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Nutritional impairment in juvenile idiopathic arthritis

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***Objective*. To investigate the relationship between nutritional impairment, measured by body mass index (BMI), expressed as an age- and sex-standardized standard deviation score (BMI SDS), and disease and patient characteristics in a UK cohort of children with juvenile idiopathic arthritis (JIA). A subgroup with available dietary information were analysed separately.**
***Methods*. Important disease and patient characteristics (age, gender, disease subtype, swollen joint count, painful joint count, restricted joint count, treatment and dietary assessment) were assessed as potential explanatory measures of BMI SDS in a multiple linear regression.**
***Results*. Data were collected on 123 consecutive patients. Twenty were nutritionally impaired. In multiple regression analysis excluding the dietary data, disease subtype [persistent oligoarthritis and polyarthritis (rheumatoid factor-negative)], five or more joints with reduced range of movement and being younger were associated with lower BMI SDS ($P < 0.001$). When energy and protein intake were included in the analysis for a subgroup of children, the resulting model retained only disease subtype as a predictor of a low BMI SDS ($P = 0.013$).**
***Conclusions*. In this unselected population of children with JIA, 16% had evidence of undernutrition. The most commonly affected subtype was oligoarthritis, a previously unreported finding. There is no evidence from this study that this nutritional impairment results from inadequate food intake and it is likely that it is multifactorial in aetiology, disease subtype being the most important factor.**

Nutritional impairment is a recognized complication of juvenile idiopathic arthritis (JIA) [1], but the factors associated with it are not clearly understood. Suboptimal nutrition adversely affects the long-term outcome of this group of children and is a source of considerable concern to parents and patients alike [2]. Nutritional impairment affects the general well-being of the child, may adversely affect disease control and contributes to the growth disturbance that is a serious consequence of JIA in children.

A variety of measures, including height, weight, mid-upper arm circumference and four skinfolds [3], biochemical abnormalities [4], resting energy exposure [5], upper body anthropometry and biochemical measurements [6] and bioelectrical impedance [7], have previously been used to document growth disturbance and impaired nutritional status in JIA. Such variety highlights the lack of consensus over what constitutes the optimal measure of nutritional impairment for routine clinical practice in paediatrics. The body mass index [BMI: weight in kg/(height in m)^2] provides an indirect measure of body composition [8]. BMI provides a valid measure of fatness in healthy children [9] and has been used to measure nutritional status in other paediatric disease states [10]. The BMI provides an objective assessment of protein-energy depletion or excess, and as it is calculated from height and weight measurements, which are routine anthropometric measures taken in clinic, it is a practical and usable tool.

Nutritional impairment may result from reduced food intake in JIA. Appetite may be impaired as a consequence of chronic inflammatory disease or as a side-effect of drugs with gastrointestinal toxicity [1]. Dental problems and temporomandibular joint disease may affect the child's ability to eat, as may functional difficulties resulting from arthritis affecting the upper limb [1]. Studies of the relationship between energy intake and growth have produced conflicting results. Mortensen *et al*. showed reduced energy intake in children with systemic arthritis and polyarthritis who also had mean height Z scores significantly below the US population mean [3]. Bacon *et al*. demonstrated adequate intakes in children with JIA with no correlation between dietary intake and growth percentiles [4]. A Norwegian study showed a higher energy intake in children with polyarticular disease [11]. To date there have been no studies of food intake with respect to anthropometric measures in children with JIA in the UK.

Other factors contribute to impaired nutrition in children with JIA. Significantly increased resting energy expenditure has been shown in children with systemic JIA, and this may contribute to the short stature exhibited in this group [5]. Uncontrolled inflammation may also contribute directly to nutritional problems, potentially mediated by inflammatory cytokines, such as TNFα [12]. Patients with JIA are treated with a variety of medications, including non-steroidal anti-inflammatory drugs (NSAIDs), methotrexate and other second line disease modifying agents and corticosteroids. All may cause abdominal discomfort and nausea. NSAIDs and corticosteroids may be directly toxic to the upper gastrointestinal tract. Prolonged use of corticosteroids may adversely affect linear growth in JIA [13], although growth failure occurring into adulthood in a large number of patients with JIA, without a history of steroid use in over one-half, has also been described [2].

Nutritional impairment in JIA is a widely recognized clinical problem of unclear aetiology. It undoubtedly contributes to poor long-term growth, osteoporosis and chronic anaemia, all potentially significant clinical problems in children with JIA. Studies in other childhood chronic diseases have shown benefit from aggressive attention to nutrition with resulting improvements

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in growth and well-being [14]. One small, uncontrolled study has suggested similar benefit in JIA [15]. Simple dietary advice has not proved beneficial in a small number of our patients (J. E. Davidson, unpublished data).

In order to provide appropriate management of any nutritional deficit, improved understanding of the problem is required. The aim of this study is to investigate in more detail the relationship between nutritional impairment measured using the BMI, and important disease and patient characteristics, including dietary intake in children with JIA, in a UK clinic population.

Methods

The rheumatology clinic at the Royal Liverpool Children's NHS Trust provides secondary and tertiary paediatric rheumatology care. All children attending between 1 March 2001 and 30 November 2001 were invited to participate in the study. Written consent was obtained from the child, parent or carer after initial assessment in clinic. Royal Liverpool Children's NHS Trust Research and Ethics Committee approval was obtained for the study.

Data collection

The main outcome measure used to assess nutritional status in children in this study was BMI, expressed as a standardized age- and sex-dependent standard deviation (SDS) score. BMI SDS were calculated relative to UK population reference data (Child Growth Foundation, London, UK). Nutritional impairment is defined for the purpose of this study as a BMI SDS less than or equal to 1 S.D. below the mean.

The disease and patient characteristics considered as explanatory measures were age (yr), gender, diagnosis (JIA subtype), duration of disease (months), swollen joints ($\leq$4, 5 or more), painful joints (none, $\geq$1), joints with loss of range of movement ($\leq$4, 5 or more) and treatment, together with dietary assessment of energy (kcal), protein (g) and fat intake (g). The joint assessment was performed by the clinician seeing the patient in clinic. A physician global assessment score was documented using a 10 cm visual analogue scale [16].

The disease subtype was documented according to the proposed International League against Rheumatism (ILAR) classification of JIA [17]. Less common subtypes (psoriatic arthritis, enthesitis-related arthritis and unclassifiable arthritis) were combined into one group because of small numbers, leaving five subtypes for analysis.

Treatment was classified into four groups, with patients allocated to one group: (1) NSAIDs and intra-articular steroid injection (IA steroid); (2) Disease modifying anti-rheumatic drug (DMARD) without systemic steroid; (3) DMARD with systemic steroid; (4) systemic steroid alone. Cumulative dose of corticosteroid was not taken into account because of the exploratory nature of this study.

Nutrient intake was determined using a 4-day diet diary. A paediatric dietician (FA) analysed the food diary to quantify the food consumed from the recorded information. Nutrient intake was analysed by means of a software package (Micro-diet; University of Salford) and summarized in terms of protein (g), energy (kcal) and fat (g). Intakes were compared with age and sex reference standards for the UK and expressed as percentage reference nutrient intake (RNI) or percentage estimated average requirement [18]. The dietician was blinded to each subject's non-dietary data.

Sample size

As no previous data were available to do a formal sample size calculation, a minimum of 30 patients per subtype was chosen as appropriate, to give a total sample size of 150. Analysis of 30 patients in each subtype would allow the use of parametric modelling techniques, given that the BMI SDS were expected to be normally distributed, giving approximately 20 patients per variable in an exploratory analysis containing seven explanatory variables [19].

Statistical analysis

Analyses were carried out using SPSS for Windows (release 10.0.7) (SPSS Inc., Chicago, IL, USA). A univariate analysis was initially performed to see how each of the explanatory variables was associated with the BMI SDS, and to investigate multicollinearity between explanatory variables. The two-sample *t*-test and one-way analysis of variance were used for comparisons of scores within categorical variable subgroups, and associations with continuous variables were assessed using either Pearson's or Spearman's rank correlation depending upon the distribution of the variables. All variables were considered to be potential predictor variables with no *a priori* assumptions as to their contribution. Any variables that were significantly associated with BMI SDS ($P < 0.2$) were selected for entry into a multiple linear regression. The contribution of the variables to the multiple regression model was assessed using an F test and a forward stepwise selection procedure was used to determine the final model (criterion for entry, $P < 0.05$; for removal, $P > 0.1$). The assumptions of the model were tested by examination of residuals. The overall fit of the model was ascertained using an adjusted R^2 value, measuring the proportion of total variability in BMI SDS explained by the variables in the model, and the S.E. of the estimate, measuring the spread of the residuals about the fitted line.

Results

Data were collected on 123 children with JIA. The mean BMI SDS was 0.06 (S.D. 1.32, range -4.7 to 2.8). The patient characteristics and respective relationships with BMI SDS are summarized in Table 1. The explanatory variables significantly associated with BMI SDS were age, joints with loss of range of movement, swollen joints and diagnosis. The most frequently occurring disease diagnosis subtype was persistent oligoarthritis, accounting for 41% of all cases. Of the less common disease subtypes combined into the 'other' category, one child was classified as having polyarthritis (RF-positive), four as having psoriatic arthritis, six as having enthesitis-related arthritis and three as having unclassifiable arthritis (i.e. those who met criteria for either none or two or more subtypes) according to the ILAR classification system [17]. There were no significant associations between gender, disease duration, physician's global score, painful joints and medication and BMI SDS.

Twenty children had a BMI SDS $\leq$1 S.D. below the mean (i.e. an SDS score of ≤ -1.26). A summary of these patients with nutritional impairment by disease subtype is shown in Table 2. No significant differences in the proportion with nutritional impairment were detected between the different disease subtype groups.

Of the 123 children, 64 (52%) completed a 4-day diet diary on nutritional intake. A summary of the results of the diary analysis is shown in Table 3 and indicates a weak negative correlation between protein intake and BMI SDS. Comparison of those children for whom no dietary information was available with the diet diary group indicated no significant differences in patient and disease characteristics between the two groups.

Regression analysis

In exploratory univariate analyses, age, disease subtype, loss of range, swollen joints, energy and protein intake were associated

TABLE 1. Summary characteristics of JIA cohort

Patient/disease characteristic	Summary of JIA population ($n=123$)	Mean (S.D.) BMI SDS within each categorical subgroup	Relation-ship with BMI SDS P
Males	48 (39%)	0.16 (1.35)	0.487#
Females	75 (61%)	−0.01 (1.31)	
Age (yr): mean (S.D.)	10 (4.5)	–	0.003+
Disease duration (months):§ median (IQR)	43 (18, 72)	–	0.448*
Physician's global score§ median (IQR)	4 (0, 28.5)	–	0.274*
Swollen joints§			0.036#
≤4	108 (89%)	0.16 (1.26)	
≥5	13 (11%)	−0.66 (1.71)	
Painful joints§			0.842#
0	89 (75%)	0.05 (1.33)	
≥1	30 (25%)	0.11 (1.36)	
Joints with loss of range of movement§			0.060#
≤4	99 (82%)	0.17 (1.27)	
≥5	22 (18%)	−0.41 (1.52)	
Diagnosis			0.010#
Systemic arthritis	13 (11%)	0.99 (1.09)	
Oligoarthritis (persistent)	51 (41%)	−0.24 (1.22)	
Oligoarthritis (extended)	10 (8%)	0.56 (1.07)	
Polyarthritis (RF-negative)	35 (29%)	−0.16 (1.41)	
Other types of arthritis	14 (11%)	0.47 (1.38)	
Medication§			0.233#
NSAIDs and intra-articular steroid	54 (45%)	0.001 (1.25)	
DMARD without systemic steroid	28 (24%)	0.09 (1.24)	
DMARD with systemic steroid	33 (28%)	0.38 (1.26)	
Systemic steroid only	4 (3%)	−0.95 (2.74)	

Summary measures are number (percentage) unless otherwise stated.
§Missing data for disease duration (11), physician's global score (2), swollen joints (2), painful joints (4), loss of range (2) and medication (4).
Relationship assessed using t-test or analysis of variance#, Pearson correlation coefficient+ or Spearman correlation coefficient*.
IQR, interquartile range.

TABLE 2. Number of patients with nutritional impairment and age by disease subtype

Diagnosis	Number (%) with nutritional impairment ($n=123$)	Mean age (yr) (S.D., range)
Systemic arthritis ($n=13$)	0 (0%)	13.2 (4.0, 3–18)
Oligoarthritis (persistent) ($n=51$)	11 (22%)	8.6 (4.6, 1–18)
Oligoarthritis (extended) ($n=10$)	1 (10%)	9.1 (3.6, 4–15)
Polyarthritis (RF-negative) ($n=35$)	7 (20%)	10.7 (3.7, 2–18)
Other types of arthritis ($n=14$)	1 (7%)	13.5 (3.5, 4–16)

TABLE 3. Nutritional analysis of 4-day diet diaries in 64 children with JIA

Nutritional intake	% of recommended nutritional intake: median (IQR)	Correlation* with BMI SDS (95% CI)	P
Energy (kcal)	86.6 (74.7, 102.4)	−0.21 (−0.43, 0.04)	0.10
Protein (g)	180.9 (144.2, 232.5)	−0.29 (−0.50, −0.04)	0.02
Fat (g)	121.0 (110.7, 128.8)	−0.08 (−0.32, 0.17)	0.53

*Spearman's rank correlation coefficient.

with BMI SDS ($P<0.2$) and selected for inclusion in the multiple regression analysis. In multiple regression analysis excluding the nutritional data, however, only the first three explanatory variables were retained in the model ($F_{6,114}=5.08$, $P<0.001$, adjusted $R^2=0.17$, S.E. of the estimate =1.21). The contribution of each variable to the model is shown in Table 4, and indicates that being diagnosed with persistent oligoarthritis or polyarthritis (RF-negative), having five or more joints with loss of range of movement and being younger are associated with lower BMI SDS. The statistically significant coefficients from the model show that, on average, children with persistent oligoarthritis were 1.21 points lower on the BMI SDS scale than those with systemic arthritis, and children with polyarthritis (RF-negative) were 0.9 points lower respectively. Participants with five or more joints with loss of range of movement were, on average, one point lower on the BMI SDS scale than those with four or fewer affected joints, and for each yearly increase in age the BMI SDS increased by 0.06 points. Exclusion of one child with a very low and influential BMI SDS of −4.7 in a sensitivity analysis did not change the results.

TABLE 4. Factors affecting BMI SDS determined by multiple linear regression

Variable	Regression coefficient (95% CI)	Standardized regression coefficient	P
Diagnosis*			
Oligoarthritis (persistent)	−1.21 (−2.01, −0.41)	−0.45	0.003
Oligoarthritis (extended)	0.13 (−0.95, 1.21)	0.03	0.809
Polyarthritis (RF-negative)	−0.90 (−1.69, −0.10)	−0.31	0.027
Other type of arthritis	−0.51 (−1.45, 0.44)	−0.12	0.291
Joints with loss of range#	−1.00 (−1.64, −0.36)	−0.29	0.003
Age (yr)	0.06 (0.002, 0.11)	0.19	0.041

*Systemic arthritis is the reference category to which the other four categories are being compared.
#<4 vs. ≥5.

When energy and protein were included in the analysis, which therefore contained only those 64 children for whom diet diary information was available, the resulting model included only disease subtype as a significant predictor of nutritional impairment ($F_{4,59}=3.49$, $P=0.013$, adjusted $R^2=0.14$, S.E. of the estimate =1.15), the same two disease categories making significant

contributions. Log transformation of the dietary data did not improve the results. All models satisfied the assumptions of multiple linear regression in terms of normality, homoscedasticity, linearity and independence of error terms.

Discussion

The disease characteristics associated with nutritional impairment in our unselected sample were persistent oligoarthritis and RF-negative polyarthritis, having five or more joints with loss of range of movement, and a younger age. Twenty (16%) of the 123 patients with JIA had nutritional impairment, as defined by a BMI SDS $\leq$1 S.D. below the mean of the study population (i.e. an SDS ≤ -1.26). Interestingly, and contrary to other studies [20], no patients with systemic arthritis were represented in this group. The subtype with the highest percentage of nutritional impairment was persistent oligoarthritis (22%). Although overall it was not possible to demonstrate a significant difference between the proportions of nutritional impairment in the different JIA subtypes, the finding that children with persistent oligoarthritis were at least as likely as those with the other subtypes to have nutritional impairment is a novel finding in JIA. It is also in keeping with the clinical impression that persistent oligoarthritis is not a disease which only affects the joints, but may be associated with significant systemic upset.

We chose to include the number of joints with a reduced range of movement as a variable in the model as a clinical indicator of previously active polyarthritis, but acknowledge that there is no evidence that this is more or less sensitive than other methods of clinical joint assessment. For example, in this study the number of swollen joints was highly correlated with the number of joints with a reduced range of movement (Spearman's correlation coefficient 0.68) and proved almost as effective an indicator in a sensitivity analysis excluding the latter measure.

The small number of children with polyarthritis (RF-positive), psoriatic arthritis, enthesitis-related arthritis and unclassifiable arthritis formed a heterogeneous subgroup of patients, and combination into a single group was done to allow inclusion in the analysis. It is recognized that these are distinct conditions that may not necessarily be treated in the same way. The extent to which these subgroups are at risk of nutritional impairment when considered separately remains to be seen in larger studies.

Assessment of nutritional status by using measures of height and weight alone may not be the most appropriate method [21]. The use of the BMI as a tool for the assessment of nutritional impairment remains controversial. Criticisms can be made of other measures, including triceps skin fold thickness, subscapular skin fold thickness, arm and arm muscle circumference, and arm muscle area, for which there are limited standard data, especially in non-Caucasian populations [22]. Time constraints and availability of trained personnel within the out-patient setting may also make the collection of such information difficult. Interpretation of the BMI in children is facilitated by the availability of reference data, and it is possible and recommended to express the BMI as a standardized score (SDS or *Z* score) relative to the reference data [23]. However, it remains unclear what level of BMI SDS equates to nutritional impairment, and the cutoff of 1 S.D. below the mean that we have taken is recognized to be an arbitrary value, but one which we felt to be clinically relevant.

Pietrobelli and colleagues demonstrated that BMI was strongly associated with total body fat and the percentage of body weight as fat in a healthy paediatric population [9]. However, the authors caution care in interpretation of BMI across groups that differ in age or when predicting an individual's total body fat or percentage of body weight as fat. It is recognized that there are theoretical disadvantages in using BMI as a measure of nutritional status in children with JIA. Growth, body composition and timing of puberty in chronic inflammatory disease states (such as JIA) may be abnormal. This may arise as a consequence of the disease process itself, and some children may have abnormal body composition (e.g. they may be overfat) as an adverse affect of treatment with glucocorticosteroids (in this study steroid use was not predictive of BMI SDS and therefore was not selected for inclusion in the multiple regression analysis). Such factors may lead to difficulty interpreting BMI. Children with persistent oligoarthritis would not be expected to have such body composition abnormalities: our finding of nutritional impairment in this subtype of JIA is likely to be of clinical relevance.

This convenience sample, collected consecutively, provided a representative cross-section of patients with JIA, therefore minimizing selection bias associated with highly specialized tertiary referral centres. Anthropometric data were collected on 123 patients with JIA. It was not possible to collect the proposed data on 30 children from all JIA subtypes due to insufficient numbers of children attending our clinic within the time period of the study. Although not all disease subtypes were adequately represented in the analysis, emphasizing the exploratory nature of this study, the relative preponderance of female patients with JIA and the observation that the most frequently occurring JIA subgroup was oligoarthritis (persistent) are consistent with previously reported epidemiological UK data [24]. It is likely, however, that the proportion of patients observed with persistent oligoarthritis is lower than would be observed in a cohort with newly diagnosed JIA, as more in this subtype would be expected to be lost to follow-up over time. Our data set included a single female patient with polyarthritis who had a BMI SDS of -4.7 and was therefore severely nutritionally impaired. This patient had over 30 joints with loss of range of movement.

Energy intake was not shown to be predictive of BMI SDS, implying that simple intervention with increased energy intake is not likely in itself to correct nutritional impairment. Sixty-four patients and families out of 123 approached completed and returned a 4-day diet diary. Such a rate of return is typical in the experience of this dietetic department. There are potential difficulties interpreting this type of nutritional intake data. It is recognized that diet diaries are frequently returned by those without nutritional problems, and therefore do not represent a population with poorer eating. In this study there were no significant differences between the BMI SDS or any other measured disease characteristics between the group who completed the diet diary and the group that did not in this study, including disease subtype. Eating practices may change when intake is being monitored, although this may be more likely if the child is obese or being overfed [8]. The median protein intake of those who completed the diaries was 180.9% of recommended intake, and the median energy intake was 86.6% of recommended intake. The recent National Diet and Nutrition Survey showed a mean protein intake of 249% for 4- to 6-yr-old boys and 120% for the older age groups [25]. The dietetic opinion in our institution is that as the RNI for protein is less than 10% of total energy intake this is a lower than desirable level for children with chronic illness, which affects nutritional state. The children in this study do not differ from their peers in terms of protein intake (FA, personal communication). The weak negative association between protein intake and BMI SDS was therefore explained as an artefact of the reference standard. When the results from the diet diaries were included in the model for a subgroup of patients completing the diaries, only disease subtype (persistent oligoarthritis and RF-negative polyarthritis) was retained as a significant predictor of nutritional impairment.

There is evidence to support the role of inflammatory cytokines modulating body composition in adults with rheumatoid arthritis [26], in experimental mice [27] and in cancer-induced cachexia in children [28], but to date we are not aware of any specific such evidence in JIA. This cohort of patients was studied during a period when biological response-modifying drugs, such as the anti-TNF agents, were not available. The efficacy of the anti-TNF

drug etanercept in controlling polyarthritis has been shown in a randomized, controlled trial [29], but it is only licensed for use in active polyarthritis unresponsive to conventional therapy with methotrexate. In individual patients with severe polyarthritis, it has been noted that treatment with etanercept has improved their nutritional state. Whether this results from overall better disease control or directly from TNF blockade is unclear and suggests an area of interest for further study. It is likely that patients with persistent oligoarthritis have a different cytokine profile from those with other JIA subtypes, and as etanercept is not currently licensed for use in persistent oligoarthritis and is unlikely to be offered to most such patients, it is not possible to know whether its use would minimize nutritional impairment in this at-risk subgroup.

Conclusions

This study has shown that impaired nutritional status affects a significant percentage of children with JIA, including those with persistent oligoarthritis. There is no evidence to suggest that nutritional impairment results from reduced energy intake and it is likely that for an individual patient its aetiology is multifactorial, disease subtype being an important risk factor.

Rheumatology	Key messages
	• Nutritional impairment is a risk factor in all subtypes of juvenile idiopathic arthritis, including oligoarthritis.

The authors have declared no conflicts of interest.

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