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ORIGINAL RESEARCH

Adipokine profile in long-term juvenile dermatomyositis, and associations with adipose tissue distribution and cardiac function: a cross-sectional study

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ABSTRACT

Objectives In long-term juvenile dermatomyositis (JDM), altered adipose tissue distribution and subclinical cardiac dysfunction have been described. Our aims were to compare adipokine levels in patients with JDM after long-term disease with controls, and explore associations between adipokines and (1) adipose tissue distribution and (2) cardiac function.

Methods The study cohort included 59 patients with JDM (60% female, mean age 25.2 years, mean disease duration 16.9 years), and 59 age/sex-matched controls. Updated Pediatric Rheumatology International Trials Organization criteria for clinically inactive JDM were used to stratify patients into active (JDM-active) or inactive (JDM-inactive) disease groups. Lipodystrophy was clinically assessed in all patients. In all study participants, we measured adipose tissue distribution by dual-energy X-ray absorptiometry and cardiac function by echocardiography. Serum adipokines (adiponectin, apelin-12, lipocalin-2, leptin, visfatin and resistin) were analysed using ELISA.

Results Patients with JDM had higher leptin levels compared with controls ($p \leq 0.01$). In JDM-active, apelin-12 and visfatin were higher compared with JDM-inactive ($p \leq 0.05$). In JDM-total and JDM-active, lower adiponectin correlated with lipodystrophy and total fat mass. Also, systolic dysfunction correlated with: lower adiponectin in JDM-total, JDM-inactive and JDM-active, and with lower apelin-12 in JDM-total and JDM-active and resistin in JDM-active (all $p \leq 0.05$). Lower adiponectin correlated with diastolic dysfunction in JDM-total and JDM-active.

Conclusion After long-term disease, leptin levels were unfavourably regulated in patients with JDM compared with controls, and apelin-12 and visfatin in JDM-active versus JDM-inactive. We found associations between adipokines and both adipose tissue distribution and cardiac systolic function in all patients with JDM, which was most prominent in patients with active disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ After long-term disease, patients with juvenile dermatomyositis (JDM) show signs of subclinical cardiac dysfunction and unfavourable adipose tissue distribution.

⇒ In JDM, little is known about adipokine profile and associations with adipose tissue distribution and cardiac function.

WHAT THIS STUDY ADDS

⇒ We here showed that after long-term disease, patients with clinically active JDM had higher levels of apelin-12 and visfatin compared with patients with inactive disease.

⇒ Cardiac systolic function was positively associated with apelin-12 in all patients with JDM, and more strongly in patients with clinically active disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings indicate involvement of the adipokines: leptin, apelin-12, visfatin and adiponectin in JDM, other than a relation to obesity, which should be studied further.

INTRODUCTION

Multiorgan pathologies are found in idiopathic inflammatory myopathies (IIMs) including juvenile dermatomyositis (JDM). The main characteristics of JDM are skin rashes and proximal muscle weakness, probably caused by vasculopathy.[1] Furthermore, the heart can be affected although mostly subclinical.[1] Another frequent consequence to JDM is altered adipose tissue distribution with the presence of lipodystrophy[2] and increased abdominal adipose tissue[3] as recently reported from our study group.[4]

Adipokines are cytokines produced mainly in adipose tissue cells, with an effect on fat distribution, blood pressure, metabolism and vascular homeostasis.[5] Adipose tissue consists of adipocytes and immune cells, and when expanding, adipocytes increase in size and

more immune cells accumulate. In this context, both cell types generate an inflammatory milieu due to altered proinflammatory cytokine release.[6] In the general population, most adipokines such as resistin,[7] apelin-12,[8] visfatin,[9] leptin[10] and lipocalin-2 (also known as neutrophil gelatinase-associated lipocalin (NGAL)[11 12] increase in obesity, with the exception of adiponectin,[13] which is decreased. In autoimmune diseases, the situation might be more complex. In fact, there is evidence that adipokines associate with disease activity and systemic inflammation independent of total body mass index (BMI),[14–19] also shown in JDM.[14 16] However, to our knowledge, adipokine levels and their relation to the adipose tissue distribution have not been studied in long-term JDM.

In the general population, it is well established that obesity-related inflammation is associated with cardiovascular diseases with impaired cardiac contractile (systolic) and relaxation (diastolic) function, especially in individuals with central adiposity.[5] Subclinical cardiac diastolic dysfunction has been found in adult-onset DM[20 21] after short-term disease. Both diastolic and systolic dysfunction (mostly subclinical) have been reported in our JDM cohort of adults and children clinically examined after long-term disease.[22 23] Studying the same cohort of patients with JDM and controls, we recently described an altered body composition with increase in body fat percentage and abdominal fat accumulation (this included increased android to gynoid fat mass ratio and visceral adipose tissue (VAT)) with associations with cardiac and metabolic dysfunction.[24 25]

In view of the unfavourable adipose tissue distribution associated with impaired cardiometabolic function in long-term JDM, we aimed to explore the role of adipokines in this clinical setting. Aims of the study were to compare the adipokine profile in patients with JDM versus controls and in patients with active versus inactive disease. Further, we aimed to explore associations between the selected adipokines and adipose tissue distribution as well as cardiac systolic and diastolic function.

PATIENTS AND METHODS

Study population

In this cross-sectional study, the eligibility criteria for the Norwegian nationwide JDM cohort have been described in detail.[4] Briefly, patients were included if they had age <18 years at disease onset, age ≥6 years at the follow-up examination, disease duration >24 months, and a probable or definitive diagnosis of DM according to the Bohan and Peter criteria.[26] These inclusion criteria were met by the 66 patients diagnosed in Norway between January 1970 and June 2006. Four of those were deceased and 62 were tracked through the National Population Register; 59 of 62 (95%) patients participated in the JDM cohort study.[4] Sex and age-matched controls (1:1) were randomly drawn from the National Population Register as previously described in detail.[27] Exclusion criteria for the controls were among others cardiac and other autoimmune diseases including JDM.[27]

Data collection and clinical measurements

Patients with JDM and controls were comprehensively clinically examined during a follow-up examination visit of 1–2 days at Oslo University Hospital (OUS) (September 2005–May 2009). The examination included echocardiography, dual-energy X-ray absorptiometry (DXA) scanning for body composition and blood sampling as previously described in detail.[4 23 24] Muscle strength/endurance was assessed by unilateral Manual Muscle Test 8 (MMT-8) (0–80) and Childhood Myositis Assessment Score (CMAS) (0–52). In the patients, we assessed disease activity by the Disease Activity Score for JDM (0–20) and cumulative organ damage by the Myositis Damage Index (0–40).[4] Clinically inactive disease was defined according to updated Pediatric Rheumatology International Trials Organization (PRINTO) criteria as the presence of physician's global assessment of overall disease activity ≤0.2, and at least three of the following: (a) serum creatine kinase ≤150 units/L, (b) MMT-8 ≥78 and (c) CMAS ≥48.[28] Patients with clinically inactive disease were defined as JDM-inactive and the remaining were defined as having active disease or JDM-active. A self-reporting questionnaire was used to assess average physical activity inducing sweating or breathlessness and reported as physical activity hours/week.

Serum analyses

Non-fasting blood samples were drawn at the follow-up examination. Lipid profile and erythrocyte sedimentation rate were measured at the accredited medical biochemistry laboratory, Department of Medical Biochemistry, OUS, Rikshospitalet according to a standard protocol. The remaining serum blood samples were stored in smaller batches at −80°C.

Adipokines were analysed in serum batches in 2014 by ELISA according to the manufacturer's protocol. The chosen adipokines were: resistin (DY1359), adiponectin (DY1065), leptin (DY398), lipocalin-2/NGAL (DY1757) (all R&D Systems Minneapolis, Minnesota, USA), visfatin (EK-003-80) and apelin-12 (EKE-057-23) (both from Phoenix Pharmaceutical Burlingame, California, USA). Samples from all patients and controls were analysed at the same time to minimise the run-to-run variability.

Adipose tissue distribution

We analysed adipose tissue data retrieved from the original DXA scans which were performed at the follow-up examination. For this study, the data were reanalysed in the same software version, as described earlier.[24] In brief, in all study participants, total fat mass was measured by a narrow fan-beam densitometer scan according to the manufacturer's protocol (GE Healthcare Lunar Prodigy Advance, Madison, Wisconsin, USA). VAT was quantified in the android region of the trunk using the application (CoreScan; GE Healthcare). The android region

of interest (ROI) contained both VAT and subcutaneous adipose tissue (SAT). The software estimated the quantity of SAT in the android ROI, and the amount of VAT was computed by subtracting SAT from the total android fat in study participants ≥18 years (38 patients and 36 controls) and is presented as total mass (kg).[25]

Cardiac function measures

Cardiac function was assessed by echocardiography (Vivid 7 ultrasound scanner, GE-Vingmed Ultrasound, Horten, Norway) as described earlier.[23] Mitral annulus (MA) displacement was assessed by anatomical M-mode in lateral and septal position using the four-chamber apical view. Left ventricular (LV) length was assessed as the distance from the endocardial border of the apex to the mid-portion of the MA plane. Systolic function was measured as long-axis strain (LAS) and calculated as MA displacement expressed as a percentage of LV end-diastolic length. Diastolic function was recorded as early diastolic tissue velocity (e').[22]

Statistics

For normally distributed continuous data, differences between patients and controls were tested by paired samples t-test, and differences between JDM subgroups by independent samples t-test. The X^2 test was used for categorical data. We used Spearman's or Pearson's correlation coefficients to determine correlations when appropriate. Strengths of correlations were defined as weak r_{sp}=0.1–0.30, moderate r_{sp}=0.31–0.60 and strong r_{sp}=0.61–1.0; only moderate and strong correlations were presented and discussed. P values of ≤0.05 were considered statistically significant. Due to the hypothesis-generating nature of the study, we did not correct for multiple comparisons.

RESULTS

Characteristics and disease variables in patients

Mean (SD) age of patients at follow-up was 25.2 (12.5) years and the mean disease duration 16.9 (10.6) years (table 1). According to the updated PRINTO criteria, 21 (35.6%) had inactive disease and 38 (64.4%) had active disease (table 1). All the 10 (16.9%) patients who received prednisolone at follow-up were JDM-active (table 1). Patients had lower low-density lipoprotein-cholesterol, total cholesterol and high-density lipoprotein-cholesterol than controls, while triglyceride was higher in patients than controls (table 1). Further, both systolic/LAS% and diastolic/e' function were reduced in patients versus controls (p≤0.01) (table 1). Lipodystrophy was found in 10 (16.9%) patients and none of the controls. VAT was measured in all study participants ≥18 years and was higher in patients compared with controls (p≤0.05) (table 1). There were no significant differences in total fat mass, VAT, cardiac function, or lipid levels between JDM-active and JDM-inactive patients.

Serum adipokine levels in study participants

Leptin levels were higher in JDM-total than controls (p≤0.05) (table 2). In JDM-active, visfatin and apelin-12 were both higher compared with JDM-inactive (p≤0.05 and p≤0.01, respectively) (table 2). When stratifying JDM-total according to the occurrence of lipodystrophy, patients with lipodystrophy had lower adiponectin levels compared with patients without (mean (SD) 2.4 µg/mL (2.8) vs 5.4 µg/mL (1.7); p≤0.01).

Correlations between adipokines and fat distribution variables in study participants

In JDM-total and JDM-active, adiponectin correlated moderately and negatively with the occurrence of lipodystrophy and with total fat mass (table 3). Also, there was a moderate and negative correlation between adiponectin and VAT in JDM-total and controls, and more strongly in JDM-active (table 3). Further, lipocalin-2 correlated moderately and positively with total fat mass in JDM-active and controls and with VAT in JDM-inactive (table 3). Resistin correlated moderately and positively with total fat mass in JDM-total and JDM-inactive (table 3). In JDM-inactive, both apelin-12 and visfatin correlated moderately and negatively with VAT. A similar correlation between apelin-12 and VAT was found in controls (table 3). Leptin correlated strongly and positively with total fat mass in all groups (table 3).

Associations between adipokines and cardiac function in study participants

In JDM-total, we found both adiponectin and apelin-12 to correlate moderately and positively with LAS% (systolic function) (figure 1A,B). No correlations were found between LAS% and lipocalin-2 and resistin in neither JDM-total nor controls (figure 1C,D). When correlating adipokines with LAS% in JDM-active patients, we found moderate positive correlations with adiponectin and apelin-12, and moderate negative correlations with lipocalin-2 and resistin (figure 1E,H). Also, in JDM-inactive, we found a moderate positive correlation between LAS% and adiponectin (figure 1E). In both JDM-total and JDM-active, adiponectin correlated moderately and positively with e' (diastolic function) (figure 2A,B).

DISCUSSION

Our study is the first to demonstrate associations of circulating adipokines with measures of adipose tissue distribution and cardiac function in JDM. After long-term disease duration, patients with JDM had higher levels of leptin compared with controls, and in patients with JDM-active, apelin-12 and visfatin were higher compared with JDM-inactive disease. Lower levels of the anti-inflammatory adipokine adiponectin correlated with unfavourable fat distribution including the presence of lipodystrophy, increased VAT and increased total fat mass in both JDM-total and JDM-active. Higher adiponectin and apelin-12 exhibited potential cardioprotective properties in JDM, showing

Table 1 Characteristics and disease variables in patients with JDM at follow-up and controls, and in patients with active and inactive disease

	JDM-active (n=38)	JDM-inactive (n=21)	JDM-total (n=50–59)	Controls (n=50–59)
Characteristics and disease variables				
Disease duration, years	15.9 (10.7)	18.6 (10.3)	16.9 (10.6)	NA
Female, n	26 (68.4)	10 (47.6)	36 (61)	36 (61)
Age at FU, years	24.3 (13.2)	27.0 (11.2)	25.2 (12.5)	25.3 (12.5)
Weight, kg	60.6 (22.5)	66.3 (14.6)	62.6 (20.1)	65.6 (20.1)
Height, cm	162 (17)	170 (9)*	165 (15)	169 (16)
BMI, kg/m^2	21.9 (5.1)	22.7 (4.5)	22.3 (4.8)	22.5 (4.5)
Prednisolone treatment at FU, n	10 (26)	0	10 (17)	NA
Cumulative prednisolone at FU, g	11.1 (13.0)	8.8 (9.4)	10.3 (7.9)	NA
DAS	6.14 (2.4)	2.1 (1.8)**	4.7 (2.9)	NA
MDI total at FU	4.8 (3.1)	3.3 (2.8)	3 (2.6)	NA
MMT-8 at FU	74.9 (5.4)	79.1 (1.1)**	76.4 (4.8)	79.7 (0.8)**
CMAS at FU	46.9 (6.2)	50.7 (2.0)**	48.3 (5.5)	51.2 (0.2)**
ESR, mm/hour	8.3 (6.5)	6.3 (4.9)	7.4 (6.2)	5.7 (4.7)
hs-CRP, mg/L	1.0 (0.1–8.5)	1.0 (0.1–19.8)	1.0 (0.1–19.8)	0.6 (0.12–20.7)
Glucose, mmol/L	5.0 (0.9)	5.3 (0.8)	5.1 (0.9)	4.9 (0.7)
Creatine kinase, U/L	52.6 (15.2)	61.1 (9.6)*	55.7 (14.0)	62.5 (15.1)**
Physical activity, hours/week	3.7 (1.1)	3.6 (1.5)	3.7 (1.3)	4.3 (1.4)
Lipids				
Triglycerides, mmol/L	1.4 (1.0)	1.6 (1.9)	1.5 (1.4)	1.0 (0.5)*
LDL-cholesterol, mmol/L	2.3 (0.7)	2.3 (0.7)	2.3 (0.7)	2.7 (0.8)**
HDL-cholesterol in women, mmol/L	1.3 (0.2)	1.3 (0.3)	1.3 (0.3)	1.6 (0.4)**
HDL-cholesterol in men, mmol/L	0.9 (0.3)	1.1 (0.4)	1.0 (0.3)	1.3 (0.3)**
Total cholesterol, mmol/L	4.3 (0.8)	4.2 (0.9)	4.2 (0.8)	4.6 (0.9)**
Apolipoprotein(A), mg/L	325 (226)	329 (226)	326 (224)	365 (361)
Adipose tissue distribution				
Lipodystrophy, n	7 (18)	3 (14)	10 (17)	0
Total fat mass, kg	19.4 (9.1)	19.4 (9.4)	19.4 (9.2)	18.0 (8.2)
VAT, g	565 (184–986)[c]	726 (162–1272)[d]	577 (178–1072)[a]	232 (72–751)*
Cardiac function				
Long axis strain, %	16.7 (2.7)	16.4 (2.2)	16.6 (2.5)	17.7 (2.0)**
e', cm/s	11.3 (2.8)	11.2 (2.5)	11.3 (2.7)	12.4 (2.1)**

Values are mean (SD) or median (IQR), and n (%).
HDL in women pair n=35, active n=25, HDL in men pair n=22, active n=11, LDL and total cholesterol active n=26, VAT a: n=38, b: n=35, c: n=23, d: n=15. Paired samples and independent samples were used to compare differences between patients and controls and between JDM-active and JDM-inactive, respectively. X^2 was used to compare differences in categorical data.
*P≤0.05 and **p≤0.01 between study groups.
BMI, body mass index; CMAS, Childhood Myositis Assessment Scale; DAS, Disease Activity Score for JDM; e', early diastolic tissue velocity; ESR, erythrocyte sedimentation rate; FU, follow-up; HDL, high-density lipoprotein; hs-CRP, high-sensitive C reactive protein; JDM, juvenile dermatomyositis; LDL, low-density lipoprotein; MDI, Myositis Damage Index; MMT-8, Manual Muscle Test 8; NA, not applicable; VAT, visceral adipose tissue.

positive correlations with cardiac systolic function. Adiponectin was also positively correlated with diastolic function. In contrast, higher resistin and lipocalin-2 correlated with impaired cardiac systolic function, only in the JDM-active group.

The obesity-related apelin-12 was higher in JDM-active compared with JDM-inactive, although there were no significant differences in apelin-12 between JDM-total and controls. To our knowledge, this is the first time apelin-12 is studied in any autoimmune disease. Interestingly, under hypoxic conditions, cellular apelin-12 secretion increases and subsequently stimulates angiogenesis.[29 30] Since vasculopathy with concomitant hypoxia is a hallmark of JDM,[1] increased levels of apelin-12 in patients with active disease might be a consequence of this compensatory mechanism.

Table 2 Adipokines in patients with JDM and controls, and in patients with active or inactive disease

	JDM-active (n=38)	JDM-inactive (n=21)	JDM-total (n=59)	Controls (n=59)
Adiponectin*	5.0 (2.9)	4.7 (2.9)	4.9 (2.8)	5.8 (2.7)
Apelin-12	1.0 (0.5)*	0.7 (0.2)	0.9 (0.5)	0.9 (0.4)
Lipocalin-2	98.9 (34.5)	96.5 (40.3)	98.1 (36.3)	92.6 (40.0)
Leptin	17.5 (14.5)	12.9 (16.4)	15.8 (15.2)	9.9 (9.9)*
Resistin	13.6 (5.5)	13.0 (6.2)	13.4 (5.7)	12.6 (5.4)
Visfatin	6.6 (3.4)**	4.6 (1.6)	5.9 (3.0)	6.0 (2.6)

Values are ng/mL and mean (SD). Paired samples t-test and independent samples t-test were used to compare differences between patients and controls, and JDM-active and JDM-inactive patients, respectively.
*P≤0.05 and **p≤0.01 between JDM-active and JDM-inactive, and *p≤0.05 between patients and controls.
*Values are µg/mL.
JDM, juvenile dermatomyositis.

Higher levels of the proinflammatory visfatin were found in JDM-active than in JDM-inactive and higher levels of leptin found in JDM-total compared with controls. Both visfatin and leptin have been found increased in patients with IIM[16 17] and in patients with rheumatoid arthritis (RA),[18 31] all compared with controls. In mice, leptin deficiency protects against development of various autoimmune diseases, including systemic lupus erythematosus

Table 3 Correlations between adipokines and fat measures in patients with JDM and controls, and in patients with active and inactive disease

	JDM-active (n=38)	JDM-inactive (n=21)	JDM-total (n=59)	Controls (n=59)
Adiponectin				
Lipodystrophy	−0.40*	−0.39	−0.39**	NA
VAT	−0.63**	−0.49	−0.52**	−0.43**
Total fat mass	−0.56**	−0.03	−0.38**	−0.20
Lipocalin-2				
Lipodystrophy	−0.27	−0.24	−0.16	NA
VAT	−0.17	0.33*	0.02	−0.08
Total fat mass	0.32*	0.00	0.24	0.35**
Resistin				
Lipodystrophy	−0.09	−0.27	−0.15	NA
VAT	0.10	−0.12	−0.02	−0.16
Total fat mass	0.30	0.52*	0.38**	0.19
Apelin-12				
Lipodystrophy	−0.01	−0.32	−0.05	NA
VAT	−0.09	−0.43*	−0.12	−0.36*
Total fat mass	−0.15	0.07	−0.08	−0.23
Visfatin				
Lipodystrophy	−0.18	−0.26	−0.16	NA
VAT	−0.03	−0.52*	−0.09	−0.26
Total fat mass	−0.05	−0.08	−0.06	−0.26*
Leptin				
Lipodystrophy	0.05	−0.17	−0.02	NA
VAT	0.29	−0.04	0.24	0.27
Total fat mass	0.62**	0.69**	0.67**	0.59**

Lipodystrophy n=10, VAT n=15 and 23 in JDM-inactive and JDM-active, respectively. Values are Spearman's or Pearson's correlations as appropriate.
*P≤0.05 and **p≤0.01.
JDM, juvenile dermatomyositis; NA, not applicable; VAT, visceral adipose tissue.

Fig. 1.

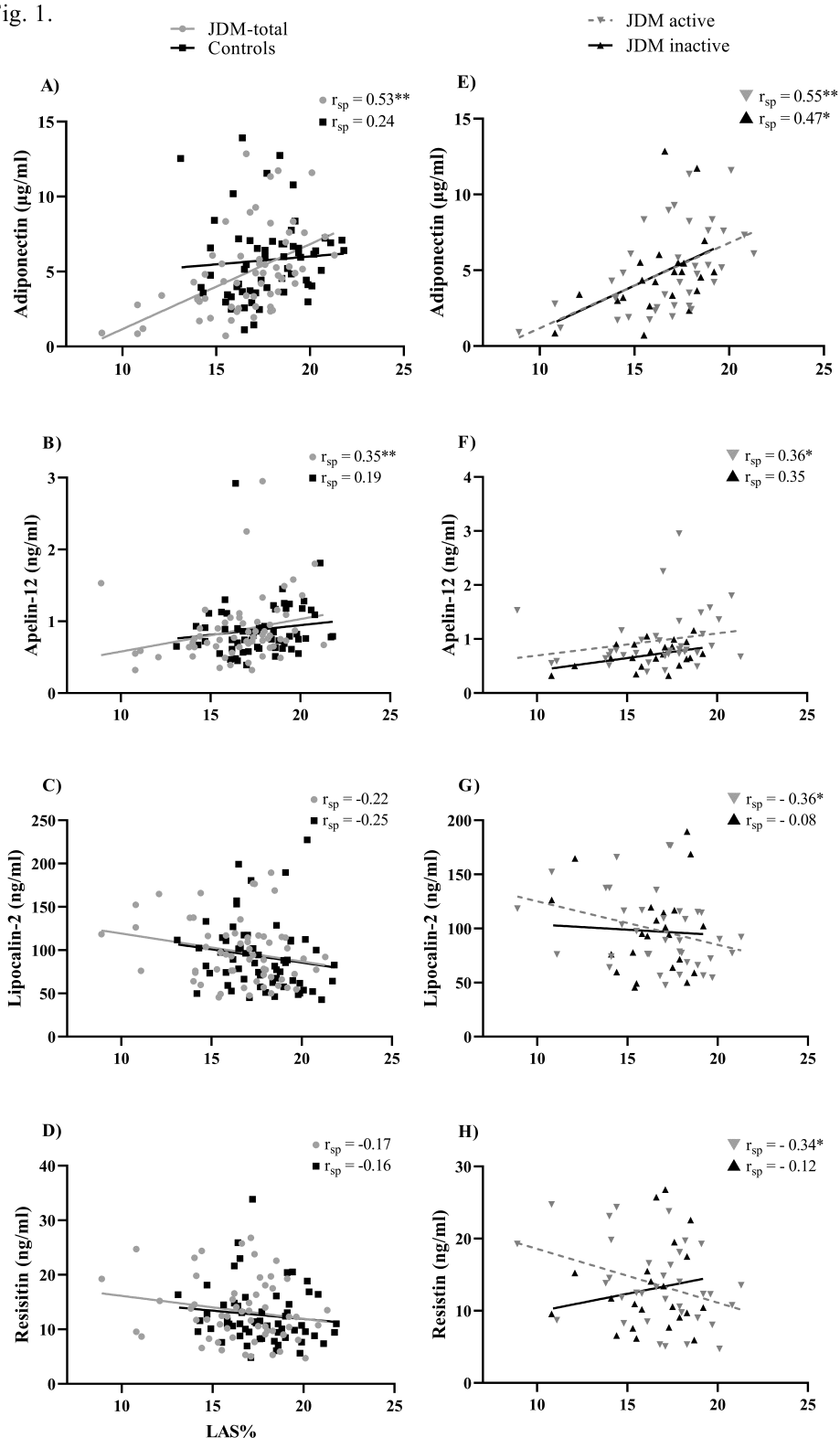

Figure 1 Correlations between systolic function and adipokines. (A–D) Correlations in all patients with juvenile dermatomyositis (JDM-total) compared with controls. (E–H) Correlations in patients with active compared with patients with inactive disease. (A and E) adiponectin, (B and F) apelin-12, (C and G) lipocalin-2 and (D and H) resistin. *P≤0.05, **p≤0.01. LAS, long-axis strain; r_{sp}, Spearman's correlation coefficient.

Fig. 2.

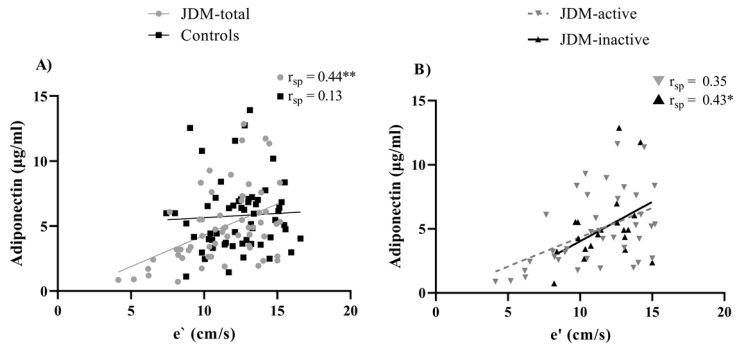

Figure 2 Correlations between diastolic function and adiponectin. (A) Correlations in all patients with juvenile dermatomyositis (JDM) compared with controls. (B) Correlations in patients with active versus inactive disease. *P≤0.05, **p≤0.01. e', early diastolic tissue velocity; r_{sp}, Spearman's correlation coefficient.

and RA.[32] Also, a positive correlation between leptin and C reactive protein (CRP) in non-obese healthy individuals has been shown.[33] Further, visfatin has been associated with disease activity in patients with IIM,[16] and might be involved in regulating angiogenesis in a non-beneficial cardiovascular manner.[34] Interestingly, the two adipokines have several immune-modulatory effects.[34] As such, visfatin and leptin might be involved in development or maintaining inflammation and/or disease activity in JDM; however, we have no data to support this notion.

We found lower levels of the anti-inflammatory adiponectin to be associated with higher VAT, more total fat mass and the presence of lipodystrophy in JDM-total, as well as in the JDM-active group. Also, the level of adiponectin was lower in patients with lipodystrophy than in patients without lipodystrophy. It is well established that adiponectin decreases with visceral fat accumulation.[6 13] Importantly, lower adiponectin could also be a result of reduced adipose tissue mass as found in patients with generalised lipodystrophy,[35] which might also be the case for the patients with JDM in our study.

Higher resistin correlated with increased total fat mass in JDM-total and in JDM-inactive. A positive correlation was found between resistin and measures of fat mass in younger obese subjects when looking at changes over time.[36] Interestingly, studying human cells, obese adipocytes secreted more resistin compared with lean adipocytes and subsequently contributed to impaired myogenesis, especially in older muscle cells.[7]

Lipocalin-2 correlated moderately and visfatin negatively with VAT in JDM-inactive. Lipocalin-2 has been found to correlate with both BMI and CRP in overweight to obese individuals,[12] which indicates an involvement of lipocalin-2 in low-grade inflammation. Associations between visfatin and measures of adipose compartments are inconclusive.[9 37] As such, we have no explanation for our finding in JDM.

As expected, leptin was associated with total fat mass in all patient subgroups as well as in controls. Leptin is secreted from subcutaneous fat cells, proportional with adipocyte growth,[38] and has previously been shown to correlate with total fat mass, in both healthy adults[10] and in patients with RA.[18 39]

Moving to cardiac function, both lower adiponectin and apelin-12 were associated with impaired systolic function (measured by LAS%) in all patient subgroups (but not controls and not significant for apelin-12 in JDM-inactive). Besides being upregulated in obesity and mostly associated with metabolic abnormalities in the general population,[29] there is evidence that apelin-12 is beneficial to cardiac function[29] similar to higher adiponectin levels.[40 41] Improved systolic function correlated with higher levels of apelin-12 in patients with mild to severe heart failure[42] and with higher levels of adiponectin in patients with inflammatory cardiomyopathy.[40] Also, in experimental studies, cardiomyocyte contraction improved after exposure to both adipokines.[43 44] Apelin-12 might provide increased angiogenesis as discussed earlier, also in the heart.

We found better diastolic function with higher levels of adiponectin in JDM-total and JDM-active. Similar to our findings, adiponectin was found independently and positively associated with diastolic function in the general population.[41] Also, lower adiponectin has been found in both humans and rodents with myocarditis and impaired diastolic function.[40 45] These data support a possible beneficial role for both adiponectin and apelin-12 upon cardiac function, which may also apply for patients with JDM.

In JDM-active, higher resistin and lipocalin-2 were associated with impaired systolic function. Interestingly, both resistin and lipocalin-2 seem to be involved with the severity of heart failure,[46 47] indicating an involvement for both adipokines in cardiomyocytes. Experimental studies have shown that resistin impaired cardiomyocyte

contraction in rats[48] and that both resistin and lipocalin-2 induced cardiomyocyte hypertrophy,[12 48] which is frequently found in systolic dysfunction. Importantly, there was no difference in systolic function between patients with active versus those with inactive disease in our cohort.[22] The role for resistin and lipocalin-2 upon systolic function in active disease should be studied further.

Our results might suggest that in JDM assessed after long-term disease, adipokines are released from dysfunctional adipose tissue as well as from other tissues affected by the disease. The increase in leptin might induce or maintain JDM due to an immune-modulatory mechanism besides the traditional leptin/obesity-related inflammatory effect. The novel finding of increased apelin-12 and visfatin in JDM-active might be involved in angiogenesis, which may have an impact on cardiac function. As such, it is important to keep in mind that in patients with unfavourable adipose tissue distribution, the adipokine profile is presumably altered. The adipokine profile found in long-term JDM might be an added burden on the inflammatory state of the disease.

Strengths and limitations

The present study represents a longstanding JDM outcome study in which 95% of all identified and tracked patients with JDM participated. Thus, our results are less biased toward serious cases compared with other outcome studies.[49] Our age-matched and sex-matched controls represent the general population as they were randomly drawn from the Norwegian population registry. There are some limitations to our study besides those earlier mentioned. Unfortunately, lipodystrophy was not further categorised into generalised, partial or focal based on the patient's fat loss. Leptin is highly responsive to food intake as it is a satiety hormone providing cross-talk between adipocytes and the satiety centre in the hypothalamus. For accurate measurements, blood sampling should have been done after an overnight fast. However, in our study, blood was drawn at approximately the same time point during the late morning. Also, being a cross-sectional study, no conclusions can be drawn as to the causal effect of the adipokines on cardiac function. Our study was performed some years ago and included patients who might not have been subjected to optimal treatment.

CONCLUSION

Our study demonstrates an imbalance in proinflammatory and anti-inflammatory adipokines, which suggests adipocyte dysfunction in JDM after long-term disease. Further, the unfavourable adipose tissue distribution and subclinical cardiac dysfunction are associated with these imbalanced adipokine levels, especially in patients with active disease. The finding of increased apelin-12 and its association with systolic function in JDM-active patients is novel. The underlying mechanisms need to be further explored.

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REFERENCES

1 Feldman BM, Rider LG, Reed AM, *et al*. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. *Lancet* 2008;371:2201–12.
2 Huemer C, Kitson H, Malleson PN, *et al*. Lipodystrophy in patients with juvenile dermatomyositis -- evaluation of clinical and metabolic abnormalities. *J Rheumatol* 2001;28:610–5.
3 Bingham A, Mamyrova G, Rother KI, *et al*. Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. *Medicine (Baltimore)* 2008;87:70–86.
4 Sanner H, Gran J-T, Sjaastad I, *et al*. Cumulative organ damage and prognostic factors in juvenile dermatomyositis: a cross-sectional study median 16.8 years after symptom onset. *Rheumatology (Oxford)* 2009;48:1541–7.
5 Even SEL, Dulak-Lis MG, Touyz RM, *et al*. Crosstalk between adipose tissue and blood vessels in cardiometabolic syndrome: implication of steroid hormone receptors (MR/GR). *Horm Mol Biol Clin Investig* 2014;19:89–101.
6 Mancuso P. The role of adipokines in chronic inflammation. *Immunotargets Ther* 2016;5:47–56.
7 O'Leary MF, Wallace GR, Davis ET, *et al*. Obese subcutaneous adipose tissue impairs human myogenesis, particularly in old skeletal muscle, via resistin-mediated activation of NFκB. *Sci Rep* 2018;8:15360.
8 Boucher J, Masri B, Daviaud D, *et al*. Apelin, a newly identified adipokine up-regulated by insulin and obesity. *Endocrinology* 2005;146:1764–71.

9 Berndt J, Klöting N, Kralisch S, *et al*. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. *Diabetes* 2005;54:2911–6.
10 Ostlund RE, Yang JW, Klein S, *et al*. Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. *J Clin Endocrinol Metab* 1996;81:3909–13.
11 Liu X, Hamnvik O-PR, Petrou M, *et al*. Circulating lipocalin 2 is associated with body fat distribution at baseline but is not an independent predictor of insulin resistance: the prospective Cyprus metabolism study. *Eur J Endocrinol* 2011;165:805–12.
12 Marques FZ, Prestes PR, Byars SG, *et al*. Experimental and human evidence for lipocalin-2 (neutrophil gelatinase-associated lipocalin [NGAL]) in the development of cardiac hypertrophy and heart failure. *J Am Heart Assoc* 2017;6:e005971.
13 Arita Y, Kihara S, Ouchi N, *et al*. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. 1999. *Biochem Biophys Res Commun* 2012;425:560–4.
14 Olazagasti JM, Hein M, Crowson CS, *et al*. Adipokine gene expression in peripheral blood of adult and juvenile dermatomyositis patients and their relation to clinical parameters and disease activity measures. *J Inflamm (Lond)* 2015;12:29.
15 Filková M, Hulejová H, Kuncová K, *et al*. Resistin in idiopathic inflammatory myopathies. *Arthritis Res Ther* 2012;14:R111.
16 Hulejová H, Kryštůfková O, Mann H, *et al*. Increased visfatin levels are associated with higher disease activity in anti-jo-1-positive myositis patients. *Clin Exp Rheumatol* 2016;34:222–9.
17 Loaiza-Félix J, Moreno-Ramírez M, Pérez-García FL, *et al*. Serum levels of adipokines in patients with idiopathic inflammatory myopathies: a pilot study. *Rheumatol Int* 2017;37:1341–5.
18 Chihara K, Hattori N, Ichikawa N, *et al*. Re-Evaluation of serum leptin and adiponectin concentrations normalized by body fat mass in patients with rheumatoid arthritis. *Sci Rep* 2020;10:15932.
19 Romero-Corral A, Sierra-Johnson J, Lopez-Jimenez F, *et al*. Relationships between leptin and C-reactive protein with cardiovascular disease in the adult general population. *Nat Clin Pract Cardiovasc Med* 2008;5:418–25.
20 Wang H, Liu H-X, Wang Y-L, *et al*. Left ventricular diastolic dysfunction in patients with dermatomyositis without clinically evident cardiovascular disease. *J Rheumatol* 2014;41:495–500.
21 Lu Z, Wei Q, Ning Z, *et al*. Left ventricular diastolic dysfunction -- early cardiac impairment in patients with polymyositis/dermatomyositis: a tissue Doppler imaging study. *J Rheumatol* 2013;40:1572–7.
22 Schwartz T, Sanner H, Gjesdal O, *et al*. In juvenile dermatomyositis, cardiac systolic dysfunction is present after long-term follow-up and is predicted by sustained early skin activity. *Ann Rheum Dis* 2014;73:1805–10.
23 Schwartz T, Sanner H, Husebye T, *et al*. Cardiac dysfunction in juvenile dermatomyositis: a case-control study. *Ann Rheum Dis* 2011;70:766–71.
24 Witczak BN, Bollerslev J, Godang K, *et al*. Body composition in long-standing juvenile dermatomyositis: associations with disease activity, muscle strength and cardiometabolic measures. *Rheumatology (Oxford)* 2022;61:2959–68.
25 Marstein HS, Witczak BN, Godang K, *et al*. Adipose tissue distribution is associated with cardio-metabolic alterations in adult patients with juvenile-onset dermatomyositis. *Rheumatology (Oxford)* 2022:keac293.
26 Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;292:344–7.
27 Sanner H, Aaløkken TM, Gran JT, *et al*. Pulmonary outcome in juvenile dermatomyositis: a case-control study. *Ann Rheum Dis* 2011;70:86–91.
28 Almeida B, Campanilho-Marques R, Arnold K, *et al*. Analysis of published criteria for clinically inactive disease in a large juvenile dermatomyositis cohort shows that skin disease is underestimated. *Arthritis Rheumatol* 2015;67:2495–502.
29 Wysocka MB, Pietraszek-Gremplewicz K, Nowak D. The role of apelin in cardiovascular diseases, obesity and cancer. *Front Physiol* 2018;9:557.
30 Eyries M, Siegfried G, Ciumas M, *et al*. Hypoxia-Induced apelin expression regulates endothelial cell proliferation and regenerative angiogenesis. *Circ Res* 2008;103:432–40.
31 Gómez R, Conde J, Scotece M, *et al*. What's new in our understanding of the role of adipokines in rheumatic diseases? *Nat Rev Rheumatol* 2011;7:528–36.
32 Taylor EB. The complex role of adipokines in obesity, inflammation, and autoimmunity. *Clin Sci (Lond)* 2021;135:731–52.
33 Hribal ML, Fiorentino TV, Sesti G. Role of C reactive protein (CRP) in leptin resistance. *Curr Pharm Des* 2014;20:609–15.
34 Dakroub A, Nasser SA, Kobeissy F, *et al*. Visfatin: an emerging adipocytokine bridging the gap in the evolution of cardiovascular diseases. *J Cell Physiol* 2021;236:6282–96.
35 Haque WA, Shimomura I, Matsuzawa Y, *et al*. Serum adiponectin and leptin levels in patients with lipodystrophies. *J Clin Endocrinol Metab* 2002;87:2395.
36 Azuma K, Katsukawa F, Oguchi S, *et al*. Correlation between serum resistin level and adiposity in obese individuals. *Obes Res* 2003;11:997–1001.
37 Pagano C, Pilon C, Olivieri M, *et al*. Reduced plasma visfatin/pre-B cell colony-enhancing factor in obesity is not related to insulin resistance in humans. *J Clin Endocrinol Metab* 2006;91:3165–70.
38 Obradovic M, Sudar-Milovanovic E, Soskic S, *et al*. Leptin and obesity: role and clinical implication. *Front Endocrinol (Lausanne)* 2021;12:585887.
39 Otero M, Lago R, Gomez R, *et al*. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;65:1198–201.
40 Bobbert P, Scheibenbogen C, Jenke A, *et al*. Adiponectin expression in patients with inflammatory cardiomyopathy indicates favourable outcome and inflammation control. *Eur Heart J* 2011;32:1134–47.
41 Kozakova M, Muscelli E, Flyvbjerg A, *et al*. Adiponectin and left ventricular structure and function in healthy adults. *J Clin Endocrinol Metab* 2008;93:2811–8.
42 Chong KS, Gardner RS, Morton JJ, *et al*. Plasma concentrations of the novel peptide apelin are decreased in patients with chronic heart failure. *Eur J Heart Fail* 2006;8:355–60.
43 Farkasfalvi K, Stagg MA, Coppen SR, *et al*. Direct effects of apelin on cardiomyocyte contractility and electrophysiology. *Biochem Biophys Res Commun* 2007;357:889–95.
44 Yan W, Zhang F, Zhang R, *et al*. Adiponectin regulates SR ca (2+) cycling following ischemia/reperfusion via sphingosine 1-phosphate-camkii signaling in mice. *J Mol Cell Cardiol* 2014;74:183–92.
45 Sam F, Duhaney T-AS, Sato K, *et al*. Adiponectin deficiency, diastolic dysfunction, and diastolic heart failure. *Endocrinology* 2010;151:322–31.
46 Takeishi Y, Niizeki T, Arimoto T, *et al*. Serum resistin is associated with high risk in patients with congestive heart failure -- a novel link between metabolic signals and heart failure. *Circ J* 2007;71:460–4.
47 Yndestad A, Landrø L, Ueland T, *et al*. Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. *Eur Heart J* 2009;30:1229–36.
48 Kim M, Oh JK, Sakata S, *et al*. Role of resistin in cardiac contractility and hypertrophy. *J Mol Cell Cardiol* 2008;45:270–80.
49 Tsaltskan V, Aldous A, Serafi S, *et al*. Long-term outcomes in juvenile myositis patients. *Semin Arthritis Rheum* 2020;50:149–55.