Effect of Inflammatory Activity and Glucorticoid Use on Nutritional Variables in Patients with Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To assess nutritional status in patients with juvenile idiopathic arthritis (JIA) and the influence of inflammatory activity and glucocorticoid use.

Methods. One hundred sixteen patients were evaluated. Disease subtype and disease activity were defined by the attending physician, and the cumulative glucocorticoid dose was recorded from chart review. Percentiles of body mass index (BMI) and triceps skinfold (TSF) and the Z score for height were determined: low weight and low adiposity were diagnosed when BMI and TSF were below the 5th percentile. Short stature was defined by a Z score of height for age < –2. Serum concentration of insulin-like growth factor-I (IGF-I) was measured by radioimmunoassay.

Results. The prevalences of low weight, low adiposity, and short stature were 16.4%, 20.7%, and 10.4%, respectively. Low IGF-I serum level was found in 14 patients (12.1%). The factors negatively associated with the Z score of height in multivariable regression analysis were disease duration (partial correlation coefficient –0.370, 95% confidence interval: –0.527 to –0.188; $p < 0.001$), erythrocyte sedimentation rate (ESR) (–0.357, –0.516 to –0.174; $p < 0.001$), and polyarticular or systemic disease subtype (–0.290, –0.459 to –0.100; $p = 0.003$), while there was no significant correlation with the cumulative dose of glucocorticoids (0.086, –0.111 to 0.277; $p = 0.391$). None of these variables was significantly correlated with the percentiles of BMI and TSF, albeit confidence intervals for these correlation coefficients were relatively large. Patients with a systemic or polyarticular disease subtype tended to present lower percentiles of BMI ($p = 0.051$).

Conclusion. Nutritional status is frequently compromised in patients with JIA. Duration and disease subtype and the ESR are factors independently associated with short stature. The cumulative dose of glucocorticoids was not independently associated with short stature or with other nutritional variables, although a relevant negative effect of glucocorticoid dose on BMI and TSF cannot be entirely excluded. (J Rheumatol 2006;33:601–8)

Key Indexing Terms:
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Juvenile idiopathic arthritis (JIA) is the most common chronic arthritis in childhood[1]. Involvement of nutritional status (anthropometric and biochemical) has often been reported in this disease. Among the anthropometric variable abnormalities observed in JIA, previous studies suggest that the prevalence of low weight is between 4.0% and 46.6%[2-5] and that the prevalence of short stature is between 10.0% and 41.0%[4,6-12]. Possible causes for these abnormalities include anorexia[2], food restrictions[13], nutrient malabsorption[14], increased catabolism and energy requirement[15], limitation of physical activities[16], reduced vitamin D absorption[17], reduced growth hormone secretion[6], and treatment with glucocorticoids[7].

Among the biochemical markers of nutritional state, lower serum concentrations of albumin, iron, and insulin-like growth factor-I (IGF-I) are often observed in JIA[4]. Serum levels of IGF-I, which is considered the best nitrogen balance marker and is the effector agent of growth hormone[18], are often reduced and are associated with short stature in patients with JIA[4,6,19].

Several clinical features have been associated with nutritional involvement: duration and activity of the disease[4,6,8,12,15], reduced dietary intake[2], systemic or polyarticular subtype of disease[4,5,8,12,20], and the use of glucocorticoids. However, there are discordant reports concerning the associa-

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tion of the use of glucocorticoids with reduced stature, with some studies showing a relevant association[4,7,12,19,21,22] and others with negative results[5,6,8,20].

Considering these divergent data in the literature, our objective was to study the prevalence of low nutritional status in a group of patients with JIA, as well as the influence of inflammatory activity and glucocorticoid use.

MATERIALS AND METHODS

Patients. The study was performed at the Rheumatology Outpatient Clinic at Hospital de Clínicas de Porto Alegre. All available patients referred from 3 clinical centers treating children with rheumatism in the city of Porto Alegre were recruited consecutively. One hundred sixteen patients (74 female, 42 male, aged 2 to under 20 yrs) fulfilled the current diagnostic criteria for JIA[23]. Exclusion criteria were the presence of other chronic diseases or the impossibility of performing the anthropometric measures.

Clinical assessment. After recruitment, the patients were submitted to a standardized interview assessing disease characteristics, use of medication, anthropometric measures, and family income. The presence of disease activity was determined through clinical assessment by pediatric rheumatologists. The disease was considered active when the clinical assessment indicated the presence of inflammation in one or more joints. The cumulative dose of glucocorticoid was recorded as the equivalent dose of prednisone (mg). Involvement of the temporomandibular joint (TMJ) was diagnosed by the presence of associated symptoms and radiographic evaluation (plain radiograph and computerized tomography scan), when necessary.

Anthropometric variables. The anthropometric data were measured according to the World Health Organization (WHO) standards and always by the same researcher (LS). Weight was measured on a Filizola scale, with 10-gram graduation; the patients were barefoot and wearing a standard gown. Stature was measured with a stadiometer; the patients were barefoot, standing with their feet together, heels against the wall, and the height reading was rounded to the closest 0.5 cm[24]. The Z score for height was calculated according the reference standard of the US National Center for Health Statistics (NCHS)[25] and used to classify short stature as moderate (Z score < -2 and ≥ -3) or severe (Z score < -3)[24]. The body mass index (BMI) was calculated using the weight/square of height formula and was compared with reference values of the curves of BMI percentiles for children developed by the NCHS in collaboration with the US Centers for Disease Control and Prevention (CDC)[24,25]. Percentiles obtained in this manner were classified according to the WHO scale (low weight: values below the 5th percentile; eutrophy between the 5th and 85th percentiles; and overweight above 85th percentile)[24]. The triceps skinfold (TSF) was measured on the posterior side of the nondominant arm, in the middle of the line that connects the acromion to the olecranon. Measurements were performed 3 consecutive times, and the result obtained was the mean of measurements. A scientific plicometer (Cescorf, Porto Alegre, Brazil), with a precision of 0.1 mm, was used for measurement. Results were compared to tables distributed in percentiles[26]. According to the WHO[24], values below the 5th percentile represent low adiposity; values between 5 and 90 represent normality; values above 90th percentile represent high adiposity.

Biochemical variables. Venous blood samples were collected on the same day as the clinical evaluation for complete blood count, erythrocyte sedimentation rate (ESR), albumin, and total calcium measurements. Serum aliquots obtained after centrifugation were frozen at –80°C until testing of IGF-I levels, which was performed using a 2-site immunoradiometric assay (IRMA)[27] (IRMA Active IGF-I DSL-5600 test kit; Diagnostic System Laboratories, Webster, TX, USA); this included a simple extraction stage in which IGF-I is separated from its conjugated proteins in the serum. The acid/ethanol extraction, neutralization, and analysis were performed in a single assay. IGF-I levels are expressed in ng/ml. The Z score of IGF-I for each patient was determined using reference values for age and sex, as described by the manufacturer. Patients with a Z score < -2 were considered to have a low IGF-I concentration. Anemia was defined according to the hemoglobin cutoff values for age and sex suggested by the CDC[28]. The total lymphocyte count was considered low when $< 1500/mm^3$. Reference values for serum albumin were 3.5–4.8 g/dl and for total calcium 8.6–10 g/dl.

Informed consent was obtained from each patient, parents, or legal guardian. The study was approved by the Ethics in Research Committee at Hospital de Clínicas de Porto Alegre.

Statistical analysis. Data were analyzed using Epi-Info v. 6[29] and SPSS for Windows v. 11.0[30]. Categorical variables were presented as numbers and proportions. Quantitative variables were tested graphically (with normal probability plots) and statistically (Kolmogorov-Smirnov goodness-of-fit test) for normality of distribution. Variables with a normal distribution were presented as mean and standard deviation (SD), and between-group comparisons were performed using Student t test or analysis of variance (ANOVA) with Tukey's test. Non-normal quantitative variables were presented as median plus 25th/75th percentiles, and between-group comparisons were performed using the Mann-Whitney or Kruskal-Wallis test. Pearson (r_p) and Spearman (r_s) correlation coefficients, along with 95% confidence intervals, were used to test for correlations involving normal and non-normal continuous variables, respectively. The association between categorical variables was tested using the chi-square test and Fisher's exact test. Values of $p < 0.05$ (2 tailed) were considered statistically significant.

To evaluate the association of clinical variables with the Z score of stature a multivariable linear regression model was prepared. The selection of independent variables to the model was based on the capacity of the variable to represent a specific aspect of the disease (no automatic method of variable selection was used). The assumptions of the regression model were assessed by Kolmogorov-Smirnov test for normality of residuals, White's test for heteroscedasticity, the evaluation of variance inflation factors (VIF) for detection of collinearity, and tests for nonlinear associations with the aid of the Gretl software[31]. Residual analysis was performed to detect Y-dimension outliers, which were defined as cases with studentized deleted residuals with absolute values > 3.0. Evaluation for the presence X-dimension outliers was performed analyzing the leverage values (a value > 2p/n was considered high, where n is the number of cases and p is the number of parameters being estimated). Highly influential cases were identified as those with Cook's distances > 4/(n – k – 1), where k is the number of independent variables. The logarithmic transformation of independent variables was tried before exclusion of the case when an extreme outlier was detected. Partial correlation coefficients (partial r) and 95% CI were estimated for independent variables included in the model.

RESULTS

Demographic and clinical characteristics of patients are described in Table 1. Females, Caucasians, and the polyarticular form of the disease predominated. Patients with the polyarticular and systemic forms of JIA presented a higher prevalence of current use and larger cumulative dose of glucocorticoids.

Table 2 gives the anthropometric characteristics (according to WHO criteria) in the sample. The general prevalences of low weight and low adiposity identified by BMI and TSF were 16.4% and 20.7%, respectively. Short stature was present in 10.4% of the patients. Patients with polyarticular JIA presented the highest prevalence of low weight according to BMI (24.5%).

Comparison of biochemical variables by disease subtype is shown in Table 3. Higher prevalences of anemia and lymphopenia were observed in the polyarticular and systemic forms of the disease, although the differences were not statistically significant. The calcium level was lower in the poly-

Table 1. Demographic and clinical characteristics of patients by disease subtype.

	Oligoarticular, n = 48	Polyarticular, n = 53	Systemic, n = 12	Psoriatic, n = 3	Total, n = 116
Female, n (%)	30 (62.5)	36 (67.9)	5 (41.7)	3 (100)	74 (63.8)
Caucasians, n (%)	42 (87.5)	46 (86.8)	11 (91.7)	2 (66.7)	101 (87.1)
Age, yrs, mean (SD)	10.1 (4.1)	11.7 (4.1)	11.0 (3.7)	12.4 (6.5)	11.0 (4.1)
Age at disease onset, yrs, median	4.0	5.0	4.5	10.0	5.0
(25th, 75th percentile)	(2.0, 7.4)	(2.5, 8.0)	(3.6, 6.7)	(4.0, 11.0)	(2.2, 8.0)
Active disease, n (%)	24 (50.0)	35 (66.0)	5 (41.7)	2 (66.7)	66 (56.9)
Duration of disease, yrs, median	4.5	5.4	4.7	3.7	4.7
(25th, 75th percentile)	(3.0, 6.6)	(2.6, 9.1)	(2.3, 8.2)	(1.3, 8.1)	(2.7, 8.3)
Current corticosteroid therapy, n (%)	14 (29.2)	32 (60.4)	7 (58.3)	1 (33.3)	54 (46.6)
Cumulative dose of glucocorticoids,	400	1800	1687.5	900	1420
mg*, median (25th, 75th percentile)	(0.0, 1800)	(630, 3150)	(281, 4342.5)	(0.0, 1725)	(70.0, 2657.5)

* Equivalent to dose of prednisone.

Table 2. Patients' classification of body mass index (BMI), triceps skinfold (TSF), and stature according to the World Health Organization. Values represent number (%). Percentages are calculated on the total number of patients in each disease subtype.

	Oligoarticular, n = 48	Polyarticular, n = 53	Systemic, n = 12	Psoriatic, n = 3	Total, n = 116
BMI					
Low weight	5 (10.4)	13 (24.5)	1 (8.3)	0 (0.0)	19 (16.4)
Eutrophy	26 (54.2)	31 (58.5)	10 (83.3)	3 (100)	70 (60.3)
Overweight	17 (35.4)	9 (17.0)	1 (8.3)	0 (0.0)	27 (23.3)
TSF					
Low adiposity	8 (16.7)	12 (22.6)	3 (25.0)	1 (33.3)	24 (20.7)
Eutrophy	32 (66.7)	35 (66.0)	9 (75.0)	2 (66.7)	78 (67.2)
Excessive	8 (16.7)	6 (11.3)	0 (0.0)	0 (0.0)	14 (12.1)
Stature					
Eutrophy	47 (97.9)	44 (83.0)	10 (83.3)	3 (100)	104 (89.6)
Moderately short	1 (2.1)	5 (9.4)	0 (0.0)	0 (0.0)	6 (5.2)
Severely short	0 (0.0)	4 (7.6)	2 (16.7)	0 (0.0)	6 (5.2)

Table 3. Comparison of biochemical indices for nutritional status by disease subtype.

	Oligoarticular, n = 48	Polyarticular, n = 53	Systemic, n = 12	Psoriatic, n = 3	Total, n = 116	p*
Anemia, n (%)	14 (29.2)	24 (45.3)	6 (50.0)	1 (33.3)	45 (38.8)	0.278
Lymphopenia, n (%)	1 (2.1)	9 (17.0)	1 (8.3)	0 (0.0)	11 (9.5)	0.070
Albumin, g/dl, mean (SD)	4.5 (0.3)	4.5 (0.3)	4.4 (0.3)	4.7 (0.2)	4.5 (0.3)	0.161
Total calcium, mg/dl, mean (SD)†	9.6 (0.5)[a]	9.3 (0.5)[b]	9.2 (0.5)[ab]	9.4 (0.4)[ab]	9.4 (0.5)	0.039
Reduced levels of IGF-I, n (%)	4 (8.3)	7 (13.2)	3 (25.0)	0 (0.0)	14 (12.1)	0.382

* ANOVA, chi-square, or Fisher's exact test. † Superscripted letters represent statistically different groups ($p < 0.05$) identified by Tukey test. IGF-I: insulin-like growth factor-I.

articular and systemic forms. No patient presented low levels of serum albumin.

Table 4 compares the anthropometric characteristics presented by the different disease subtypes. The polyarticular disease group presented the greatest stature deficit among all groups. There were no significant differences of BMI or TSF percentiles among the groups. However, comparing a group formed by the polyarticular and systemic subtypes with a group formed by oligoarticular and psoriatic subtypes, the former tended to present lower percentiles of BMI [median (25th, 75th percentile) 37.5 (9.5, 80.0) vs 60.0 (20.0, 95.0), respectively; $p = 0.051$].

Table 5 evaluates correlations between clinical disease characteristics and the anthropometric variables. The ESR, duration of disease, and cumulative dose of glucocorticoids correlated significantly with the reduction in patient stature in

Table 4. Comparison of Z scores of stature, BMI percentiles, and triceps skinfold (TSF) percentiles by disease subtype.

	Oligoarticular, n = 48	Polyarticular, n = 53	Systemic, n = 12	Psoriatic, n = 3	Total, n = 116	p*
Z score of stature, mean (SD)†	0.57 (1.13)[A]	–0.80 (1.70)[B]	–0.51 (1.98)[AB]	–0.05 (0.21)[AB]	–0.18 (1.62)	< 0.001
Percentile of BMI, median (25th, 75th percentile)	51.0 (18.7, 95.0)	37.5 (7.5, 80.0)	41.2 (28.5, 81.0)	80.0 (62.5, 80.0)	47.5 (17.5, 83.5)	0.205
Percentile of TSF, median (25th, 75th percentile)	17.5 (7.5, 68.7)	17.5 (5.0, 62.5)	25.0 (4.0, 68.7)	37.5 (3.0, 80.0)	18.7 (5.0, 62.5)	0.937

* ANOVA or Kruskal-Wallis test. † Superscripted letters represent statistically different groups ($p < 0.05$) identified by Tukey test.

Table 5. Nonparametric correlations of clinical variables with the Z score of stature and the percentiles of body mass index (BMI) and triceps skinfold (TSF).

	Z Score of Stature, r_s (95% CI)*	p	Percentile of BMI, r_s (95% CI)*	p	Percentile of TSF, r_s (95% CI)*	p
Cumulative glucocorticoid dose, n = 116	–0.23 (–0.40, –0.05)	0.013	–0.05 (–0.23, 0.13)	0.585	–0.08 (–0.26, 0.10)	0.371
Duration of disease, n = 116	–0.39 (–0.54, –0.23)	< 0.001	–0.11 (–0.29, 0.07)	0.221	–0.02 (–0.20, 0.16)	0.818
ESR, n = 111†	–0.47 (–0.60, –0.31)	< 0.001	–0.04 (–0.22, 0.15)	0.697	0.02 (–0.17, 0.20)	0.869

* Spearman correlation coefficient and 95% confidence interval. † Five cases were excluded because of missing values.

these bivariate analyses. None of the independent variables tested here was significantly correlated with the percentiles of BMI and TSF, albeit the confidence intervals for the correlation coefficients were relatively large.

Patients with clinically active disease had lower Z scores for stature in comparison to patients with inactive disease [mean –0.53 (SD 1.79), n = 66, versus 0.28 (SD 1.25), n = 50, respectively; p = 0.007]. However, there were no significant differences between patients with active and inactive disease in the percentiles for BMI [median (25th, 75th percentile) 50.0 (17.5, 85.0) vs 45.0 (17.5, 82.0), respectively; p = 0.788) and in the percentiles for TSF [17.5 (5.0, 70.0) vs 20.0 (7.5, 62.5), respectively; p = 0.825].

A single patient presented involvement of the TMJ, and the anthropometric and biochemical variables were compromised. The results of the anthropometric classifications were low weight for BMI, low adiposity for TSF, and short stature with a Z score < –5. Anemia and lymphopenia were observed among the laboratory variables.

A model of multivariable linear regression whose dependent variable is the Z score for stature was created. The variables considered possibly relevant to determine the dependent variable were included in the model. The variable cumulative glucocorticoid dose had to be logarithmically transformed ($\log_{10}$ [cumulative dose + 1]) because of a case with an extremely high value, representing an important outlier with a leverage value of 0.73 and Cook's distance 1.17 (if not transformed). The final model is presented in Table 6. Disease duration, ESR, and the polyarticular or systemic subtypes were associated independently and additively to reduced patient stature, while the mother's height was correlated with higher stature. The cumulative dose of glucocorticoid was not an independent predictor of reduced height scores. The assumptions of multivariable linear regression were fully met, and the model explained approximately 50% of the variance of the Z score for stature. The exclusion of 9 cases identified as outliers or highly influential cases from the final model improved the overall coefficient of determination ($R^2 = 0.57$, adjusted $R^2 = 0.54$), but did not change the coefficients of the independent variables significantly. In this model (with outliers and highly influential cases excluded), the cumulative dose of glucocorticoid presented a nonsignificant positive correlation with the Z score for height (partial r 0.159, 95% CI:, –0.047 to 0.352, p = 0.129).

Fourteen patients (12.1% of the total number of cases, 7 with polyarticular disease, 4 the oligoarticular form, and 3 the systemic subtype) presented reduced IGF-I levels. The Z score for IGF-I level was positively correlated with the Z score for height (r_P 0.236, 95% CI: 0.056 to 0.401, p = 0.011). However, a linear regression model including a quadratic and a cubic term of the Z score for IGF-I showed a better correlation with the Z score for height (multiple r 0.379, 95% CI:, 0.210 to 0.526, p = 0.001), suggesting the possibility of a nonlinear association between these 2 variables. The disease duration (r_S –0.051, 95 % CI:, –0.231 to 0.133, p = 0.587) and cumulative corticosteroid dose (r_S–0.124, 95% CI: –0.299 to 0.060, p = 0.185) were not significantly correlated with the Z score for IGF-I. Patients with the systemic or polyarticular subtypes had Z scores for IGF-I similar to those with oligoarticular or psoriatic subtypes [mean –0.78 (SD 1.21) vs –0.80

Table 6. Multivariable linear regression model using Z score of patients' stature as dependent variable.

Independent Variables	B*	Partial Correlation Coefficients (95% CI)†	p
Duration of the disease, yrs	–0.134	–0.370 (–0.527, –0.188)	< 0.001
ESR, mm/h	–0.019	–0.357 (–0.516, –0.174)	< 0.001
Polyarticular or systemic disease subtype**	–0.783	–0.290 (–0.459, –0.100)	0.003
Cumulative glucocorticosteroid dose ($\log_{10}$ [$dose_{mg}$ + 1])	0.078	0.086 (–0.111, 0.277)	0.391
Active disease**	–0.340	–0.133 (–0.320, 0.064)	0.183
Mother's height, cm***	0.076	0.398 (0.220, 0.551)	< 0.001
Constant††	–10.675	—	< 0.001

R^2 = 0.50; adjusted R^2 = 0.47; n = 107 (9 cases were excluded from the model because of missing data in some variables). Kolmogorov-Smirnov test of residuals = 0.651, p = 0.791. White's test = 17.69, p = 0.855. The highest VIF was 1.34. Nonlinearity tests: quadratic = 2.82, p = 0.589; logarithmic = 2.33, p = 0.507.* Partial regression coefficients. † 95% confidence interval of partial correlation coefficients. ** Variables defined numerically: yes = 1, no = 0. *** Mother's height was chosen for inclusion in the model because it had fewer missing values and was more reliable information than father's height. †† Value of the dependent variable when all independent variables are equal to zero.

(SD 1.09), respectively; p = 0.921]. However, there was a negative correlation between the ESR and the Z score for IGF-I (r_S –0.345, 95 % CI:, –0.500 to –0.170, p < 0.001), and patients with clinically active disease had lower Z scores for IGF-I than other patients [mean –0.98 (SD 1.06) vs –0.54 (SD 1.23), respectively; p = 0.039] In multivariable regression analysis (including the same independent variables presented in Table 6), the one variable significantly associated with the Z score for IGF-I was the ESR (partial r –0.422, 95% CI:, –0.570 to –0.247, p < 0.001). In this model, the cumulative glucocorticoid dose ($\log_{10}$ [cumulative dose + 1]) was not significantly correlated with low IGF-I scores (partial r 0.056, 95% CI:, –0.141 to 0.249, p = 0.573). There were no significant correlations of the Z score of IGF-I with the BMI percentile (r_S 0.008, 95% CI:, –0.175 to 0.190, p = 0.932) or with the TSF percentile (r_S 0.070, 95% CI: –0.113 to 0.249, p = 0.450).

Associations between family income and the nutritional (Z score of stature, percentiles of BMI and TSF) and laboratory variables (anemia and calcemia) were tested, and no statistically significant association was observed (data not shown).

DISCUSSION

We assessed the nutritional, anthropometric, and biochemical variables in patients with JIA in order to identify the relationship between these variables and the clinical characteristics of the disease.

Several studies have demonstrated the involvement of nutritional variables in JIA. Among the anthropometric variables, short stature is often observed and may lead to psychological problems related to the patient's self-esteem. In our study the observed prevalence of low stature was 10.4%, while in the literature it varies from 10% to 41%[4,6-12]. The great variation of the prevalence of short stature in the literature may be accounted for by the selection of patients and different classification methods used in the various studies. Simon, *et al*[7] observed a prevalence of short stature of 41% (measuring the final height), but this study exclusively evaluated patients with the systemic disease subtype who had been undergoing treatment with glucocorticoid for a long time. A high prevalence of short stature (38.8%) was also identified by Miller, *et al*[10], where the criterion for the classification was a stature/age index below the 20th percentile, while the WHO classification considers short stature only if it is below the 3rd percentile. Henderson, *et al*[11] observed a prevalence of short stature of 19% (classified as values below the 5th percentile). Allen, *et al*[6], who used the Z score to assess stature (the same method as used in our study), reported a 26% prevalence of short stature. However, these authors considered short stature a Z score < –1.5 SD, different from the criterion recommended by the WHO and used here (< –2.0 SD). In a Brazilian study[9] that included 41 patients with the oligoarticular and polyarticular forms of JIA, the prevalence of short stature was 19.5%, using criteria identical to those we employed. The short stature prevalences in other studies with similar selection and classification criteria for patients varied from 10% to 15%[4,8,12].

In our study, the polyarticular and systemic disease subtype, the disease duration, and the ESR were significantly and independently associated with reduced height. Previous studies reached similar conclusions relative to disease subtype[4,5,8,12,20], disease duration[4,6,8,12], and disease activity and severity[4,12]. Considering that the polyarticular form, together with the systemic form, presents a more severe inflammatory picture[2,4,6,9], these findings confirm the importance of the severity and persistence of the inflammatory process in growth deficit.

The association between corticosteroid therapy and short stature is controversial. A few observational studies have associated the use, duration, or cumulative dose of glucocorticoid with reduced height[4,7,12,19,21,22]. Most of these studies did not use multivariable analysis to adjust for possible con-

founding factors like disease subtype and duration and severity of disease[7,19,21,22]. Zak, *et al*[12] and Garcia-Consuegra Molina, *et al*[4] presented multiple linear regression models (using automatic methods of variable selection) where the use of glucocorticoids was considered an independent factor for reduced height or low growth velocity. The final models presented by those authors did not take into consideration the possible influence of variables like subtype and duration of disease, which were excluded by the stepwise variable selection methods. These methods of variable selection may have a low power to detect confounding factors (particularly when working on small samples)[32] and the set of variables selected may be difficult to reproduce in other samples taken from the same population[33]. Given the observational design of the studies, it may be difficult to discriminate between the effects of glucocorticoids and of disease severity on stature, since glucocorticoids are frequently used to control articular inflammation resistant to nonsteroidal antiinflammatory drugs and disease modifying antirheumatic drugs.

In contrast, other studies[5,6,8,20] analyzing small samples (maximum 67 patients) did not reveal associations between corticosteroid therapy and short stature. These negative results may be related to the low statistical power to detect clinically relevant effects. In our study, with a relatively large sample of patients, we found a significant correlation between the cumulative glucocorticoid dose and lower scores for height in bivariate analysis (Table 5). However, after adequate adjustment for important confounding variables (duration and subtype of disease, ESR) in multivariable linear regression analysis, we observed no independent association between corticosteroid therapy and short stature. Keeping in mind the limitations of cross-sectional studies, the 95% confidence interval of the partial correlation coefficient (–0.111 to 0.277; Table 6) makes it unlikely that a clinically relevant negative effect of glucocorticoids on height has gone undetected. A more definitive conclusion on the independent effect of corticosteroids on stature may only be possible with well controlled cohort studies or randomized controlled trials.

The prevalence of low weight in our study (16.4%) is within the range of values presented by previous studies[2-5], and is particularly close to the results presented by Lofthouse, *et al*[5], which used classification criteria comparable to ours. The association of weight and adiposity with the clinical disease features of JIA has also been studied. Lofthouse, *et al*[5] observed lower BMI and percentage body fat in patients with polyarticular disease subtype compared to controls. Haugen, *et al*[22], studying 220 adult patients with JIA, observed similar BMI in patients with active and inactive disease and healthy controls, but patients presented lower percentage body fat than controls. Cleary, *et al*[3] found lower BMI in patients with persistent articular inflammation and higher number of joints with loss of range of motion. We observed no association of the disease duration, ESR, and the disease activity with the percentiles of BMI and TSF. However, the polyarticular and the systemic subtype tended to present lower percentiles of BMI, suggesting a possible association between the inflammatory state and low weight.

The cumulative dose of corticosteroids was not significantly associated with the percentiles of BMI and TSF. Considering the relatively large confidence intervals of the correlation coefficients, a small to moderate negative effect of the corticosteroid dose on BMI and TSF cannot be excluded. However, results similar to ours were obtained by Allen, *et al*[6] and Liem, *et al*[8], who did not find an association between corticosteroid use and weight. A possible explanation for these negative results is that the increase in appetite and the accumulation of subcutaneous fat promoted by glucocorticoids may be counterbalanced by the catabolism promoted by disease activity in JIA. Given that larger doses of glucocorticoids are usually taken by patients with more active disease (as also observed in our sample), the absence of a relevant effect of glucocorticoid on the percentiles of BMI and TSF may be an expected result.

IGF-I, formerly known as somatomedin-C, is the main effector of growth hormone in bone and other tissues[18]. Reduced IGF-I serum concentrations have been observed in 9%–35% of patients with JIA[4,6,19]. In our sample, reduced serum IGF-I levels occurred in 14 patients (12.1% of the sample) and short stature was present in 4 of these patients. As previously observed[4,6,19], reduced IGF-I levels were associated with lower height scores. Garcia-Consuegra Molina, *et al*[4] found significant negative correlations (in bivariate analysis) of duration of active disease and the cumulative glucocorticoid dose with the IGF-I scores. In our study, ESR and disease activity were the clinical variables associated with lower IGF-I levels. The nonsignificant negative correlation between cumulative glucocorticoid dose and IGF-I score reverted to a nonsignificant positive correlation after adjustment for the effect of other variables (particularly the ESR) in multivariable regression analysis. These results corroborate the conclusion that persistent inflammatory activity is responsible for the short stature observed in patients with JIA, while the use of corticosteroids may have, at most, a small deleterious effect on growth.

There is evidence suggesting that the inflammatory process and its nutritional consequences in JIA could be accounted for mainly by the effects of cytokines such as tumor necrosis factor, interleukin 1 (IL-1), and IL-6[15]. These cytokines promote a state of metabolic acidosis that is associated with increased activity of osteoclasts and inhibition of growth hormone secretion, favoring the involvement of linear growth and hypercatabolism[15]. Our observations of a larger growth deficit in patients with higher inflammatory activity reinforce the idea of the participation of proinflammatory cytokines in this complication. These observations are relevant considering the emergence of new therapies that inhibit the action of these cytokines.

Food restriction secondary to involvement of the temporo-

mandibular joint (TMJ) and of oral health could be considered one of the possible causes of nutritional involvement in JIA[13,34,35]. However, there are no studies evaluating the association between involvement of the TMJ and nutritional status of patients with JIA. In our sample, TMJ dysfunction was clearly seen in a single patient, suggesting that this factor has limited relevance in the nutritional involvement of JIA.

Given the eating problems and the increased catabolism and energy expenditure associated with inflammation[2,13-15], it is possible that a nutritional rehabilitation may be beneficial for these patients, helping to maintain normal physical development. For instance, a hypercaloric diet during the more active phases of the disease could ameliorate the state of excessive catabolism, potentially reducing the losses in stature that occur during these periods. To test this hypothesis appropriately, it would be necessary to perform a randomized controlled trial in this group of patients. However, some studies demonstrate that it is possible to improve the nutritional status and growth rate of patients with chronic diseases by intervention in the form of diet therapy, as reported in studies on patients with chronic renal failure[36], cystic fibrosis[37], and Crohn's disease[38].

Considering the significant prevalence of nutritional abnormalities observed in patients with JIA and the relationship of short stature with the duration and subtype of the disease and the ESR, the importance of early, strict control of the inflammatory process is highlighted in our study.

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