Body composition and adipokines in patients with juvenile idiopathic arthritis and systemic glucocorticoids

K. Markula-Patjas[1], H. Valta[2], M. Pekkinen[3], S. Andersson[2], K. Aalto[2], P. Lahdenne[2], H. Viljakainen[2], O. Mäkitie[2-4]

[1]Paediatric Research Centre, University of Tampere and Tampere University Hospital, Tampere, Finland; [2]Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [3]Folkhälsan Research Centre, Helsinki, Finland; [4]Department of Molecular Medicine and Surgery, and Centre for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden.

Abstract

Objective

The aim of this cross-sectional study was to explore body composition, and the relationship of serum adipokines with bone mass and disease activity, in a cohort of JIA patients with at least three months' exposure to systemic glucocorticoids (GC).

Methods

Fifty patients with JIA (34 girls, median age 12.4 years and disease duration 6.3 years) and 88 controls matched for gender and age participated in this study. Bone mineral content (BMC) and areal bone mineral density (BMD) of the lumbar spine and whole body, as well as body composition were assessed with dual-energy x-ray absorptiometry. Fasting serum leptin and adiponectin were measured.

Results

Fat and lean mass were similar between patients and controls, but patients had slightly decreased BMD Z-scores. Serum leptin and adiponectin concentrations were similar. Disease activity was low, and no correlation with adipokines was observed. Patients with bone age-corrected lumbar spine BMD Z-score ≤-1.0 ("low BMD") did not show alterations in body composition, GC exposure or current disease activity, but had decreased BMC-to-lean mass ratio ($p<0.001$) and tendency for increased serum leptin ($p=0.064$). However, no association of leptin with BMD in multivariate analysis existed in patients or controls. An inverse association between adiponectin and whole body BMD was observed in both groups.

Conclusion

Normal body composition was observed in a JIA cohort with low-dose GC exposure. Patients with "low BMD" tended to have increased serum leptin, but leptin did not associate with BMD. In this cohort with low disease activity, no correlation between adipokines and disease activity was present.

Key words

juvenile idiopathic arthritis, glucocorticoids, body composition, adipokines, bone mineral density

Kati Markula-Patjas, MD
Helena Valta, MD, PhD
Minna Pekkinen, PhD
Sture Andersson, MD, PhD
Kristiina Aalto, MD, PhD
Pekka Lahdenne, MD, PhD
Heli Viljakainen, PhD
Outi Mäkitie, MD, PhD

Please address correspondence to:
Dr Kati Markula-Patjas,
Paediatric Research Centre,
University of Tampere,
P.O. Box 2000,
33521 Tampere, Finland.
E-mail: kati.markula-patjas@pshp.fi

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Introduction

Patients with juvenile idiopathic arthritis (JIA) are prone to disease complications, including negative effects on body composition and bone health. Previous studies report a tendency for decreased lean body mass (1, 2) and increased fat mass (1-4), resulting from several factors (5). Pubertal delay may postpone physiological gender-specific changes of body composition in JIA (6). Malnutrition (7) may follow due to loss of appetite, increased protein catabolism induced by inflammatory cytokines (8) and, in systemic arthritis, increased basal energy expenditure (9). Reduced muscle mass and strength result from limited physical activity, chronic inflammation and glucocorticoids (GC) (8, 10). In turn, GCs induce accumulation and redistribution of body fat (11).

Bone loss, resulting especially from enhanced osteoclast function but also blunted bone formation, is induced by inflammatory cytokines, such as tumour necrosis factor α (TNF-α), and interleukins 1, 6 and 17 (12). Moreover, GCs interfere with calcium balance and suppress bone formation while favouring bone resorption (13). Diminished muscle mass and impaired muscle function limit loading, thereby decreasing bone mass accrual (10, 14). Low body fat content associates with detrimental hormonal changes (15) and low bone mineral density (BMD) (16). Increased fat mass may, despite increased mechanical loading, exert negative effects on bone. Obese children have more fractures (17) and reduced BMD for their weight (18, 19). Also in JIA, obesity seems to be a risk factor for fractures (20). Excess fat may be especially harmful for bone mass accrual during and after the pubertal growth spurt (21, 22). The underlying mechanisms are largely unknown, but fat-derived adipokines are suggested to play a causative role.

Adipokines are pleiotropic proteins secreted mostly from white adipose tissue, and being widely involved in human physiology (23). Leptin and adiponectin, the two most studied adipokines, participate in bone homeostasis, but controversies remain about their relationship with bone mass. Leptin acts on bone-forming osteoblasts through two different routes: an indirect inhibitory effect through the central nervous system (24), and a direct positive effect locally in the bone microenvironment (25). Both positive and negative effects of adiponectin on bone metabolism and bone mass have been reported (26, 27). Clinical studies on adults have found a positive or absent association between serum leptin and BMD (28), and results in children are even more conflicting (29-32). Results on adiponectin in adults and children suggest an inverse or absent relationship with BMD (30, 32, 33). We have previously shown a tendency for an inverse association between leptin and serum bone turnover markers independently of fat mass in patients with severe JIA and high adiposity (4), but no studies have evaluated the relationship of adipokines with bone mass in JIA.

Adipokines are recognised as regulators of immunity and inflammation. Leptin stimulates IL-6 production in synovial fibroblasts in patients with rheumatoid arthritis (RA) (34). Further, serum leptin levels are elevated and possibly relate to more aggressive disease course in RA (35). Although regarded mostly as an anti-inflammatory adipokine, adiponectin in certain conditions induces also proinflammatory effects. Studies on RA show a positive association between adiponectin and radiologic progression, but results concerning disease activity are more inconsistent (36). In children with rheumatic diseases, the relationship between adipokines and disease activity is largerly unknown.

We aimed to explore body composition and the relationship of serum leptin and adiponectin with bone mass and disease activity in a cohort of GC-treated JIA patients and their healthy controls.

Materials and methods

The present study was carried out at the paediatric rheumatology division of Children's Hospital, Helsinki University Central Hospital, Finland. The original cohort consisted of 62 consecutive patients with JIA, aged 4.6–17.9 years, diagnosed according to the revised criteria (37) at least two years prior to the study. All patients had received sys-

temic (peroral) glucocorticoids for at least three months (median 24 months) during their disease course. Altogether 63% of the patients had been on GC therapy during the 2 years preceding the study, and 87% had used alternate-day regimen for more than 90% of the total duration of their GC therapy (38). As no controls younger than 7 years of age were available, patients aged below 7 years (8 patients) were excluded from the present analyses. In addition, 4 patients with incomplete whole body dual-energy x-ray absorptiometry (DXA) data were excluded. The final study cohort thus comprised 50 subjects (68% females) aged 7.2–17.9 years; all were of Caucasian origin. Controls were chosen from a cohort of 195 apparently healthy Finnish children who participated in a school-based study on vitamin D and bone health in the district of Helsinki (39). These children were between 7 and 19 years of age. One or two matched controls were selected for each patient, depending on availability: thus altogether 1.74 controls for each girl and 1.81 controls for each boy were included. A written informed consent was obtained from patients and their parents. The study protocol was approved by the Research Ethics Committee of Helsinki University Central Hospital.

Patient records were reviewed for disease- and treatment characteristics. As described earlier, in the original cohort median disease duration was 5.6 (2.0–15.1) years, and 42% of the patients were on GCs and 27% on TNF-α-antagonists at the time of the study. They had normal growth; median height was +0.1 (-2.9±1.5) SD and median height-adjusted weight +4 (-17±40) %. Median bone age-corrected Z-scores for lumbar spine (LS) and whole body (WB) area BMD were -0.4 and -0.1, respectively (38). Systemically administered GCs were converted to prednisolone equivalents for calculation of absolute and weight-adjusted cumulative doses. Measurement of height and weight, and a clinical examination by a paediatric rheumatologist, including the assessment of pubertal status according to Tanner (40), were performed. Disease activity measures included the number of active joints, global assessment of disease activity by the physician, global assessment of overall well-being by the parents, Childhood Health Assessment Questionnaire (CHAQ), and erythrocyte sedimentation rate (ESR). Active disease on medication was determined according to Wallace (41). Juvenile Arthritis Disease Activity Score for 10 joints (JADAS-10) was calculated (score range 0–40) (42). Gender-and age-matched Z-scores for body mass index (BMI) were calculated according to WHO guidelines (http://www.who.int 2007). Controls were similarly evaluated for baseline characteristics and anthropometry, but the assessment of pubertal maturation was based on gonadotropin and sex-steroid values.

Imaging studies

Bone age was determined from a plain radiograph of the left hand by one of the authors (OM) according to Greulich-Pyle (43), and was considered normal when differing less than one year from calendar age. Bone age (delayed in 14, normal in 29, and advanced in 7 patients) was used for analyses instead of calendar age in patients, unless otherwise indicated. Bone mineral content (BMC, g) and areal BMD (g/cm^2) of the LS (L1-L4) and WB, were assessed with DXA (Hologic Discovery A, Waltham, MA, USA). Z-scores for BMD values were calculated according to equipment-specific age- and sex-adjusted reference database for US Caucasian children, which in the absence of a national Finnish database has been shown to be appropriate for Finnish children (44). Fat mass, trunk fat mass, and lean mass were also assessed similarly for patients and controls. One patient had spinal compression changes in the lumbar area (38), and his results were excluded from all analyses concerning BMC or BMD of the lumbar spine.

Biochemistry

Fasting early morning blood samples were collected and stored at -80°C until analysed. Serum leptin and adiponectin concentrations were assessed using human leptin and adiponectin ELISA (R&D Systems). Girls over eight and boys over ten years were assessed for gonadotropins and sex steroids (follicle-stimulating hormone, luteinising hormone, and estradiol or testosterone). ESR was measured only in patients.

Table I. Disease characteristics in patients.

Disease characteristics	Patients (n=50) median (range)
Age at diagnosis, yrs	4.7 (1.1–15.3)
Disease duration, yrs	6.3 (2.0–15.1)
ANA positive, n (%)	11 (22%)
Uveitis, n (%)	15 (30%)
JIA subtype, n	
oligoarthritis, persistent	4
oligoarthritis, extended	14
polyarthritis, rf-	29
polyarthritis, rf+	1
systemic arthritis	2
Parameters of disease activity	
No. active joints	0.0 (0–8)
Physician's global assessment	5.0 (0–80)
Patient's global assessment	3.5 (0–87)
CHAQ	0.0 (0–1.625)
ESR	8.5 (2–65)
JADAS-10*	2.4 (0–18.3)
Active disease, n (%)**	21 (42%)
GC time, yrs	2.2 (0.25–12.5)
Time since finishing GC therapy, yrs#	1.3 (0.3–5.0)
Cumulative GC dose, mg	2863 (453–21201)
Cumulative GC dose, mg/kg	102 (11–1095)
Current GC dose, mg/d##	2.5 (1.25–10.0)
Current GC dose, mg/kg/d##	0.05 (0.02–0.3)
Biologicals previously, n (%)	19 (38%)
at the time of the study	16 (32%)

*Disease activity score, values between 0 and 40. **Active disease on medication according to Wallace. #n=30. ##n=20.

Statistical analysis

Data analyses were performed with SPSS for Windows 21 (SPSS Inc., Chicago, IL, USA). Data are presented as median with range or interquartile range (IQR) showing the 25 and 75 percentile values. P-values for group comparisons were calculated with Mann-Whitney U-test, or for categorical variables with Chi square test or Fisher's exact test. Spearman correlation was used for correlations. Comparison between groups with adjustments was tested with univariate analysis of variance (ANOVA). Association between adipokines and bone variables, after controlling for confounding factors, were analysed with linear regression. Logarithmic transformations were utilised for non-normally distributed values as appropriate. Data

Table II. Whole body DXA data and adipokine concentrations in 50 patients with JIA and 88 healthy controls.

	Controls		Patients		
	median	IQR	median	IQR	*p*-value
LS area, cm^2	45.8	40.2 – 55.1	46.1	40.4 – 54.5	0.889
LS BMC, g	34.42	26.46 – 51.41	33.3	24.0 – 47.0	0.369
LS BMD, g/cm^2	0.755	0.655 – 0.925	0.710	0.590 – 0.859	0.106
LS BMD Z-score*	0.0	-0.5 – +0.6	-0.5	-1.2 – +0.6	**0.006**
WB area, cm^2	2020	1777 – 2353	1979	1617 – 2267	0.341
WB BMC, g	1619	1322 – 2109	1533	1154 – 1977	0.233
WB BMD, g/cm^2	0.783	0.739 – 0.901	0.776	0.690 – 0.891	0.176
WB BMD Z-score*	0.1	0.0 – +0.08	-0.2	-0.9 – +0.8	**0.009**
Total fat, %	26.9	21.2 – 31.4	27.1	23.0 – 32.3	0.516
Fat mass, g	11968	7969 – 15061	11994	7727 – 16885	0.693
Trunk fat, %	20.9	15.7 – 25.8	21.4	16.1 – 26.4	0.830
Trunk fat mass, g	3910	2506 – 5434	3935	2290 – 5817	0.787
Lean mass, g	30628	24913 – 36838	31653	23085 – 35956	0.852
Lean mass/height, g/m	19897	17188 – 22171	20695	16417 – 22508	0.951
WB Bone area/height, cm^2/m	1330	1239 – 1411	1305	1169 – 1418	0.393
BMC/lean mass, g/g	0.053	0.050 – 0.056	0.051	0.048 – 0.054	**0.002**
S-leptin, ng/ml	5.4	2.8 – 9.0	6.6	2.9 –10.2	0.263
S-adiponectin, µg/ml	8.8	6.8 – 12.3	7.6	6.3 –11.7	0.270

*Corrected for bone age in patients. LS: lumbar spine; BMC: bone mineral content; BMD: bone mineral density; WB: whole body. *P*-values were determined by Mann-Whitney U-test.

were further examined by dividing the patients into two groups ("low-BMD" and "normal-BMD" groups), based on LS BMD Z-score, and using Z-score -1.0 as a cut point; two patients with Z-score values of -1.0 were included in the low-BMD groups.

Results

Table I presents disease characteristics in the 50 subjects with JIA. At the time of the study, 20 patients (40%) were on systemic GC therapy. Mostly alternate-day regimen was used, since in 84% of the patients, every-day regimen accounted for less than 10% of the total GC therapy duration. During the course of the disease, intra-articular GC (median 7, range 0–37 injections) had been given to 92% of the patients. At the time of the study, 76% of the patients used methotrexate, 22% hydroxychloroquine, 4% sulfasalazine, 10% leflunomide, and 32% TNF-α-antagonists. Only six patients (12%) did not participate in school physical education, and most of the patients (62%) had a regular leisure time sport activity. Anthropometric data did not differ between patients and controls (Supplementary Table I).

Data on DXA measurements are presented in Table II. Body composition did not differ between controls and patients. Bone variables were otherwise rather similar, but patients had lower median LS BMD Z-score (p=0.006), even when adjusted for height Z-score (p=0.010). WB BMD Z-score was also lower in patients (p=0.009). Bone area for height and lean mass for height were similar between the groups, but BMC-to-lean mass ratio was lower in patients. Parameters of disease activity or the cumulative weight-adjusted GC-dose did not correlate with bone mass values, but the current weight-adjusted GC-dose correlated inversely with WB BMD (r=-0.304, p=0.032); a similar trend was seen with LS BMD (r=-0.272 and p=0.059). The amount of physical activity could not be reliably compared between groups.

Serum leptin and adiponectin concentrations did not differ between patients and controls even when adjusted for fat mass (p=0.400 for leptin and 0.373 for adiponectin). No correlations between adipokines and disease activity appeared. Adipokine concentrations did not differ between those with or without anti-TNF-α therapy.

Patients were further examined for body composition and disease characteristics in "low-BMD" and "normal-BMD" subgroups, firstly based on LS BMD Z-score for calendar age with a cut point at -1.0 (n=16 and n=34, respectively). While age was similar, bone age delay appeared in 56% of those with low BMD but only in 15% of those with normal BMD. Patients with low BMD seemed to have lower median Z-scores for height (p=0.025) and BMI (p=0.005), and reduced bone area for height (p=0.039) and lean mass for height (p=0.039). However, when subgroups were determined based on bone age-corrected LS BMD Z-score cut point at -1.0, no differences in anthropometry, body composition, disease duration or cumulative GC exposure were present. Only decreased BMC-to-lean mass ratio was evident in the low-BMD group. (Supplementary Table II and Fig. 1). These patients tended to have active disease during the last 6 months more often, but current disease activity was similar. In those who were currently on GC, the weight-adjusted daily GC-dose tended to be higher in the low BMD group. (Supplementary Table II) Serum leptin concentration tended to be higher (median 8.2, IQR 5.5–16.4 *vs*. median 5.3, IQR 2.5–8.7, p=0.064) in the low BMD group. The difference remained non-significant when adjusted for gender and fat mass (p=0.061). Adiponectin concentration was similar between subgroups (p=0.979).

Association of adipokines with bone mass was tested with different covariates (an additive model). No association between leptin and BMD existed after adjustments for gender, height, pubertal stage and fat mass either in controls or patients. Adiponectin associated inversely with LS BMD (standardised beta coefficient -0.112, p=0.036) and WB BMD (beta -0.127, p=0.047) in controls. Inverse association with WB BMD (beta -0.204, p=0.018), but not LS BMD, was observed also in patients, when correction for bone age instead of pubertal stage was performed.

Discussion

We observed normal body composition in a cohort of patients with JIA and preceding systemic GC exposure. Even patients with bone age-corrected LS BMD ≤-1.0 showed similar growth and body composition but reduced BMC-

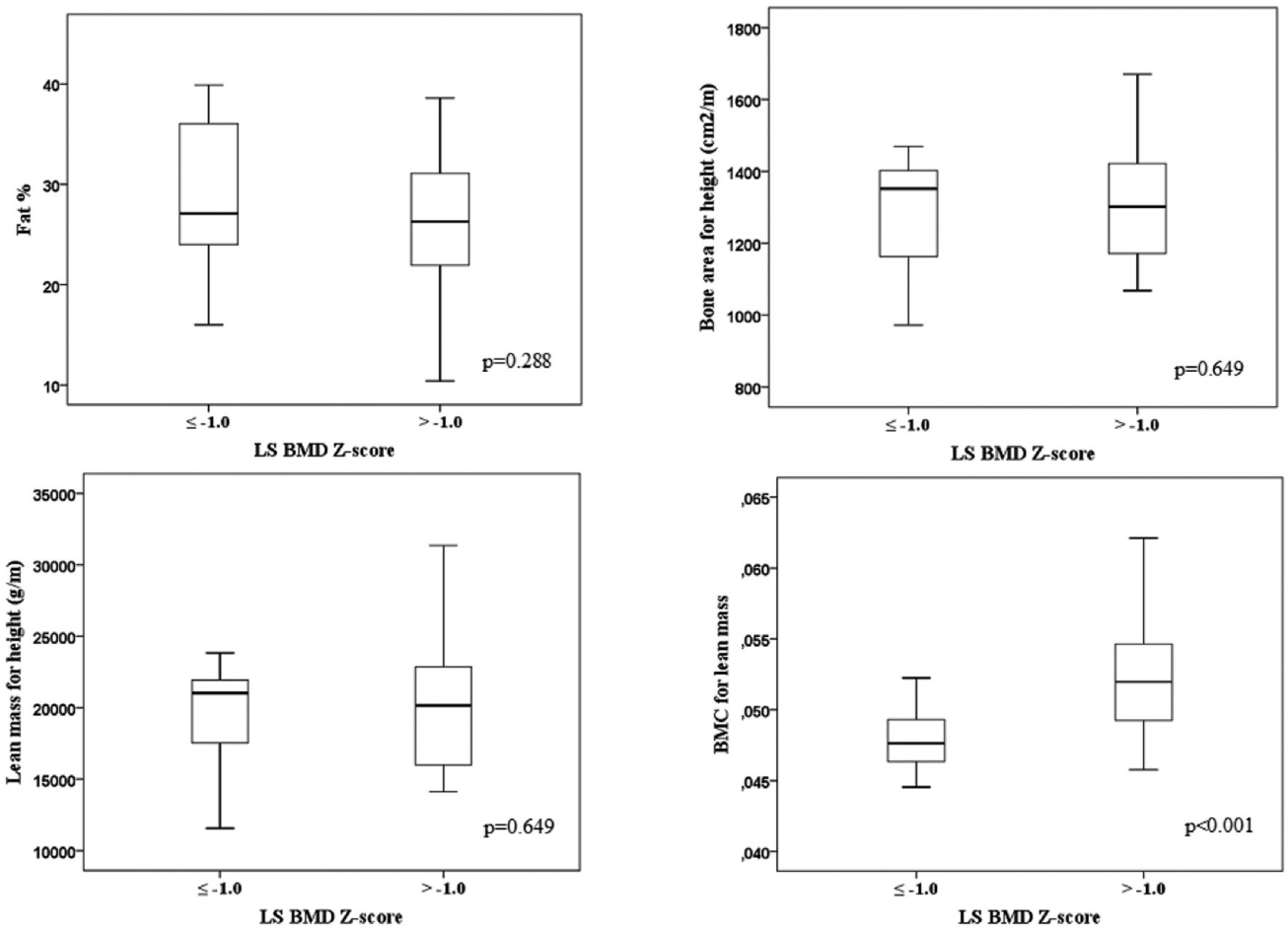

Fig. 1. Comparison of body composition in patients according to bone age-corrected LS BMD Z-score; a cut-off value of -1.0 was used.

to-lean mass ratio when compared with those with a BMD Z-score > -1.0. In this JIA cohort with mostly low disease activity, serum leptin and adiponectin concentrations were similar to controls, and did not correlate with disease activity.

We evaluated body composition in a cohort comprising 50 JIA patients with median disease duration of 6.3 years and systemic GC exposure for at least three months. Some patients required steroids in addition to traditional DMARDs and anti-TNF therapy to attain low disease activity or full remission (45). Furthermore, some patients were treated with steroids during a time when TNF-modulators were not yet actively used. Earlier DXA data on cohorts with high-dose GCs (1) or partial GC-exposure (2-4) suggest a tendency for decreased lean mass and increased fat mass in JIA patients. Surprisingly we observed no differences in body composition between the groups. Correspondingly, while changes of body composition may be prominent in early disease (2), another study on young adults with JIA and median disease duration of 15.5 years showed that patients in remission had even a better nutritional status with less body fat and more lean mass than healthy controls (46). Although 42% of our patients had an active disease on medication (41), current disease activity was mostly low, largely to aggressive medication. In addition, physical activity was mostly not limited. Furthermore, although 40% of the patients were still on GCs at the time of the study, they had mainly used rather low doses and alternate day regimen, which is likely to reduce negative effects on body composition (47). Some studies show increased BMI (48) and lean mass-to-fat mass ratio (49) with anti-TNF-α therapy, used by 32% of our patients, although their effects on body composition are not well known. According to our results, we conclude that along with modern treatment, systemic low-dose GC therapy may not necessarily lead to growth retardation and altered body composition in non-systemic JIA.

Low LS BMD for calendar age seemed to relate to short stature and reduced muscle mass. However, when comparing subgroups based on bone age-adjusted LS BMD Z-score, no differences in growth or body composition were evident but BMC-to-lean mass ratio was reduced in the low BMD group. Either GC exposure or current disease activity did not differ, but those with low BMD more often tended to have recent disease activity, suggesting that deleterious effects of inflammatory cytokines on bone are likely to contribute to low BMD (12).

Recent research suggests that adipokines may play a role in the complex and possibly age-dependent relationship between fat and bone (50). Interestingly a subgroup of patients with

Supplementary Table I. Anthropometric data for the 50 patients with JIA and the 88 healthy controls.

	Controls		Patients		
	median	range	median	range	*p*-value
Boys / girls, %	33 / 67		32 / 68		0.908
Age, yrs	12.7	7.4 – 17.4	12.4	7.2 – 17.9	0.702
Bone-age, yrs			12.7	6.0 – 18.0	
Height, cm	155.3	122.5 – 187.8	152.9	109.3 – 187.0	0.436
Height Z-score	0.2	-2.0 – +2.8	0.1	-2.9 – +1.5	0.313
Weight, kg	43.6	20.9 – 86.8	48.0	18.3 – 96.4	0.926
Height-adjusted weight, %	2.0	-20.0 – +51.0	5.0	-17 – +49	0.281
BMI, kg/m^2	18.4	13.6 – 29.0	18.9	13.2 – 30.0	0.509
BMI Z-score	0.0	-2.2 – +2.5	0.2	-1.9 – +2.3	0.321
Pre- / postpubertal, n (%)	38 / 36		36 / 28		0.421

P-values were determined by Mann-Whitney U-test or Chi square test, as appropriate.

Supplementary Table II. Comparison of patients according to bone age-corrected lumbar spine BMD Z-score; a cut-off value of -1.0 was used. Data are presented as median (IQR) or n (%).

	≤-1.0 SD (n=15)		>-1.0 SD (n=34)		
	median	IQR	median	IQR	*p*-value
Girls, n (%)	11 (73)		23 (68)		0.750
Age, yrs	12.5	10.6 – 14.2	11.9	9.2 – 15.5	0.896
Bone age, yrs	13.0	11.3 – 14.0	12.5	9.4 – 15.0	0.837
Pre- / postpubertal, n (%)	5 (33)/2 (13)		13 (38) /11 (32)		0.211
Height Z-score	-0.2	-0.7 – +0.2	0.2	-0.6 – +0.8	0.158
BMI Z-score	0.6	-0.8 – +1.0	0.1	-0.6 – +0.7	0.544
Disease duration, yrs	6.9	2.8 – 9.7	6.1	4.6 – 9.1	0.896
Duration of GC exposure, yrs	2.1	1.3 – 5.8	2.6	1.1 – 5.2	0.811
Cumulative GC-dose, mg/kg	91	49– 381	124	42 – 358	0.896
Current GC therapy, n (%)	6 (40)		14 (41)		0.938
Current GC-dose, mg/kg/d*	0.12	0.04 – 0.22	0.05	0.03 – 0.08	0.062
Active disease, n (%)	9 (60)		12 (35)		0.107
JADAS-10	2.4	0.7– 5.3	2.3	0.5 – 3.5	0.379
Biological drugs currently, n (%)	6 (40)		10 (29)		0.466
Participation in school gymnastics, n (%)	11 (73)		32 (94)		0.062

*n=6 (40%) and n=14 (41%). GC: glucocorticoid; JADAS-10: juvenile arthritis disease activity score of 10 joints. *P*-values were determined by Mann-Whitney U-test or Chi square test.

low LS BMD showed a tendency for increased serum leptin concentration, but we did not observe association between leptin and BMD. Earlier studies on healthy normal-weight (30, 31) or obese (29, 32) children and adolescents have reported either positive (32), negative (29, 30) or no relationship (31) between serum leptin and BMC or BMD. Unfortunately we could not separate between visceral and subcutaneous fat compartments and this aspect remains to be explored in future studies. Consistent with earlier findings in adults (28) and children (30, 32, 33), we observed inverse association between adiponectin and BMD in both groups.

Leptin concentrations did not differ between patients and controls in the present cohorts even when adjusted for fat mass. Adiponectin concentrations were also similar. Many studies on adults with RA suggest that leptin and adiponectin mediate proinflammatory actions and serum levels may relate to disease activity (36), but we did not observe association between leptin or adiponectin and disease activity in patients with JIA. However, low current disease activity in the present cohort clearly limits the significance of this finding.

Our study was limited by the rather small sample size, which did not allow us to make comparisons between girls and boys in different stages of pubertal maturation. Our cohort mainly represents non-systemic JIA. DXA has limitations in assessing bone and body composition especially in those with low or high fat mass, but this is unlikely to impact our main results. Our study would have been improved by evaluation of nutrition and weight-bearing physical activity as determinants of body composition. It cannot be excluded that medication, especially GCs and biological drugs, could have impacted serum adipokine levels (11, 36). With these limitations in mind, our study provides preliminary data on body composition and the association of adipokines with BMD in JIA with systemic low-dose GC exposure.

In conclusion, modern therapies allowing good disease control seem to enable normal body composition in patients with JIA, even in those who are exposed to systemic low-dose GC. However, when alternative medications are available even low-dose GC should be avoided. Future studies especially on cohorts with high disease activity are warranted to show whether leptin and adiponectin or other adipokines associate with disease activity in JIA. As the relationship of leptin and adiponectin with bone metabolism and bone mass seems to be rather complicated and is not fully understood, future research is needed.

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