Inactive Disease in Enthesitis-related Arthritis: Association of Increased Body Mass Index

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ABSTRACT. ***Objective.*** Patients with enthesitis-related arthritis (ERA) were less likely to achieve and sustain inactive disease than children with other subtypes of juvenile idiopathic arthritis. The aim of this study was to evaluate the effect of increased body mass index (BMI) on clinical features of the disease and to investigate whether being overweight or obese limits the possibility of achieving clinically inactive disease in patients with ERA.

Methods. The hospital charts of 72 patients with ERA were reviewed. Demographic and clinical findings were recorded. Patients were divided into 2 groups according to whether they had "healthy weight" (BMI < 85th percentile) or "increased weight" (BMI ≥ 85th percentile) at baseline. The primary outcome of this study was to achieve inactive disease at 1 year after the initiation of therapy. The inactive disease criterion of Wallace, *et al* was used to define inactive disease status.

Results. Twenty patients had increased BMI. The frequency of tarsitis and ankle involvement was higher in patients with increased weight. Thirty-seven patients were inactive at the end of 1 year. In univariate analyses, male sex, increased BMI, ankle involvement, and tarsitis were found to be associated with failure to achieve inactive disease. Multivariate backward stepwise regression analyses revealed that failure to achieve clinically inactive disease was associated with increased BMI and ankle involvement.

Conclusion. Being overweight or obese was associated with failure to achieve inactive disease in patients with ERA. Because body weight is a modifiable factor, individualized interventions may have clinical implications for better therapeutic outcome. (J Rheumatol First Release March 15 2016; doi:10.3899/jrheum.151208)

Key Indexing Terms:
ENTHESITIS-RELATED ARTHRITIS BODY MASS INDEX INACTIVE DISEASE

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in childhood. It represents a nonhomogeneous group of disorders that share the clinical manifestation of arthritis lasting at least 6 weeks while under the age of 16 years[1,2,3,4]. Enthesitis-related arthritis (ERA) is one of the 7 subtypes of JIA classified by the International League of Associations for Rheumatology (ILAR)[5]. It describes the form of the disease that mainly affects male patients after the age of 6 years and is characterized by the association of enthesitis and arthritis. These patients are prone to develop inflammatory spinal pain and sacroiliitis, which later can be classified as juvenile ankylosing spondylitis (AS). The ILAR criteria do not distinguish between the 2 phenotypes of ERA: axial and peripheral disease. The course of ERA can be mild or severe. Several studies indicated that patients with ERA were less likely to achieve and sustain inactive disease than children with other subtypes of JIA[6,7].

Overweight and obesity are widespread medical problems affecting children and adolescents in many countries around the world[8,9,10]. According to the World Health Organization, overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health[11]. There is much evidence that obesity increases the risk for several cardiometabolic, pulmonary, and psychosocial complications for children as well as for adults[12]. Also, increased body mass index (BMI) is associated with changes in both the biomechanical and inflammatory environments within the joint, particularly in osteoarthritis[13,14,15]. The involvement of mechanical stress and its related consequences on inflammatory enthesitis has also been recognized[16]. In addition, experimental models showed that joint mechanical stress, without discernible microdamage or injury, led to spondyloarthritis (SpA)[17,18]. Previous studies showed that obesity was associated with some rheumatological diseases in adults, such as psoriatic arthritis (PsA) and rheumatoid arthritis (RA)[19,20]. Further, increased body weight was associated with worse disease activity in adults with RA, AS, and PsA[21,22,23,24]. However, data about the association between obesity and disease activity in patients with JIA are limited

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to a few studies[25,26]. In ERA, the effect of being overweight or obese on disease-specific features is not known. The aim of our study was to evaluate the effect of increased body weight on clinical features of the disease and to investigate whether being overweight or obese limits the possibility of achieving clinically inactive disease status in patients with ERA.

MATERIALS AND METHODS

All patients diagnosed with ERA between January 2005 and June 2014 in the Pediatric Rheumatology Department of the Dokuz Eylül University Hospital (Izmir, Turkey) were retrospectively evaluated. Institutional Ethical Review Board approval was obtained prior to our study. The ILAR diagnostic criteria[5] were used to define the disease as presence of arthritis and enthesitis, or arthritis or enthesitis plus 2 of the following: sacroiliac joint tenderness or inflammatory spinal pain, HLA-B27 positivity, onset of arthritis in boys aged > 6 years, family history of HLA-B27–associated disease, and symptomatic anterior uveitis with the exclusions of psoriasis, presence of rheumatoid factor, and systemic signs. There were 82 patients diagnosed with ERA in the study period. The initial data for height were missing in the records in 6 patients, and 4 patients did not complete the 1-year followup at our unit. Thus, a total of 72 patients with ERA were enrolled in our study.

The initial BMI of all children was calculated as weight divided by height squared (kg/m^2). BMI values were plotted using the 2000 US Centers for Disease Control growth charts (BMI for age)[27]. Children were classified as obese if their BMI was ≥ 95th percentile, overweight if their BMI was at or above the 85th percentile and below the 95th percentile, and healthy weight if their BMI was between the 5th and the 84th percentiles[21]. Prevalence of underweight (BMI < 5th percentile) was also determined; however, there was a very small number of patients (n = 5) in this category, hence they were grouped under healthy weight for statistical analysis. Patients were divided into 2 groups according to whether they had "healthy weight" (BMI < 85th percentile) or "increased weight" (BMI ≥ 85th percentile). Because the BMI category might have varied in 1 year, we also evaluated the BMI category after 1 year.

The following physical examination findings of the initial visit were recorded: presence of active enthesitis as localized tenderness of the patella (at the 2, 6, or 10 o'clock positions), at the insertion of the Achilles tendon on the calcaneus, and at the insertions of plantar fascia on calcaneus; presence of active arthritis; presence of tenderness on direct compression over sacroiliac joints; presence of tarsitis; and presence of symptomatic anterior uveitis. The patients and/or parents were asked if the patient had inflammatory spinal pain. Inflammatory spinal pain was defined as lower back pain with insidious onset, which improved with exercise and was associated with > 30 min of morning stiffness[28,29]. The duration of morning stiffness for other joints was also recorded. In case of sacroiliac tenderness and/or inflammatory spinal pain at medical history, the diagnosis of sacroiliitis was confirmed radiologically by conventional radiographs or magnetic resonance imaging. The New York scoring method for the sacroiliac joints was used for conventional radiographs[30]. Bone marrow edema within the sacrum and/or adjacent ilium was accepted as the finding of sacroiliitis on MRI[31,32]. Patients were evaluated by the same pediatric rheumatologists (BM or EÜ) at each visit. Patients had routine followup visits to our outpatient clinic every 1–3 months according to their clinical situation. All the above- mentioned physical examinations and queries were repeated at each visit.

The initial and followup values of the erythrocyte sedimentation rate (ESR) for each patient and HLA-B27 status were recorded. High ESR was defined as an ESR value > 20 mm/h.

According to our standard treatment protocol, all patients were first treated with nonsteroidal antiinflammatory drugs. For resistant patients, sulfasalazine or methotrexate were added as disease-modifying antirheumatic drugs (DMARD). In addition, a short course of low-dose prednisone (0.5 mg/kg/day or less) was considered as a bridge therapy for achieving rapid pain control while awaiting the full therapeutic effects of recently initiated DMARD in patients with high physician's global visual analog scale (VAS). If the patient was unresponsive to at least 3- to 6-month course of DMARD, antitumor necrosis factor-α (anti-TNF) treatment was added (etanercept or adalimumab). The access to anti-TNF treatment was more difficult in 2005–2007 than it was in recent years. This might have caused a delay in initiation of anti-TNF treatment in those years.

The primary outcome of our study was the presence of inactive disease at 1 year after the initiation of therapy. The inactive disease criteria of Wallace, *et al*[33] was used to define inactive disease status. The criteria for inactive disease included absence of active arthritis, fever, rash, serositis, splenomegaly, generalized lymphadenopathy attributable to JIA, and active uveitis; normal ESR or C-reactive protein (CRP) levels; and a physician's global assessment (PGA) of disease activity indicating clinical disease quiescence. In addition to the Wallace criteria, no active enthesitis and no inflammatory spinal pain were accepted as a must for clinically inactive disease for our study.

Statistical analysis. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc.) version 16.0 for Windows. Data were expressed as mean ± SD or median and interquartile range (IQR) when appropriate. The categorical variables were reported as counts and percentages. The Student t test was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. A p value < 0.05 was considered as significant. In bivariate analysis, we evaluated the association of the absence of clinically inactive disease at 1 year as the outcome variable with other independent variables: male sex, family history of AS, HLA-B27, increased BMI, enthesitis of the lower extremities, sacroiliitis, hip involvement, ankle involvement, knee involvement, tarsitis, and high ESR by the chi-square test. Multivariate logistic regression analysis was performed using candidate predictors significant at p < 0.10 in the bivariate analyses. We used backward stepwise logistic regression elimination to determine final significant predictors and retained variables significant at p < 0.05 in the final multivariate model. Hosmer-Lemeshow goodness-of-fit statistics were used to assess model fit.

RESULTS

Demographic and clinical data of the 72 patients with ERA enrolled in our study are summarized in Table 1.

There were 11 girls (15%) and 61 boys (85%). The mean age at first symptom onset was 12 ± 2.7 years (min 6.0, max 16.0 yrs). The median age at diagnosis was 14 years (IQR 11.5–16 yrs). The median delay time for diagnosis was 7 months (IQR 2.5–21 mos). Twenty patients (27.8%) had a family history of AS. Among 64 patients in whom HLA-B27 was checked, 38 patients (59.4%) were HLA-B27–positive. The mean ESR at diagnosis was 38.5 ± 29 mm/h (min 4, max 130 mm/h). Forty-three patients (59.7%) had high ESR (> 20 mm/h) at the time of diagnosis. Forty-six patients (63.8%) at time of diagnosis had enthesitis, 33 (45.8%) had sacroiliitis, 24 (33.3%) had hip involvement, 31 (43%) had ankle involvement, 17 (23.6%) had knee involvement, and 19 (26.4%) had tarsitis. Thirty-eight patients (52.7%) had peripheral disease without axial involvement. Only 5 patients (6.8%) had symptomatic anterior uveitis during the first year of the disease.

There were 5 underweight, 9 obese, 11 overweight, and 47 normal weight patients. There were 20 patients (27.8%)

Table 1. The demographic and clinical characteristics of patients at diagnosis. Values are % unless otherwise specified.

Variable	Value
Female/male, n	11/61
Age at symptom onset, yrs, mean ± SD	12 ± 2.7
Age at diagnosis, yrs, median (interquartile range)	14 (11.5–16)
Family history of AS	27.8
HLA-B27	59.4
ESR, mm/h , mean ± SD	38.5 ± 29
Initial BMI category	
Healthy BMI	72.2
Increased BMI	27.8
Enthesitis	63.8
Sacroiliitis	45.8
Ankle involvement	43
Hip involvement	33.3
Knee involvement	23.6
Tarsitis	26.4
Anterior uveitis	6.8

AS: ankylosing spondylitis; ESR: erythrocyte sedimentation rate; BMI: body mass index.

with increased BMI (BMI ≥ 85th percentile) and 52 patients with BMI < 85th percentile in our study. The frequency of tarsitis and ankle involvement was higher in patients with increased BMI, whereas sacroiliitis, hip involvement, and enthesitis were similar between 2 BMI groups (Table 2). The mean baseline ESR was not significantly different between 2 BMI groups (p = 0.467; Table 2).

The evaluation of patients based on the Wallace criteria at the 12th month of the standard treatment protocol showed that 37 patients (51.3%) achieved inactive disease at the end of 1 year. None of the patients stopped taking medication. Among the 35 patients who failed to achieve inactive disease, 35 had high PGA in VAS, 27 had active arthritis, 13 had high ESR, 10 had inflammatory spinal pain, and 8 had enthesitis. The ratio of inactive disease was not statistically significant between patients with sole peripheral disease and patients with axial involvement (20/35 vs 15/37, p = 0.159). We observed that the mean baseline BMI of the patients who achieved inactive disease status was significantly lower than that of nonachievers (19.2 ± 3.1 vs 21.7 ± 5.5, p = 0.018). The mean baseline ESR of the patients who achieved inactive disease status was not statistically different from that of nonachievers (32.2 ± 23.4 vs 45.2 ± 33, p = 0.055; Table 3).

In univariate analyses, male sex, increased BMI, ankle involvement, and tarsitis were found to be significantly associated with failure to achieve inactive disease at 1 year (p = 0.004, p = 0.005, p = 0.001, and p = 0.011, respectively). There also seemed to be an association between HLA-B27 positivity and failure to achieve inactive disease; however, it did not reach a statistically significant level (p = 0.053). Family history, high ESR at diagnosis, enthesitis, sacroiliitis, hip involvement, and knee involvement were not associated with the failure to achieve inactive disease at 1 year (p = 0.365, p = 0.598, p = 0.246, p = 0.334, p = 0.739, and p = 0.683, respectively; Table 3). Multivariate survey logistic regression models were constructed using backward and stepwise selection from all significant variables from

Table 2. Comparison of disease characteristics between 2 BMI groups. Values are n (%) unless otherwise specified.

Variable	Healthy BMI, n = 52	Increased BMI, n = 20	p
Female/male, n	10/42	1/19	0.133
Age at disease onset, yrs, mean ± SD	11.8 ± 2.8	12.6 ± 2.6	0.272
Delay for the diagnosis, mos, median (interquartile range)	12 (3–21)	5.5 (2–21)	0.571
Family history, yes/no, n	15/37	5/15	0.744
HLA-B27, positive/negative, n	27/20	11/6	0.602
Baseline ESR, mm/h, mean ± SD	40.1 ± 29.8	34.5 ± 26.2	0.467
Disease characteristics at diagnosis			
Enthesitis	34/18 (65.4)	12/8 (60)	0.670
Sacroiliitis	27/25 (52)	6/14 (30)	0.094
Hip involvement	19/33 (36.5)	5/15 (40)	0.252
Knee involvement	10/42 (24)	7/13 (53)	0.158
Ankle involvement	18/34 (34.6)	13/7 (65)	**0.020**
Tarsitis	10/42 (19.2)	9/11 (45)	**0.026**
Treatments during the first year			
Oral corticosteroids	15 (28.8)	8 (40)	0.363
IAI	9 (17.3)	4 (20)	0.814
DMARD	49 (94.2)	20 (100)	0.273
Anti-TNF	15 (28.8)	4 (20)	0.446
Inactive disease at Mo. 12	32 (61.5)	5 (25)	**0.005**

Significant p < 0.05 in bold face. BMI: body mass index; ESR: erythrocyte sedimentation rate; IAI: intraarticular corticosteroid injection; DMARD: disease-modifying antirheumatic drug (sulfasalazine or sulfasalazine plus methotrexate); anti-TNF: antitumor necrosis treatment (etanercept or adalimumab); ERA: enthesitis-related arthritis.

Table 3. Comparison between patients by disease status. Values are n (%) unless otherwise specified.

Variable	Inactive, n = 37	Active, n = 35	p
Female/male, n	10/27	1/34	**0.004**
Age at disease onset, yrs, mean ± SD	11.7 ± 2.7	12.2 ± 2.8	0.390
Delay for the diagnosis, mos, median (interquartile range)	7.5 (2–18)	6 (3–24)	0.661
Family history, yes/no, n	12/25	8/27	0.365
HLA-B27, positive/negative, n	17/18	21/8	0.053
Baseline ESR, mm/h, mean ± SD	32.2 ± 23.4	45.2 ± 33	0.055
Initial BMI group, increased/healthy, n	5/32	15/20	**0.005**
Disease characteristics at diagnosis			
Enthesitis	26 (70)	20 (57.2)	0.246
Sacroiliitis	19 (51.3)	14 (40)	0.334
Hip involvement	13 (35.1)	11 (31.4)	0.739
Ankle involvement	9 (24.3)	22 (62.8)	**0.001**
Knee involvement	8 (21.6)	9 (25.7)	0.683
Tarsitis	5 (13.5)	14 (40)	**0.011**
Treatments during the first year			
Oral corticosteroids	6 (16.2)	17 (48.5)	**0.003**
IAI	2 (5.4)	10 (28.6)	**0.008**
DMARD	34 (92)	35 (100)	0.085
Anti-TNF	5 (13.5)	14 (40)	**0.011**

Significant $p < 0.05$ in bold face. ESR: erythrocyte sedimentation rate; BMI: body mass index; IAI: intraarticular corticosteroid injection; DMARD: disease-modifying antirheumatic drug (sulfasalazine or sulfasalazine plus methotrexate); anti-TNF: antitumor necrosis factor treatment (etanercept or adalimumab).

univariate analyses. HLA-B27 positivity was also put in the regression model. The absence of clinically inactive disease was associated with increased BMI (adjusted OR 4.9, 95% CI 1.3–18.2, p = 0.019) and ankle involvement (adjusted OR 3.1, 95% CI 1.01–9.5, p = 0.048; Table 4).

The data about either weight or height at the 1-year followup were missing in 4 patients, so we calculated the BMI of 68 patients. There were 17 patients (25%) with increased BMI (BMI ≥ 85th percentile) and 51 patients with BMI < 85th percentile at 1 year. One female and 1 male patient advanced from healthy weight to increased weight, whereas 2 male patients declined to healthy weight from increased weight at 1 year. There was also a statistically significant association between BMI category at 1 year and failure to achieve inactive disease (p = 0.004). To evaluate whether short-term oral corticosteroid use significantly contributed to greater BMI, we compared 2 BMI categories at 1 year in terms of corticosteroid use. Eight patients in the

Table 4. Multivariate backward stepwise logistic regression model for predictors of failure to achieve inactive disease status at 1 year. Data refer to presence and existence of variable.

Variables	β	SE	p	Exp, β	95% CI for OR
Step 1					
Male sex	1.319	1.156	0.254	3.741	0.388–36.061
Increased BMI	1.367	0.707	0.053	3.925	0.982–15.684
HLA-B27	0.651	0.641	0.310	1.917	0.546–6.737
Ankle involvement	0.642	0.642	0.318	1.899	0.540–6.685
Tarsitis	0.616	0.726	0.396	1.851	0.446–7.681
Step 2					
Male sex	1.305	1.155	0.258	3.689	0.384–35.452
Increased BMI	1.463	0.698	0.036	4.317	1.099–16.950
HLA-B27	0.620	0.640	0.333	1.858	0.531–6.509
Ankle involvement	0.820	0.607	0.176	2.271	0.692–7.460
Step 3					
Male sex	1.567	1.123	0.163	4.794	0.530–43.346
Increased BMI	1.375	0.682	0.044	3.957	1.040–15.046
Ankle involvement	0.961	0.586	0.101	2.613	0.828–8.248
Step 4					
Increased BMI	1.583	0.674	0.019	4.868	1.300–18.233
Ankle involvement	1.131	0.573	0.048	3.100	1.010–9.532

SE: standard error; BMI: body mass index.

increased BMI group and 15 patients in the healthy BMI group used oral corticosteroids. There was not a significant difference regarding corticosteroid use between the 2 BMI groups at 1 year (p = 0.363).

DISCUSSION

Our study showed that being overweight or obese was associated with failure to achieve clinically inactive disease status in patients with ERA. To our knowledge, ours is the first study about the association of increased body weight with disease outcome in patients with ERA. Previous studies showed that the presence of persistently elevated ESR, early hip and ankle involvement, and high numbers of affected joints were associated with poor prognosis in ERA[34,35]. Our study further added that obesity and overweight were associated with poorer outcome in ERA.

There are only 2 studies about the association between obesity and disease activity in patients with JIA[25,26]. Pelajo, *et al*[25] examined the association between obesity and disease activity in 154 patients with JIA. They used the Juvenile Arthritis Disease Activity Score 27 (JADAS-27) to assess the disease activity. In the cross-sectional study, 18% of patients with JIA were obese and 12.4% were overweight. They included 29 patients with ERA, of whom 5 (17.2%) were obese and 5 (17.2%) were overweight. The prevalence of obesity was not significantly different among the subgroups of JIA. The authors reported that obesity did not have a significant effect on JADAS-27 scores after adjusting for age, sex, and JIA subtype. In another cross-sectional study reported by Amine, *et al*[26], in which 58 patients with JIA were enrolled, 41.4% of patients were overweight and 22.4% were obese. They reported that overweight and obesity were associated with significant functional impairment, assessed using the Childhood Health Assessment Questionnaire, and also associated with active disease, assessed using a VAS measured by the physician. Forty-three percent of patients with ERA were overweight. They did not find a significant relationship between the subtypes of JIA and obesity or overweight. In our study, 27.4% of patients with ERA were obese or overweight, in accordance with Pelajo, *et al*[25]. The higher rates of obesity and overweight in Moroccan patients reported by Amine, *et al*[26] might be because of the geographic, racial, and ethnic diversity of the sample.

Regarding the studies showing that obesity and overweight were associated with changes in mechanical and inflammatory environments within the joint[13,14,15], we hypothesized that increased BMI might act as both mechanical stress and an inflammatory contributor, which might harm disease-specific features on ERA. In the more recent years, the involvement of mechanical stress and its related consequences on inflammatory enthesitis are well recognized[16]. Further, experimental studies focused on the $TNF^{\Delta ARE}$ spondyloarthropathy model demonstrated that joint mechanical stress without significant injury led to enthesitis subsequently spreading to adjacent joint structures including the synovium and bone[17,18]. Our study showed that the rate of sacroiliitis, enthesitis, and hip involvement were not significantly different in overweight and obese patients when compared with the healthy weight group; however, tarsitis and ankle involvement were higher in patients with increased BMI. To our knowledge, ours is the first study showing the relationship between increased BMI and clinical features of the disease characteristics in patients with ERA. Besides being a mechanical stressor, several studies suggested that the excessive adipose tissue in obese individuals might have negative immunomodulatory properties and pharmacokinetic consequences[36,37,38]. Adipose tissue may act as an active endocrine organ that releases several proinflammatory cytokines, such as TNF-α and interleukin 6 as well as some specific adipokines, which also have proinflammatory properties leading to a chronic low-grade systemic inflammation[36,37,38]. Even though increased body weight was shown to be associated with increased inflammatory markers, such as ESR and CRP[39,40,41], our present study could not show this association. Similarly, in other studies about JIA, ESR and CRP did not correlate with BMI[42,43].

Previous studies showed that increased body weight was associated with worse disease activity in adults with AS[24,44,45]. Gremese, *et al*[44] retrospectively evaluated the effect of BMI in response to TNF-α therapy in 170 patients with active AS. They showed that being overweight and obese was associated with a lower rate of success in obtaining response status in patients with axial SpA treated with 12 months of anti-TNF drugs. In another retrospective study including 155 patients with AS, Ottaviani, *et al*[45] showed that a high BMI impaired the response to infliximab after 6 months. The results of our study are in concordance with these previous adult studies.

Our study has some limitations. First, enthesitis and sacroiliitis are challenging to detect on physical examination, and diagnosis of these entities may be underestimated by physicians. We did not use the dolorimeter pain index or imaging studies to detect enthesitis; however, we radiologically confirmed sacroiliitis. We believe that evaluation of the patients by the same pediatric rheumatologists might help to minimize the related discrepancy. Second, the patients were using different treatments at the time of evaluation. However, there were no significant differences between the 2 BMI groups regarding the rate of medications used in the first year. Despite many advances in the treatment of JIA, there is still a lack of evidence for the treatment of several disease subtypes such as ERA. There is not a suggested standard guideline for ERA. Also, there are no data about whether systemic corticosteroids can be used as bridge therapy in patients with ERA. We used short-term corticosteroids in 32% of our patients as bridge therapy. The greater percentage of children receiving oral corticosteroids were in the active disease group. To evaluate whether short-term oral cortico-

steroid use significantly contributed to greater BMI, we compared corticosteroid use in 2 BMI categories at 1 year and found no significant difference between the 2 BMI groups. Other limitations of our study are its retrospective design and relatively small sample size, which may not be large enough given the number of predictors we analyzed. Therefore, further prospective studies including larger number of patients are required to support our results.

Our study suggested that being overweight or obese was associated with the failure to achieve inactive disease in patients with ERA. Because body weight is a modifiable factor, individualized interventions may have potential clinical implications for better therapeutic outcome in patients with ERA.

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