Association of body mass index with Juvenile Idiopathic arthritis disease activity: a Portuguese and Brazilian collaborative analysis

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ABSTRACT

Objective: To investigate the relationship between body mass index (BMI) and disease activity in patients with Juvenile Idiopathic Arthritis (JIA).

Methods: Patients with JIA, aged ≤18 years, registered at the Rheumatic Diseases Portuguese Register (Reuma.pt) in Portugal and Brazil were included. Age- and sex-specific BMI percentiles were calculated based on WHO growth standard charts and categorized into underweight (P<3), normal weight (3≤P≤85), overweight (85<P≤97) and obesity (P>97). Disease activity was assessed by Juvenile Arthritis Disease Activity Score (JADAS-27). Uni- and multivariable analyses were performed.

Results: A total of 275 patients were included. The prevalence of underweight, normal weight, overweight and obesity was 6.9%, 67.3%, 15.3% and 10.5%, respectively. Underweight patients had significantly higher number of active joints (p<0.001), patient's/parent's global assessment of disease activity (PGA) (p=0.020), physician's global assessment of disease activity (PhGA) (p<0.001), erythrocyte sedimentation rate (ESR) (p=0.032) and overall higher JADAS-27 (p<0.001), compared to patients with normal weight, overweight and obesity.

In the multivariable regression, normal weight (B=-9.43, p<0.01), overweight (B=-9.30, p=0.01) and obesity (B=-9.12, p=0.01) were significantly associated with lower disease activity compared to underweight, when adjusted for age, gender, country, ethnicity, JIA category and therapies used. The diagnosis of RF- (B=3.65, p=0.006) or RF+ polyarticular JIA (B=5.29, p=0.024), the absence of DMARD therapy (B=5.54, p<0.001) and the use of oral GC (B=4.98, p=0.002) were also associated with higher JADAS-27.

Conclusion: We found an independent association between underweight and higher disease activity in patients with JIA. Further studies are needed to understand the underlying mechanisms of this association.

Keywords: Juvenile idiopathic arthritis; Body mass index;

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INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease in childhood. It comprises a group of heterogeneous conditions with distinct phe-

notypes and variable course and prognosis[1]. Over the last years, new treatment options have offered major improvements in long-term outcomes[2]. Yet, some children still fail to achieve disease remission and experience persistent or recurrent arthritis into adulthood[3,4]. A systematic review revealed that less than 50% of patients achieve sustained remission in the first ten years following diagnosis, even in contemporary cohorts[5].

Young age at onset, female gender, diagnostic delay, symmetric disease, systemic or polyarticular subtypes, presence of rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (ACPA), and high levels of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) have been suggested as predictors of persistent active disease, although not unanimously across different studies[6-8].

The influence of body mass index (BMI) on JIA disease activity is poorly studied. In adults with Rheumatoid Arthritis (RA), obesity has been associated with high disease activity, a decrease in the odds of achieving remission[9,10] and an impaired quality of life[11]. Likewise, weight loss (≥5 kg) was associated with a significant improvement in RA disease activity[12]. A potential explanation is through the role of adipose tissue on the activation of pro-inflammatory pathways[13,14]. Several adipokines (leptin, resistin, visfatin, among others) secrete various cytokines such as TNF, IL-1 , IL-6, which bear pro-inflammatory properties, resulting in more active disease in obese patients. On the other hand, increased body weight can be partly caused by lack of physical activity, due to joint pain, stiffness, fatigue or other short or long-term disabilities.

Paradoxically, some studies have revealed an inverse relationship between BMI and the risk of radiographic progression in RA[15-17]. Furthermore, a cross-sectional study showed that, in addition to obesity, underweight was also associated with increased disease activity in RA[18].

Given the observations in RA we hypothesize that there is an association between BMI and JIA disease activity. Thus, in this study, we aim to test if this association exists.

MATERIALS AND METHODS

STUDY DESIGN AND POPULATION

This is a cross-sectional analysis based on the Rheumatic Diseases Portuguese Register (Reuma.pt)[19]. Reuma.pt is a prospective longitudinal real-world data registry developed by the Portuguese Society of Rheumatology to record data from patients with various rheumatic diseases, including JIA. Partnerships have been done with centers in other countries, namely Brazil, which have the same version of the database for their own use.

Patients with JIA, according to the 2001 revised International League of Associations for Rheumatology (ILAR) criteria[20], aged ≤ 18 years, who were registered in Reuma.pt in Portugal and Brazil up to May 2019 and who had available data on BMI and disease activity were included.

For registry of data in Reuma.pt, parent's informed consent and patient's assent were obtained, as appropriate. This study was approved by the scientific committee of Reuma.pt and by the Ethics Committee of Centro Hospitalar de Lisboa Ocidental (registry number 20170700050). Reuma.pt was approved by the National Committee for Data Protection. The study was conducted according to the Declaration of Helsinki.

DATA COLLECTION

The following data were collected at the time of the first visit registered in Reuma.pt: age, gender, ethnicity, country, BMI, JIA category according to ILAR classification criteria, disease duration, number of swollen and tender joints, patient's/parent's pain visual analogue scale (VAS 0-10cm), patient's/parent's global assessment of disease activity (PGA, VAS 0-10 cm), physician's global assessment of disease activity (PhGA, VAS 0-10 cm), ESR, CRP and current therapy with glucocorticoids (GC), conventional and biological disease-modifying antirheumatic drugs (DMARDs).

Disease activity was assessed by Juvenile Arthritis Disease Activity Score 27-joint reduced count (JADAS--27)[21], a composite validated score. The overall JADAS--27 score ranges from 0 (no activity) to 57 (highest disease activity). For all JIA categories, the state of inactive disease was defined as JADAS-27≤1, a validated cutoff developed by Consolaro *et al*[22].

Age- and gender-specific BMI percentiles (P) were calculated based on World Health Organization (WHO) growth standard charts (23). According to their BMI percentiles, patients were allocated into four different categories: underweight (P<3), normal weight (3≤P≤85), overweight (85<P≤97) and obesity (P>97).

STATISTICAL ANALYSIS

Categorical variables are shown as frequencies and per-

centages. Continuous variables are presented as mean and standard deviation (SD). Normal distribution was assessed using Kolmogorov–Smirnov test.

Fisher's exact test, chi-square test or one-way analysis of variance (as appropriate) were used to compare demographic and clinical characteristics between different BMI categories. Differences between countries (Portugal and Brazil) were examined using t-test, Fisher's exact test or chi-square test.

Linear regression was used to investigate the association of JADAS-27 with BMI categories. To correct for possible confounding effects, two multivariable linear regression models were developed. Model 1 was adjusted for age, gender, ethnicity, country, disease duration and JIA category. Model 2 was adjusted for those covariates plus use of DMARDs and glucocorticoids.

Statistical significance was defined as a p-value of less than 0.05. Statistical Package for Social Science (SPSS) version 23 was used for data analysis.

RESULTS

A total of 275 patients from 20 different centers were included in this study. Nearly 88% were from Portugal and 12% from Brazil. Most patients (62.2%) were female. Overall, the mean age at the first registered visit was 10.2 ± 4.6 years, and the mean disease duration was 1.7 ± 2.9 years. Persistent oligoarticular (31.9%), rheumatoid factor-negative (RF-) polyarticular (25.9%) and enthesitis-related arthritis (14.8%) were the most prevalent JIA categories. Mean JADAS-27 was 7.1 ± 6.9 and 22.2% of patients had inactive disease. Only 10.2% of patients were on glucocorticoids; 65.4% were on conventional DMARDs (cDMARDs) and 14.9% on biological DMARDs (bDMARDs).

The prevalence of underweight, normal weight, overweight and obesity was 6.9%, 67.3%, 15.3% and 10.5%, respectively. Table I shows the distribution of the demographic and clinical characteristics of patients grouped by BMI categories. There were no significant differences in terms of age, gender, country, ethnicity, disease duration, use of GC, cDMARDs or bDMARDs between groups. Persistent oligoarticular was the most prevalent JIA category for all groups, except for underweight patients, who had predominantly enthesitis-related arthritis. Still, this difference concerning JIA categories did not reach statistical significance (p=0.063).

Patients from Brazil had significantly lower disease duration (0.8 ± 2.3 vs 1.9 ± 2.9 years, p=0.009) and higher JADAS-27 scores (9.9 ± 10.6 vs 6.7 ± 7.1, p=0.002), compared to those from Portugal. Nonetheless, there were no significant differences between countries in terms of age, gender, JIA category, therapies used and, importantly, prevalence of BMI categories.

Overall, there was a statistically significant difference in JADAS-27 mean scores between BMI categories. A post-hoc test using Tukey's method revealed that underweight patients had significantly higher JADAS-27 scores than normal weight (p<0.001), overweight (p<0.001) and obese patients (p=0.014). Meanwhile, there were no significant differences in JADAS-27 mean between normal weight and overweight or obesity groups, though the latter had slightly higher absolute values (Table I).

The same findings were observed for each of the individual components of JADAS-27 (Figure 1). Underweight patients had significantly higher number of active joints, higher PGA, PhGA and ESR, comparing to the other groups. Regarding CRP, there was no statistically significant difference between the four groups, although underweight patients had the highest absolute CRP values, followed by obese patients.

To further evaluate the association of BMI and JIA disease activity, linear models were performed (Table II). In the univariable linear regression, underweight was significantly associated with higher JADAS-27, compared to normal weight, overweight and obesity. Younger age, shorter disease duration, black race, living in Brazil, RF- polyarthritis, RF+ polyarthritis, the absence of DMARD therapy and the use of GC were also associated with higher JADAS-27.

In the model 1 of multivariable analysis, the same variables, except the country, remained significantly associated with higher disease activity. When GC and DMARD therapies were added to the model (model 2), the association of normal weight, overweight and obesity with lower disease activity persisted significant, compared to underweight patients, as well as those under DMARD therapy. The presence of RF- or RF+ polyarthritis and the use of oral GC were associated with higher JADAS-27.

DISCUSSION

We found an independent association between underweight and higher disease activity in patients with JIA.

TABLE I. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF JIA PATIENTS BY BMI

	All	Underweight	Normal weight	Overweight	Obesity	p-value
Age, years (mean ± SD)	10.2 ± 4.6	12.8 ± 4.8	10.0 ± 4.6	9.7 ± 4.9	10.5 ± 4.7	0.09
Females, n (%)	171 (62)	10 (53)	116 (63)	27 (64)	18 (62)	0.84
Country (Portugal), n (%)	243 (88)	15 (79)	163 (88)	40 (95)	25 (86)	0.29
Ethnicity, n (%) (n=221)						
European Caucasian	194 (88)	9 (82)	129 (88)	33 (85)	23 (92)	
Non-European Caucasian	8 (4)	0	6 (4)	2 (5)	0	
Black	8 (4)	2 (18)	3 (2)	2 (5)	1 (4)	0.69
Biracial	6 (3)	0	4 (3)	1 (3)	1 (4)	
Romani	2 (1)	0	2 (1)	0	0	
Asiatic	3 (1)	0	2 (1)	1 (23)	0	
JIA category, n (%) (n=263)						
Persistent oligoarthritis	84 (32)	1 (6)	61 (34)	13 (33)	9 (33)	
Extended oligoarthritis	22 (8)	1 (6)	13 (7)	7 (18)	1 (4)	
RF-negative polyarthritis	68 (26)	6 (33)	46 (26)	9 (23)	7 (26)	
RF-positive polyarthritis	19 (7)	3 (17)	13 (7)	0	3 (11)	0.06
Systemic-onset	15 (6)	0	8 (5)	5 (13)	2 (7)	
Enthesitis-related arthritis	39 (15)	7 (39)	25 (14)	4 (10)	3 (11)	
Psoriatic arthritis	14 (5)	0	11 (6)	1 (3)	2 (7)	
Undifferentiated arthritis	2 (1)	0	2 (1)	0	0	
Disease duration, years (mean ± SD) (n=255)	1.7 ± 2.9	2.0 ± 3.1	1.6 ± 2.8	1.4 ± 2.6	2.8 ± 2.5	0.69
JADAS-27 (mean ± SD)	7.1 ± 6.9	18.7 ± 10.7	5.9 ± 7.0	5.4 ± 7.0	8.8 ± 10.3	<0.01
Inactive disease1, n (%)	61 (22)	0	44 (24)	11 (26)	6 (21)	0.11
GC use, n (%)	28 (10)	3 (16)	21 (11)	1 (2)	3 (10)	0.29
GC dosage, mg/kg/day (mean ± SD)2	0.3 ±0.2	0.30 ±0.1	0.24 ±0.2	0.24 ± 0	0.31± 0.2	0.60
cDMARD use, n, % (n=188)	123 (65)	9 (69)	86 (67)	14 (56)	14 (67)	0.76
bDMARD use, n, % (n=188)	28 (15)	4 (31)	19 (15)	3 (12)	2 (10)	0.36

1. Defined as JADAS-27≤1.
2. Prednisolone dose or equivalent.
JIA: Juvenile Idiopathic Arthritis; RF: rheumatoid factor; JADAS-27: Juvenile Arthritis Disease Activity Score 27-joint reduced count; GC: glucocorticoids; cDMARD: conventional disease-modifying antirheumatic drugs; bDMARD: biological disease-modifying antirheumatic drugs.

In fact, underweight patients have higher ESR, patient or parent global assessment, physician global assessment, number of active joints, and overall higher JADAS-27 scores, comparing to patients with normal weight, overweight and obesity.

The association between the use of systemic GC and higher disease activity reflects the need of a potent and rapidly effective therapeutic option, in order to achieve a more rapid disease control. On the other hand, the use of DMARD therapy was associated with lower disease activity, as expected.

Our study included patients from two different countries. In spite of that, there were no significant differences in patients' characteristics between countries, with the exception of a lower disease duration and higher JADAS-27 scores in Brazilian patients. This could be the result of an entry of patients into the Reuma.pt database earlier in the course of the disease, when control of disease activity is still less achieved. The lack of use of biological therapies in Brazilian patients is also in line with an earlier disease state. In any case, there were no differences regarding BMI categories between Portuguese and Brazilian patients.

Only a few studies have addressed the impact of BMI on JIA disease activity. In 2012, Pelajo *et al*. performed a cross-sectional analysis of 154 subjects, of whom 18% were obese and 12% overweight, but failed to find any association between BMI and JADAS-27 scores[24]. On

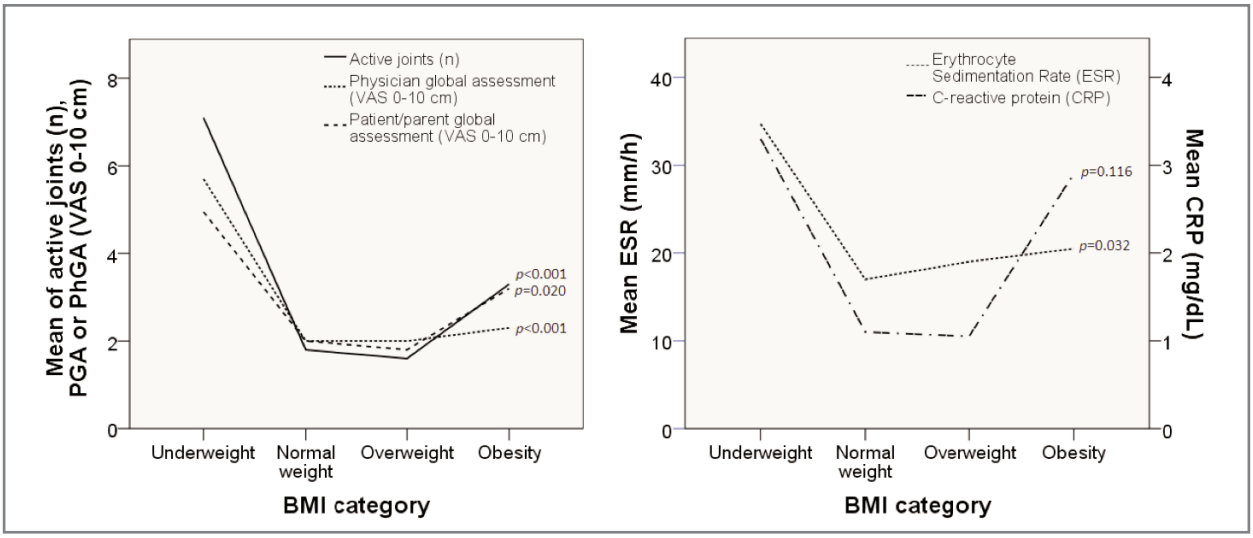

FIGURE 1. Disease activity parameters by BMI category.
BMI: Body mass index; PGA: Patient's/parent's global assessment of disease activity; PhGA: physician's global assessment of disease activity; VAS: Visual Analogue Scale.

the other hand, in another study involving 72 patients with enthesitis-related arthritis, it was shown that being overweight or obese was associated with failure to achieve clinically inactive disease at one year after the initiation of therapy. The inactive disease status was defined by the Wallace criteria plus the absence of active enthesitis or inflammatory back pain[25]. In both studies, underweight patients were grouped under normal weight, due to the small number ($n \leq 5$) of individuals in this former category.

More recently, an Italian single-center retrospective study evaluated 110 patients with JIA, of whom 80 were healthy weighted and 30 were overweight or obese[26]. Once again, there was no significant difference between BMI and ESR, CRP or total number of active joints, although involvement of the joints of lower limbs was significantly higher in overweight or obese patients, comparing to normal weight patients. Lower remission rates were also observed in overweight/obese patients, although without statistical significance. In this study, underweight patients were not included.

Similar to these previous studies, our data also showed that obese patients might have a trend toward unfavorable disease activity outcomes, comparing to normal weighted patients, as illustrated in Figure 1, although the difference was not statistically significant. Nonetheless, considering our results and those from other studies, the association between obesity and disease activity in JIA seems to be less evident than in RA. However, individuals with the same BMI do not necessarily have the same body composition and, before the onset of puberty, weight gain is mostly based on fat-free mass rather than fat-mass[27]. Hence, we should be careful when interpreting different data from the pediatric and adult populations. The use of distinct tools to assess disease activity in JIA and RA also challenges the comparison of both entities.

Nearly one-quarter of patients in our sample were overweight or obese. This rate is similar to the one recently reported in the Childhood Obesity Surveillance Initiative (COSI Portugal 2019), a program aimed at monitoring the obesity epidemic in Portuguese children aged between 6 and 8 years, in which 29.6% were overweight or obese[28]. On the other hand, there was a higher rate of underweight patients (6.9%) in our cohort, compared to the COSI sample (1.3%).

To the best of our knowledge, this is the first study identifying an independent association between low weight and high disease activity in JIA. The underlying mechanism of this association is still unclear, although we hypothesize that active disease can impair child's weight gain. Reduced BMI can be the result of high chronic systemic inflammation that can lead to cachexia, in particular, to poor appetite, loss of lean mass and increased metabolic rate[29, 30]. Longitudinal studies are needed to corroborate this hypothesis. Additionally, a previous study has shown that temporomandibular joint (TMJ) involvement in children with JIA is associa-

TABLE II. RELATIONSHIP BETWEEN JADAS-27 (DEPENDENT VARIABLE) AND DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF JIA PATIENTS.

	Univariate analysis	Multivariate analysis	
		Model 1 (R^2 = 0.235)	Model 2 (R^2 = 0.303)
	B [95% CI]	B [95% CI]	B [95% CI]
Age, years	-0.28 [-0.50 – (-0.06)]	-0.36 [-0.70-(-0.26)]	
Disease duration, years	-0.36 [-0.58-(-0.14)]		
Gender (female)	0.08 [-2.06 – 2.22]		
Country (Portugal)	-5.40 [-8.58- (-2.23)]		
Ethnicity			
European Caucasian*			
Non-European Caucasian	-3.65 [-9.79- 2.49]		
Black	6.99 [0.85 – 13.12]	5.30 [0.29 – 10.48]	
Biracial	-4.24 [-11.30-2.82]		
Romani	1.22 [-10.91-13.35]		
Asiatic	-0.73 [-10.65-9.20]		
JIA category			
Persistent oligoarthritis*			
Extended oligoarthritis	-1.24 [-5.08-2.60]		
RF-positive polyarthritis	6.20 [3.63-8.78]	7.08 [3.22 – 10.93]	5.29 [0.71 – 9.87]
RF-negative polyarthritis	8.76 [4.68-12.85]	4.90 [2.60 – 7.20]	3.65 [1.04 – 6.27]
Systemic-onset	3.02 [-1.49-7.53]		
Enthesitis-related arthritis	2.21 [-0.88-5.29]		
Psoriatic arthritis	2.94 [-1.72-7.59]		
Undifferentiated arthritis	9.00 [-2.61-20.61]		
BMI			
Underweight*			
Normal weight	-9.87 [-13.84 – (-5.89)]	-9.43 [-13.34-(-5.52)]	-9.43 [-13.75-(-5.11)]
Overweight	-10.60 [-15.16 – (-6.04)]	-9.31 [-13.82-(-4.80)]	-9.30 [-14.48-(-4.11)]
Obesity	-7.51 [-12.38 – (-2.64)]	-7.31 [-12.12-(-2.50)]	-9.12 [-14.45-(-3.80)]
Oral GC use	4.15 [0.76 – 7.55]		4.98 [1.82 - 8.15]
cDMARD use	-3.40 [-5.89-(-0.78)]		–
bDMARD use	-2.71 [-6.15 - 0.74]		–
Any DMARD use	-4.91 [-7.49-(-2.34)]		-5.54 [-7.94-(-3.15)]

*Reference group
Model 1: adjusted for age, gender, ethnicity, country, disease duration and JIA category.
Model 2: adjusted for those covariates plus use of GC and DMARDs.

ted with higher disease activity[31]. In our cohort, only 5% of patients had TMJ involvement (data not shown). Due to the very low number of patients affected, this variable was not included in the statistical analysis. However, we may hypothesize that patients with TMJ involvement may encounter some mechanical difficulties in eating, possibly affecting their nutrition and BMI.

Limitations of our study include the cross-sectional design even though the analysis was nested in a prospective longitudinal study, the low number of underweight patients, and the lack of data regarding socioeconomic status, education level of parents or caretakers, physical activity and nutrition, all of which could influence BMI. Moreover, the sample size was not sufficiently large to perform subgroup analysis and draw accurate conclusions for each JIA category, which would be relevant since JIA is not a single disease, but a group of heterogeneous conditions. In enthesitis-related arthritis, JADAS-27 disregards key features of the disease, such as axial involvement and enthesitis. Hence, a different instrument for assessment of disease activity may be warranted for this JIA category, al-

though these patients were also included in the validation study of JADAS[21].

Regarding the definition of inactive disease by Consolaro *et al*, the authors are aware that in the original validation analysis of the cutoff, JIA patients were aggregated in only two groups (oligoarthritis and polyarthritis) based on the number of affected joints[22]. Consequently, cutoff values specific for systemic arthritis, enthesitis-related arthritis, or psoriatic arthritis could not be developed. In spite of that, since patients with these ILAR categories were also included and assigned to one of the two groups in the cross-validation analysis, we considered acceptable to apply this definition to all JIA patients in our study.

Lastly, BMI has an inherent inability to distinguish between lean and fat mass[32]. Thus, the evaluation of body composition by another method, such as bioelectrical impedance analysis would have been more accurate to assess body mass. In conclusion, in JIA, low weight seems to be independently related to high disease activity. Further studies are needed to confirm these findings and understand the underlying mechanisms of this association. Importantly, the routine assessment of BMI should be part of the management of JIA patients.

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