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ORIGINAL ARTICLE

Low bone mineral density in juvenile idiopathic arthritis: Prevalence and related factors☆

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KEYWORDS
Bone mineral density;
Juvenile idiopathic arthritis;
Low bone mineral density for chronological age;
Body composition;
Bone turnover markers;
Nutritional status

Abstract
Introduction: Height adjustment is currently recommended for *Z*-score bone mineral density (BMD) assessed by dual energy X-ray absorptiometry.

At present there are no studies that evaluate the prevalence of low BMD in paediatric patients with juvenile idiopathic arthritis (JIA) in Spain following current recommendations.
Objectives: To evaluate low BMD in JIA in paediatric patients with JIA in Spain following the latest recommendations, as well as to assess associated factors.
Methods: Observational cross-sectional study of Spanish JIA patients from 5 to 16 years-old, followed-up in a Paediatric Rheumatology Unit between July 2014 and July 2015.

Anthropometric, clinical and treatment data were recorded. Dual energy X-ray absorptiometry, and bone metabolism parameters were collected, and a completed diet and exercise questionnaire was obtained.
Results: A total of 92 children participated. The population prevalence estimation of low BMD was less than 5% (95% CI).

A significant positive correlation was found in the multiple linear regression analysis between the body mass index percentile (*B*: 0.021; $P < .001$) and lean mass index (*B*: 0.0002; $P = .012$), and BMD *Z*-score adjusted for height (*Z*-SAH). A significant negative correlation was found between fat mass index (*B*: −0.0001; $P = .018$) and serum type I collagen N-propeptide (*B*: −0.0006; $P = .036$) and *Z*-SAH.

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Conclusions: Low BMD prevalence in JIA patients in our population is low.

An adequate nutritional status and the prevalence of lean over fat mass seem to promote the acquisition of bone mass. Those JIA patients with lower BMD could be subjected to an increase of bone turnover.

PALABRAS CLAVE
Densidad mineral ósea;
Artritis idiopática juvenil;
Baja densidad mineral ósea para la edad cronológica;
Composición corporal;
Marcadores del metabolismo óseo;
Estado nutricional

Baja densidad mineral ósea en artritis idiopática juvenil: prevalencia y factores relacionados

Resumen

Introducción: Actualmente se recomienda ajustar por talla el Z-score densidad mineral ósea obtenido mediante absorciometría de rayos X de doble energía en pediatría. No hay estudios en nuestro medio que evalúen la prevalencia de baja densidad mineral ósea para la edad cronológica (BDMOec) en niños con artritis idiopática juvenil (AIJ) siguiendo estas recomendaciones.

Objetivos: Estimar la prevalencia de BDMOec en niños con AIJ en nuestro medio y evaluar los factores implicados en su desarrollo.

Métodos: Estudio observacional, transversal, en españoles niños de 5-16 años con AIJ, en seguimiento por una unidad de reumatología pediátrica entre julio de 2014 y julio de 2015.

Se recogieron datos antropométricos, clínicos y de tratamiento. Se realizaron absorciometría de rayos X de doble energía, estudio metabólico óseo y encuestas sobre dieta y ejercicio.

Resultados: Participaron 92 niños. La estimación de la prevalencia poblacional de BDMOec fue inferior al 5% (IC 95%).

En el análisis multivariante el percentil de índice de masa corporal (B: 0,021; $p < 0,001$) y el índice de masa magra (B: 0,0002; $p = 0,012$) presentaron relación positiva con el Z-score de DMO ajustado por talla, mientras que el índice de masa grasa (B: −0,0001; $p = 0,018$) y el propéptido aminoterminal del colágeno tipo I (B: −0,0006; $p = 0,036$) presentaron correlaciones negativas.

Conclusiones: La prevalencia de BDMOec en los niños con AIJ en nuestro medio es baja. Un adecuado estado nutritivo y el predominio de la masa magra sobre la grasa podrían favorecer la adquisición de masa ósea. Aquellos pacientes con AIJ con DMO más baja podrían estar sometidos a un aumento del remodelado óseo.

Introduction

Osteoporosis, which traditionally has been considered an adult disease, is an increasingly prevalent disease in children due to the increased life expectancy of paediatric patients with chronic diseases and the use of osteotoxic drugs, among other factors.[1]

Dual-energy X ray absorptiometry (DXA) of the lumbar spine or the whole body is the gold standard for the measurement of bone mineral density (BMD) in the paediatric age group, as recommended by the International Society for Clinical Densitometry (ISCD) in 2007.[2] The assessment of BMD through this technique uses the *Z*-score, which expresses the number of standard deviations (SDs) that the patient's BMD deviates from the mean BMD of healthy controls of the same age and sex.[2] Many authors have also expressed the need to adjust the *Z*-score for height for a more accurate assessment,[3] and the updated 2013 recommendations of the ISCD called for doing so in children with short stature.[4]

Zemel et al. proposed a formula for the adjustment of the BMD *Z*-score (*Z*-BMD) for height that has been validated in healthy children, which eliminates the height bias from the *Z*-BMD. The authors claim that this adjustment should be performed in every child.[3]

In patients with juvenile idiopathic arthritis (JIA), as happens in other children with chronic diseases, bone accrual may be inhibited by direct and indirect mechanisms.[5]

Establishing the prevalence of osteoporosis and low BMD for chronological age (LBMDca) in this group of patients is not easy, as most of the studies published in the literature did not use current definitions,[6,7] and none were performed in the Spanish population.

In respect of the factors involved in the development of osteoporosis and LBMDca in this group of patients, the prevailing hypothesis is that of a multifactorial aetiology that would include the inflammatory activity of the disease, the drugs used for its treatment and a low level of physical activity.[5,8] However, the data on the role of some of these factors are inconsistent.

The data are also contradictory as regards the primary pathophysiological process involved in its development. While some authors defend that it is caused by an increase in bone turnover,[9] most support the hypothesis that bone turnover is actually inhibited.[10,11] The difficulty in reaching conclusions can be explained in part by the broad range of born turnover markers that are currently used. As a consequence, several collectives have recommended narrowing down these markers, and proposed the use of procollagen type I N-terminal propeptide (P1NP) and C-terminal telopeptide of type I collagen (CTx) as the reference markers to be used in every clinical trial and observational study on osteoporosis.[12,13]

The primary objective of our study was to estimate the prevalence of LBMDca in children with JIA in Spain following the latest recommendations of the de la ISCD. As a secondary objective, we decided to study the association between different factors, including bone turnover markers, and BMD in this group of patients.

Patients and methods

We conducted a cross-sectional observational study in Caucasian children aged 5–16 years with a JIA diagnosis (based on the classification of the International League of Associations for Rheumatology [ILAR]; Edmonton, 2001) followed up in a paediatric rheumatology unit between July 2014 and July 2015. We excluded patients with monoarticular forms of JIA or receiving concomitant osteotoxic treatments that had not been prescribed for JIA.

After obtaining informed consent, we collected data on anthropometric, sexual maturation, clinical and treatment variables. Furthermore, patients underwent a DXA scan (Hologic Explorer densitometer S/N 91625) with assessment of bone mass, fat mass and lean mass, as well as a bone metabolism workup that included measurement of plasma concentrations of calcium, phosphorus, magnesium, intact parathyroid hormone, P1NP, CTx and 25-hydroxyvitamin D_3. Blood samples were collected first thing in the morning following a fast of at least 6 h.

We estimated daily calcium intake by means of a food frequency survey that assessed intake in the week before the DXA scan. The estimate took into account the calcium supplements taken by some of the patients.

We measured physical activity by means of the *Physical Activity Questionnaire for Children* in children aged less than 12 years,[14] and the *Physical Activity Questionnaire for Adolescents* in those aged more than 12 years,[15] both of which have been validated and are scored on a scale of 1 through 5.

The study was approved by the clinical research ethics committee of our hospital.

Definitions

We defined short stature as a height more than 2 standard deviations below the mean for age and sex.

We recorded the Tanner stage of each participant to assess sexual maturation. For the purpose of the multivariate analysis, we classified patients by level of sexual maturation, with the prepubertal category including Tanner stages III and lower, and the pubertal category including Tanner stages IV and V.

We defined moderate hypovitaminosis D as a plasma concentration of 25-hydroxyvitamin D_3 between 15 and 20 ng/mL and severe hypovitaminosis D as a plasma concentration of less than 15 ng/mL.[16]

We defined the variable ''duration of disease activity'' as the time elapsed since the patient ceased to meet the criteria of the American College of Rheumatology for ''clinical inactive disease''.[17] Furthermore, and following the recommendations of the same organisation, we defined ''remission on medication'' to inactivity lasting at least 6 months while receiving pharmacological treatment, and ''remission off medication'' as inactivity lasting at least 12 months after discontinuation of pharmacological treatment.

We defined osteoporosis according to the 2013 ISCD criteria[4]: *Z*-BMD (adjusted for height only in children with short stature) of less than −2 with a clinically significant fracture history, understood as 2 or more long bone fractures before age 10 years, 3 or more long bone fractures before age 19 years, or a vertebral compression fracture.

We defined the condition of patients that had a *Z*-BMD of less than −2 in the absence of a clinically significant fracture history as LBMDca.

We calculated the height-adjusted BMD *Z*-score (*Z*-SAH) using the formula proposed by Zemel et al.[3]

Statistical analysis

We performed a descriptive analysis of the main variables. We checked whether continuous variables were normally distributed by means of the Kolmogorov–Smirnov test.

Hypothesis testing was conducted by means of the Student *t* test, one-way ANOVA, the Mann–Whitney *U* test and the Kruskal–Wallis *H* test, as applicable.

We assessed the association between different quantitative variables using two-tailed Pearson and Spearman correlation tests.

Lastly, we built a multivariate logistic model including variables with significant correlations in the bivariate analysis, as well as variables considered a priori to be possibly associated with BMD based on clinical criteria (Table 1). We evaluated the linearity of continuous variables by means of the Box–Tidwell test, and assessed potential interactions of puberty with the body mass index (BMI) percentile, the lean mass index (LMI) and fat mass index (FMI), as well as the association of the BMI percentile with the LMI and the FMI, and the association of the LMI with the FMI. We assessed puberty and JIA subtype as potential confounding variables. We kept these variables in the model because they were associated with changes of more than 20%.in the regression coefficients of some of the model variables.

We used the coefficient of determination (R^2) to assess the goodness of fit.

We calculated the magnitude of the association between the independent variables and the dependent variable in the model by means of regression coefficients with their corresponding 95% confidence intervals (CIs).

Table 1 Variables included in the multivariate regression model.

Sex
Age
Pubertal (yes/no)
BMI percentile
FMI
LMI
Daily calcium intake
Level of physical activity
JIA subtype
Time elapsed since onset of disease
Duration of clinical activity of disease
Plasma concentration of P1NP
Plasma concentration of 25-hidroxyvitamin D_3
Treatment with systemic glucocorticoids (yes/no)
Mean dose of prednisone per kg of body weight since birth
Treatment with synthetic DMARDs (yes/no)
Treatment with biologic DMARDs (yes/no)

BMI, body mass index; DMARD, disease-modifying antirheumatic drug; FMI, fat mass index; JIA, juvenile idiopathic arthritis; LMI, lean mass index; P1NP, procollagen type I N-terminal propeptide.

Results

The study included 92 children whose characteristics are summarised in Tables 2 and 3. None of the patients met the criteria for osteoporosis.

When we adjusted the *Z*-BMD for height in only patients with short stature, as recommended by the ISCD, our estimate of the population prevalence of LBMDca was of less than 5% (95% CI). We found a positive correction between the *Z*-BMD and the height *Z*-score (R, 0.39; $P < .05$).

When we adjusted the Z-BMD for height in all patients, the estimated population prevalence of LBMDca was of less than 3% (95% CI). In this analysis, we did not find a correlation with height.

In the bivariate analysis, we found that the *Z*-SAH was positively correlated to the BMI percentile (ρ, 0.512; $P < .001$), the LMI (Pearson r, 0.367; $P < .001$) and the FMI (ρ, 0.23; $P = .027$). We also found a negative correlation that was on the verge of statistical significance with the plasma concentration of P1NP (Pearson r, −0.195; $P = .07$) and the duration of disease activity (ρ, −0.191; $P = .07$). We did not find an association between the *Z*-SAH and calcium intake, physical activity, serum vitamin D, duration of disease activity, duration or dose of systemic glucocorticoid treatment, or treatment with synthetic or biologic disease-modifying antirheumatic drugs. We did not find significant differences between different JIA subtypes.

When we performed the multivariate linear regression analysis, we obtained a model with an R^2 of 0.374 that included the BMI percentile, LMI, FMI and P1NP as variables with a statistically significant correlation to the *Z*-SAH (Table 4). The interactions that we analysed were not statistically significant.

Table 2 Patient, disease and treatment characteristics.

Patient characteristics ($n = 92$)	
Sex (male), n (%)	33 (35.8)
Age (years), median (IQR)	11.42 (8.58–13.67)
Tanner stage, n (%)	
I	42 (45.7)
II	12 (13)
III	11 (12)
IV	17 (18.5)
V	10 (10.9)
Calcium intake (mg/day), median (IQR)	1085 (830–1150)
Level of physical activity, mean (±SD)	2.7 (0.64)
BMI percentile, median (IQR)	32 (17.75–65.00)
Obesity, n (%)	7 (7.6)
Short stature, n (%)	1 (1.1)
Disease characteristics ($n = 92$)	
Type of IJA, n (%)	
Systemic	10 (10.9)
Oligoarticular-persistent	40 (43.5)
Oligoarticular-extended	13 (14.1)
Polyarticular	22 (23.9)
Enthesitis-related	5 (5.4)
Psoriatic	2 (2.2)
Time since onset of JIA (years), median (IQR)	6.12 (3.22–9.10)
Duration of JIA activity (days), median (IQR)	363.58 (231.00–752.00)
Activity, n (%)	
Remission/inactivity off medication	21 (22.8)
Remission/inactivity on medication	46 (50)
Active disease	25 (27.1)
Received treatment ($n = 92$)	
Systemic GC, n (%)	84 (91.3)
Duration of GC therapy (days), median (IQR)[a] *($n = 84$)*	117.50 (51.25–159.75)
Mean GC dose (mg/kg/day of treatment), median (IQR)[a] *($n = 84$)*	0.33 (0.20–1.53)
Mean dose GC therapy (mg/kg/day of life), median (IQR)[a] *($n = 84$)*	0.0066 (0.0028–0.023)
Synthetic DMARD therapy, n (%)	
Current	42 (45.7)
Past[b]	89 (96.7)
Biologic DMARD therapy, n (%)	
Current	29 (31.5)
Past[b]	42 (45.7)

BMI, body mass index; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; IQR, interquartile range; SD, standard deviation.

[a] Refers to the group of patients that had received systemic GC therapy at some point during the course of disease.

[b] Treatments received through the course of the disease.

Table 3 Descriptive analysis of laboratory parameters of bone metabolism and body composition.

Body composition	
Height-adjusted *Z*-score, mean (±SD)	0.04 (0.94)
LBMDca, *n* (%)	2 (2.2)
LMI (g/m^2), mean (±SD)	12.531 (1.668)
FMI (g/m^2), median (IQR)	4.430 (2.810–6.636)
Laboratory parameters of bone metabolism	
Total calcium (mg/dL), median (IQR)	9.7 (9.3–10)
Phosphorus (mg/dL), median (IQR)	4.5 (4.2–4.8)
Magnesium (mg/dL), median (IQR)	1.9 (1.8–2.1)
iPTH (pg/mL), median (IQR)	35 (25–44.5)
P1NP(ng/mL), mean (±SD)	558.9 (282.5)
CTx (ng/mL), median (IQR)	1.2 (1–1.5)
25-hydroxyvitamin D_3 (ng/mL), mean (±SD)	33.7 (9.2)
Hypovitaminosis D, *n* (%)	32 (34.8)

CTx, C-terminal telopeptide of type I collagen; FMI, fat mass index; iPTH, intact parathyroid hormone; LBMDca, low bone mineral density for chronological age; LMI, lean mass index; P1NP, procollagen type I N-terminal propeptide.

Discussion

Although in 2007 the ISCD recommended a DXA scan of the lumbar spine or the whole body as the gold standard for the measurement of BMD in children and adolescents,[2] subsequent studies demonstrated the limitations of this approach.[3] This technique takes two-dimensional measures of a three-dimensional reality. Since it does not take into account bone depth, it underestimates BMD in children with shorter statures (smaller bones) and overestimates it in taller children (larger bones).[3]

As a consequence, in 2013 the ISCD recommended adjusting the BMD *Z*-score for height in children with short stature.[4]

Zemel et al. proposed a mathematical formula validated in a sample of healthy children to eliminate the height bias in the BMD *Z*-score.[3] This is the formula that we have used in our study to adjust the *Z*-BMD.

These authors proposed that the least biased adjustment of the BMD *Z*-score would be one that would make the score independent of height,[3] which we achieved in our study by adjusting it for height in every participant, and not only in those with short stature, as suggested in the latest recommendations of the ISCD.[4] Thus, for the purposes of the study, we thought it would be appropriate to adjust the *Z*-BMD for height in every patient before assessing its association to any other parameter.

With regard to the prevalence of osteoporosis and LBMDca in patients with JIA, it is difficult to reach conclusions based on the existing literature, as most studies were published prior to 2007,[18,19] the year that the ISCD redefined the concept of osteoporosis in children.[2] There are also studies conducted at a later date,[6,7,20] but which did not adjust the BMD *Z*-scores for height as recommended by the ISCD.[4] At any rate, the results of these studies are highly inconsistent as to the prevalence of LBMDca. Among them, we find the 2.5% reported for Finnish youth,[6] the 11.5% reported by Dey et al.[20] in a study of Indian children, and the 33% described by El Badri et al.[7] in the paediatric population of Morocco. The results of our study are consistent with those of the first article just mentioned, and diverges significantly from the results found in Indian and Moroccan children. Differences in nutritional status and unequal access to therapeutic resources may explain these variations.

In our study, the BMI percentile was directly proportional to the *Z*-SAH, independent of the FMI and the LMI. This association between BMI and BMD has already been reported in

Table 4 Multivariate model.

Variable	Unstandardised coefficient (95% CI)	Standardised coefficient	*P*
BMI percentile	0.021 (0.01 to 0.033)	0.666	<.001
LMI (g/m^2)	0.000167 (0.000038 to 0.000297)	0.302	.012
FMI (g/m^2)	−0.000120 (−0.00022 to −0.000021)	−0.405	.018
P1NP (ng/mL)	−0.000647 (−0.001253 to −0.000042)	−0.193	.036
Pubertal (yes/no)	−0.386 (−0.833 to 0.061)	−0.19	.09
JIA subtype			
D_1[a]	0.036 (−0.528 to 0.6)	0.012	.9
D_2[b]	−0.014 (−0.377 to 0.349)	−0.007	.939
D_3[c]	−0.516 (−1.206 to 0.175)	−0.149	.141
Constant	−1.761 (−3.315 to −0.208)		.027

Adjusted coefficient of determination (R^2): 0.374 F = 7.42 (P < .001).
BMI, body mass index; JIA, juvenile idiopathic arthritis; FMI, fat mass index; LMI, lean mass index; P1NP, procollagen type I N-terminal propeptide.
[a] D_1: systemic vs not systemic.
[b] D_2: oligoarticular-extended or polyarticular, vs not oligoarticular-extended or polyarticular.
[c] D_3: enthesitis-related and psoriatic vs not enthesitis-related or psoriatic.

previous studies of patients with JIA,[21] which indicates that an adequate nutritional status has a positive impact on bone accrual.

As for the role played by body composition in bone formation, multiple studies have demonstrated that lean mass is positively correlated to BMD,[7,22] as we found in our study. However, the impact of fat mass on bone health remains the subject of controversy. Although most studies to date seem to indicate a positive effect of the FMI on BMD,[23,24] we have also found studies that did not find any association[7,22] and yet others that claim that fat has a negative effect on bone,[25] which is consistent with our own findings. Although our study did not find an association between physical activity and BMD, the negative correlation with fat mass could be indirect evidence of such an association, as patients who are more physically active tend to have more lean mass and less fat mass.[26]

Bone turnover markers reflect the status of bone metabolism at a given time.[27] Several studies have analysed these markers in an attempt to determine whether the reduced BMD in children with JIA and adults with rheumatoid arthritis is due to an increase or an inhibition in bone turnover, and their findings have been contradictory.[9,10] Although these markers have proven useful in other diseases,[28,29] the lack of data on the use of these markers in osteoporosis precludes their inclusion in fracture risk algorithms,[30] so they should not be used to estimate this risk.

One of the reasons for the difficulty in reaching conclusions on the usefulness of these markers in osteoporosis is that different studies use different markers. As a result, the Bone Marker Standards Working Group of the International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine[12] and the National Bone Health Alliance of the United States[13] have recommended that P1NP and CTx be the markers used in all studies on osteoporosis.

The correct interpretation of these markers also requires to take the considerable intraindividual variability into account that results from circadian rhythms and food intake, so it is important to control fasting and the timing of sample collection to minimise the effects of this variability,[31] as we did in our study.

Following all of these recommendations, our results showed that the levels of P1NP (the bone formation marker) correlated negatively to the *Z*-SAH, which supports the hypothesis that increased bone turnover is responsible for the reduced BMD observed in this group of patients.

Although we did not find an association between the height-adjusted *Z*-BMD and the duration of active disease, multiple studies have demonstrated that proinflammatory cytokines that are present in the context of active disease in these patients can stimulate osteoclastogenesis and promote the development of osteoporosis.[32,33] Our results are probably due to the small sample size and the short time elapsed from the onset of disease in our cohort, which do not suffice for these effects to be manifest.

We also found no association between the dose, duration or age at initiation of treatment with systemic glucocorticoids and the *Z*-SAH. Although they have been described as risk factors for osteoporosis in the classical literature,[34] their effects in children with JIA are not clear. Several studies have not found an association between any variable related to glucocorticoid therapy and BMD in children with JIA,[35,36] and some authors have even proposed that the reduction in inflammatory activity achieved by these agents could have a positive effect on BMD.[37]

With reference to the effects of diet and exercise, we did not find evidence of them having an impact on BMD. Although some studies have found an association between them,[20] many others obtained results that are consistent with our findings,[36] probably due to the difficulty in assessing these variables accurately and to small sample sizes.

We also found no association with the maintenance treatment received by patients—neither biological nor synthetic disease-modifying antirheumatic drugs. There is evidence from longitudinal studies on an osteoprotective effect of some of these drugs, such as anti-TNF therapy.[38] However, a cross-sectional design like the one used in our study cannot establish this type of association.

On the other hand, we did not find statistically significant differences in BMD between the different JIA subgroups, something that has already been reported by multiple studies.[39,40] This is probably due to the small number of patients included in some of the subgroups, as well as the adequate control of disease activity that was achieved in our sample, especially in patients with systemic disease, which is the form that, in principle, carries a higher risk.

One of the limitations of our study is that we did not analyse sunlight exposure in our patients, as this factor has an impact on BMD. Furthermore, we obtained the data on nutrition and physical activity retrospectively by asking patients and their families about what had been done the previous week, which may have resulted in the loss of relevant data. On the other hand, while we took into account any calcium supplements that had been consumed in the week prior to performance of the study protocol in our calculation of the daily intake, we were unable to include calcium and/or vitamin D supplementation through the entire course of the disease in our analysis because the documentation regarding these supplements in the health records is vague, and often did not include dosage or duration. It is also important that we consider that, having excluded patients with monoarticular disease, we may have overestimated the prevalence of LBMDca in Spanish children with JIA; however, we needed to make this exception to avoid the inclusion in the study of children with monoarticular arthritis of a different aetiology. Last of all, since we conducted a cross-sectional study, we were unable to establish causality, so further research is needed to confirm the associations found in it.

In conclusion, the prevalence of LBMDca in Spanish children with JIA is low. In our study, the factors associated most strongly with BMD were nutritional status and body composition, with BMD being positively correlated with lean mass and negatively correlated with fat mass. We found an inverse correlation between P1NP levels and the height-adjusted BMD *Z*-score, which suggests an increase in bone turnover in patients with lower BMD values. For all the above reasons, we consider that we should promote healthy lifestyles, not only in ill children but also in healthy ones, with maintenance of an adequate nutritional status through a varied and balanced diet and the promotion of physical activity,

which not only enhances cardiovascular health, as has been known for a long while, but also bone health.

Conflict of interests

The authors have no conflict of interests to declare.

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