grade 2, n (%)	13 (8.8)
Grade 3, n (%)	6 (4.1)
Type of fractures in lumbar spine	
Crush, n (%)	16 (10.8)
Biconcave, n (%)	3 (2.1)
Wedge, n (%)	6 (4.1)
Dorsal spine fractures, n (%)	65 (44)
Grade 1, n (%)	26 (17.6)
Grade 2, n (%)	32 (21.6)
Grade 3, n (%)	7 (4.8)
Type of fractures in dorsal spine	
Crush, n (%)	48 (32.4)
Biconcave, n (%)	13 (8.8)
Wedge, n (%)	4 (2.7)
Serum irisin levels (ng/mL), mean ± SD	92.7 ± 74
Serum irisin levels (<73 ng/mL), n (%)	77 (52)

Quantitative variables are expressed in means ± SD and qualitative variables in frequencies (%). Reduction of vertebral height by Genant Scale: Grade 1 vertebral reduction of 20%–25%, Grade 2: reduction of vertebra by 25% to 39.9%, Grade 3: vertebral reduction greater than 40%. 50 percentiles of irisin levels: <73 ng/mL.

Most of the RA patients (98%) received synthetic-Disease-Modifying Anti-Rheumatic Drugs (csDMARD) and 12% of the patients used biologic-DMARD. The frequency of corticosteroid use was 80%, and the mean dose was 4.8 ± 3 mg/day and the use of treatment with antiresorptive (Bisphosphonates) was 12%. In the total BMD these patients had a mean of 1.8 g/cm^2, and 37% had Osteopenia and 41% had Osteoporosis (data not shown in table).

In the Table 1 is shown a description of the clinical and laboratory variables and frequency and characteristics of vertebral fractures in RA. The presence of vertebral fractures was observed in 49.3% of patients with RA; however, VFs grades 2 or 3 were observed in 49 RA patients (33.1%).

In the Table S1, Supplemental Digital Content, http://links.lww.com/MD2/A883 is shown a bivariate comparison of selected characteristics between RA and controls. No significant differences were observed in age, smoking, sedentary, menopause, hypertension or history of fragility fractures between RA and controls; the frequency of diabetes mellitus was higher in controls; whereas, RA patients had a higher frequency of VFs and osteoporosis. Serum levels of irisin were lower in RA patients compared to the controls.

Figure 1 shows the number of VFs according to its location in the dorsal and lumbar spine in 148 RA patients. Osteoporotic vertebral fractures were most frequently observed in Thoracic vertebrae: T8 (n = 22), T9 (n = 22), and T7 (n = 19).

In the Table 2 we have shown a univariable comparisons of selected epidemiological and clinical characteristics between RA with and without VFs. The RA + VFs group had a higher disease

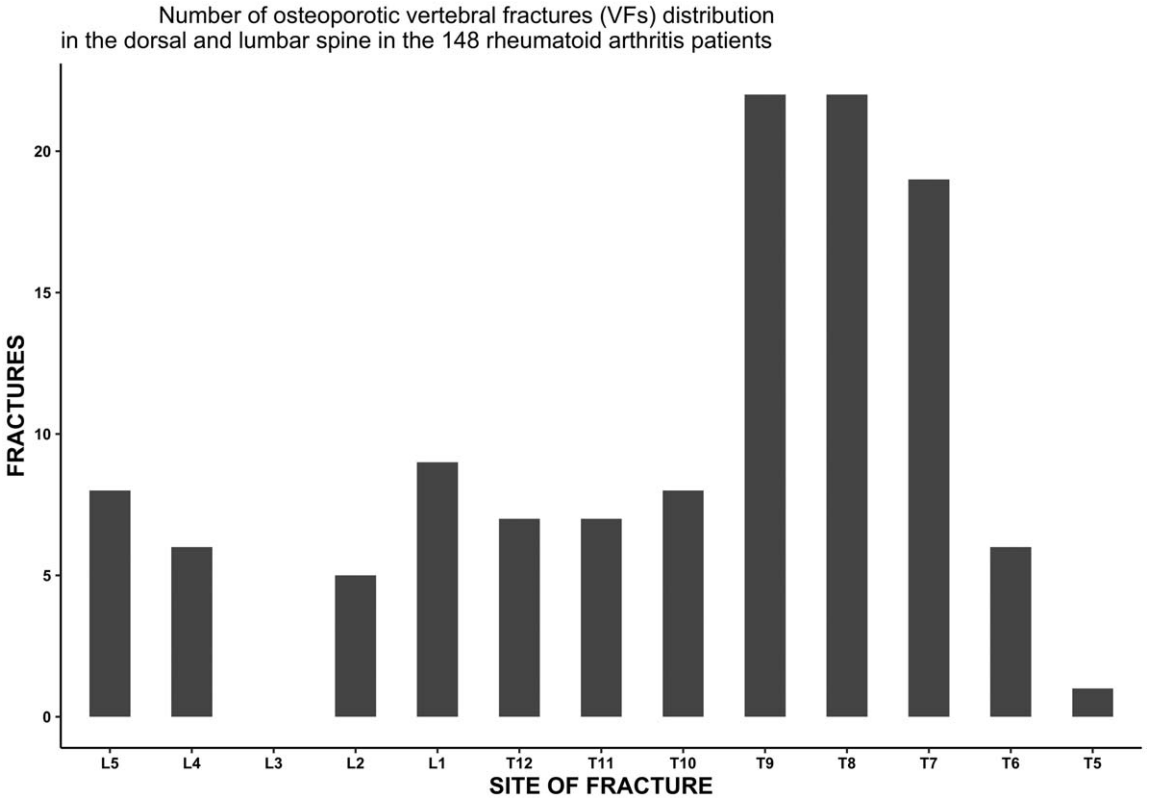

Figure 1. Number of osteoporotic vertebral fractures (VFs) distribution in dorsal and lumbar spine of 148 rheumatoid arthritis patients. Vertical axis represents the number of vertebrae with fractures. Horizontal axis represents the vertebrae evaluated for vertebral fractures.

Table 2

Comparison of selected features between Rheumatoid Arthritis with and without vertebral fractures.

Variables	RA + VFs n = 73	RA without VFs n = 75	*P*
Age (years), mean ± SD	59 ± 10	60 ± 9	.60
Cigarrette smoking, n (%)	6 (8)	6 (8)	.96
Sedentary, n (%)	45 (62)	50 (67)	.52
Menopause, n (%)	62 (85)	68 (91)	.29
Body mass index (kg/m^2), mean ± SD	28 ± 6	26 ± 5	.07
Total BMD (g/cm^2), mean ± SD	1.7 ± 0.3	1.7 ± 0.3	.75
Osteoporosis, n (%)	29 (40)	32 (43)	.67
Clinical characteristics			
Disease duration (years), mean ± SD	15 ± 9	12 ± 9	.13
DAS28-ESR, mean ± SD	3.7 ± 1	3.3 ± 1	.03
HAQ-Di >0.6, n (%)	52 (71)	43 (57)	.08
Treatments			
Synthetic-DMARDs, n (%)	73 (100)	72 (96)	.08
Biologic-DMARDs, n (%)	8 (11)	10 (14)	.64
Corticosteroids, n (%)	61 (84)	57 (77)	.25
Corticosteroids (mg/day), mean ± SD	5 ± 3	4.7 ± 3	.55
Laboratory variables			
RF (+), (>12 mg/dL), n (%)	13 (52)	25 (69)	.45
ESR increased (>22 mg/dL), n (%)	41 (56)	33 (44)	.14
Serum irisin (ng/mL), mean ± SD	74 ± 42	113 ± 92	.001

VFs: vertebral fractures, DAS28: Disease Activity Score of 28 joints, HAQ-DI: Health Assessment Questionnaire-Disability Index, Functional disability: HAQ-DI ≥0.60, DMARDs: Disease-modifying antirheumatic drugs, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate. Comparison of qualitative variables was performed using Chi Square test. Comparison of quantitative variables were made with Student *t* tests, significance was considered at $P < .05$.

activity (DAS28 score) compared to RA without VFs. The serum irisin concentrations were lower in RA + VFs vs RA without VFs. No other variables had statistical differences between RA + VFs vs RA without VFs.

In data that are not depicted in tables, we performed a subanalysis comparing patients with grade 2 or 3 of VFs vs RA patients with VFs grade 1 or non-VFs. In this subanalysis RA patients with grade 2 or 3 VFs had lower levels of irisin (69.7 ± 42.2 vs 105.6 ± 83.0, $P = .001$)

Table 3 shows the results of the multivariable logistic regression analysis evaluating factors associated with vertebral fractures in women with RA. After performing an adjustment by

Table 3

Risk factors of osteoporotic vertebral fractures in women with rheumatoid arthritis.

Risk factors	Forward method (stepwise) OR	95% CI	*P*
Duration of RA (years), mean ± SD	1.04	(1.001–1.08)	.04
Irisin <73 ng/mL	3.10	(1.55–6.20)	.001
Age (years), mean ± SD	Not in the model	–	–
DAS28-ESR score, mean ± SD	Not in the model	–	–
Functional disability	Not in the model	–	–
Body mass index (kg/m^2), mean ± SD	Not in the model	–	–

Multivariate analysis: logistic regression model. Forward method stepwise. Dependent variable: vertebral fractures, adjusted by duration of AR (years), DAS28 score and serum concentrations of irisin <73 ng/mL). (predictor variables); variables excluded: age (years), Functional disability (HAQ-DI≥0.6) and body mass index (kg/m^2), OR: odds ratio, statistical significance $P < .05$.

age, disease duration, BMI, and functional disability; the variables that increase the risk of VFs were a longer disease duration of RA and lower Irisin levels (<73 ng/mL).

4. Discussion

Our results show that more than two thirds of RA patients have low BMD in central region and around a half of these patients have osteoporotic VFs. In this study the osteoporotic VFs were more frequently observed in dorsal region. We identified that lower serum irisin concentrations in RA patients with osteoporotic VFs compared to non-fractures group. In the logistic regression analysis, the low irisin concentrations (<73 ng/mL) were associated with an increased risk of VFs independently of age, disease duration, BMI, and RA disease activity.

Irisin is a myokine that stimulates the browning of white adipose tissue leading to an increase in total body energy expenditure and decreases the obesity-linked insulin-resistance.[25,9] In vitro studies have demonstrated a relation between an increased expression of irisin and the increase on bone formation.[8]

Increasing of irisin expression enhances the osteoblast differentiation mediated by the activation of the canonical Wnt-β catenin, p38 MAPK, and ERK pathways and leads to the reduction of osteoclast differentiation through the suppression of RANKL/NFATc1 pathways.[9,8]

There are some studies that identify low irisin levels in RA compared with controls.[17,26] Our results are concordant with these studies showing lower serum levels of irisin in RA group with respect to our group of women without rheumatic disease.

There is a lack of studies assessing the relation between irisin concentrations and bone fractures in RA. However, in non-rheumatic population studies performed in elderly adults as well as postmenopausal women, a decreased of irisin concentrations have been associated with osteoporotic fractures.[14–16] Yan et al observed in elderly women older than 70 years, that low concentrations of irisin were independently associated with a higher risk of hip fractures as well as with a low BMD.[16] Palermo et al in a group of postmenopausal women observed an association between low irisin levels with VFs, although no association was observed between irisin levels and BMD, lean mass or daily physical activity.[15] On the other hand, Anasrasilakis et al observed in a univariate analysis that lower irisin concentrations were associated with history of osteoporotic fractures in postmenopausal women.[14] Nevertheless, in the adjusted analysis after controlling for confounding variables these authors conclude that irisin did not remain associated with osteoporotic fractures.[14]

Currently there is a few information about the relation between irisin levels in RA with vertebral osteoporotic fractures. Lavrova et al observed in their RA patients that low irisin concentrations were related with osteoporotic fractures in general.[17]

In the best of our knowledge this study is the first to assess the relation between irisin levels and osteoporotic VFs in RA patients. We identified that low irisin concentrations increased the risk of osteoporotic VFs in RA patients. Using an adjusted logistic regression analysis, the risk of osteoporotic VFs was increased 2.7-fold in RA patients with irisin levels below 73 ng/mL. This increased risk of VFs related with low irisin levels was independent from other factors including age, low BMI, longer disease duration of RA, and disease activity. In the best of our knowledge this is the first study that demonstrated an increased risk of VFs in RA patients associated with low irisin levels using a multivariable approach.

There is interesting information demonstrating that the risk of developing osteoporotic VFs in RA is around 6.5-fold the risk of controls.[27] Low BMD is currently considered as one of the major factors related with risk of VFs in RA.[4–6] Although a decrease of BMD is one of the major risk factors for the development of osteoporotic fractures in RA, VFs can be developed inclusive in patients with normal BMD.[5]

We also found that longer disease duration was other variable associated with osteoporotic VFs. These data are consistent with the findings described by other authors where VFs in RA have been associated with older age, persistent inflammation, glucocorticoids, and a longer disease duration.[5,6] Our finding that disease activity is related to osteoporotic VFs, is supported by the concept that high levels of pro-inflammatory cytokines mainly TNF-α and IL-6 might contribute to the activation of the mechanisms of bone resorption.[28]

Our study has the strength of being the first study performed in RA patients that identifies that lower irisin levels are an independent risk factor for osteoporotic vertebral fractures. The present study intends, through the adjustment of confounding factors, to establish the independence of these low irisin level from other known factors associated with the presence of osteoporotic fractures in RA. Among other strengthens of our study, the assessment of vertebral fractures by radiographs and DXA was made by independent researchers that ignore the results of irisin levels, minimizing the expectancy bias. Also, the assessment of vertebral fractures was made by 2 independent researchers and divergences were solved by a third experienced researcher who acts as adjudicator. This strategy limited the inappropriate classification bias.

Although our study is limited because is cross-sectional, since in this design it is not possible to identify causal associations, and we cannot identify when the patients initiate with a decreasing in their irisin levels. We consider that new studies with a longitudinal design are required to assess the temporal relation between the decrease of irisin levels and the incidence of fractures.

Nevertheless, we consider the results of our study as relevant to identify that irisin is a marker of the risk of VFs and its assessment that should be incorporated in further studies in other populations.

5. Conclusions

Low serum levels of irisin are associated with the presence of vertebral fractures in RA. These results indicate the need for longitudinal studies to clarify this association and other clinical outcomes in RA.

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