RHEUMATOLOGY

Rheumatology 2023;62:SI196–SI204
https://doi.org/10.1093/rheumatology/keac293
Advance access publication 16 May 2022

Original article

Adipose tissue distribution is associated with cardio-metabolic alterations in adult patients with juvenile-onset dermatomyositis

Henriette S. Marstein [1,2,3], Birgit N Witczak[1,3], Kristin Godang[4], Thomas Schwartz[1,2,3], Berit Flatø[5,6], Jens Bollerslev[4,5], Ivar Sjaastad [1,3,7] and Helga Sanner[2,6]

Abstract

Objectives. Primary aims were to compare adipose tissue distribution in adult patients with juvenile-onset DM (JDM), with matched controls. Secondary aims were to explore how adipose tissue distribution is associated with cardio-metabolic status (cardiac dysfunction and metabolic syndrome) in patients.

Methods. Thirty-nine JDM patients (all aged ≥18 y, mean age 31.7 y and 51% female) were examined mean 22.7 y (S.D. 8.9 y) after disease onset and compared with 39 age/sex-matched controls. In patients, disease activity and lipodystrophy were assessed by validated tools and use of prednisolone noted. In all participants, dual-energy X-ray absorptiometry (DXA) and echocardiography were used to measure visceral adipose tissue (VAT)(g) and cardiac function, respectively. Risk factors for metabolic syndrome were measured and associations with adipose tissue distribution explored. For primary and secondary aims, respectively, *P*-values ≤0.05 and ≤0.01 were considered significant.

Results. Patients exhibited a 2.4-fold increase in VAT, and reduced HDL-cholesterol values compared with controls (*P*-values ≤ 0.05). Metabolic syndrome was found in 25.7% of the patients and none of the controls. Cardiac dysfunction (systolic and/or diastolic) was found in 23.7% of patients and 8.1% of controls ($P = 0.07$). In patients, VAT levels were correlated with age, disease duration and occurrence of metabolic syndrome and cardiac dysfunction. Occurrence of lipodystrophy ($P = 0.02$) and male sex ($P = 0.04$) tended to be independently associated with cardiac dysfunction.

Conclusion. Adults with JDM showed more central adiposity and cardio-metabolic alterations than controls. Further, VAT was found increased with disease duration, which was associated with development of cardio-metabolic syndrome.

Key words: JDM, visceral adipose tissue, lipodystrophy, cardio-metabolic syndrome, metabolic syndrome, cardiac dysfunction

CLINICAL SCIENCE

Rheumatology key messages

- Juvenile onset dermatomyositis patients had 2.4 times more visceral adipose tissue than controls.
- Cardio-metabolic alterations were found in approximately 25% of the JDM patients and 8% of controls.
- Occurrence of lipodystrophy and male sex tended to be independently associated with cardiac dysfunction in JDM.

Introduction

Juvenile onset DM (JDM) is a chronic, systemic, autoimmune disease of childhood. It is characterized by muscle weakness and skin rashes. Vasculopathy is considered to be important in the pathogenesis of the disease, and internal organs may be affected [1]. Lipodystrophy is a well-known complication of JDM [2–4]. Lipodystrophy is characterized by gradual loss of subcutaneous adipose tissue (SAT) in the face, neck and limbs, possibly due to autoimmune destruction of the adipocytes [5]. Generalized lipodystrophy (a sub-form of lipodystrophy) develops

[1]Institute for Experimental Medical Research, University of Oslo and Oslo University Hospital, [2]Department of Health Sciences, Oslo New University College, [3]KG Jebsen Centre for Cardiac Research, University of Oslo, [4]Department of Endocrinology, Oslo University Hospital, [5]Institute for Clinical Medicine, Medical Faculty, University of Oslo, [6]Department of Rheumatology, Oslo University Hospital, Rikshospitalet and [7]Department of Cardiology, Oslo University Hospital Ullevål, Oslo, Norway

Submitted 21 October 2021; accepted 4 May 2022

Correspondence to: Henriette S. Marstein, Institute for Experimental Medical Research, Oslo University Hospital, Ullevål PB 4956 Nydalen, NO-0424 Oslo, Norway. E-mail: henriette.marstein@medisin.uio.no

during childhood and adolescence, and most cases occur with juvenile autoimmune diseases [5–7], especially JDM [2, 4, 5, 8].

In lipodystrophy, lack of, or dysfunctional versions of subcutaneous adipocytes with limited ability to store fat [9] is associated with the development of metabolic abnormalities such as hypertension, dyslipidaemia and impaired glucose tolerance [9–12]. These abnormalities are similarly consequences of expanded visceral adipose tissue as found in abdominal obese phenotypes [13]. Although lipodystrophy and abdominal obesity are separate phenotypes, both conditions are associated with increased risk of developing metabolic syndrome [11, 12]. A comorbidity to metabolic syndrome is cardiovascular diseases—hence, the condition is also referred to as cardio-metabolic syndrome [14]—of which cardiac dysfunction is a measure of the reduced pumping capacity of the heart [15]. Metabolic syndrome has been found in almost 50% of DM patients [16–18] and subclinical cardiac dysfunction is frequently found in JDM patients (28–72%) [19, 20].

Lipodystrophy in JDM is clinically scored as an item in the myositis damage index (MDI). We and others have found lipodystrophy to be present in 13–65% of JDM patients after both short- and long-term disease [2–4, 17, 21]. Yet assessment of lipodystrophy according to the MDI does not provide any objective measure of adipose tissue distribution or mass. These features can be measured by use of dual-energy X-ray absorptiometry (DXA). Use of DXA software enables the measurement of the amount of VAT separate from that of total body fat, and therefore provides important data that have not been reported before for JDM. The association between VAT and cardio-metabolic syndrome in this patient group has also not been studied previously.

Our primary aim was to compare the distribution of regional fat, including of VAT, in adults who had long-term JDM with that in age- and sex-matched controls. Secondary aims were to explore the association between adipose tissue phenotypes, metabolic syndrome and cardiac dysfunction.

Patients and methods

Study population

This study was part of a larger, controlled, cross-sectional study conducted in Norway which included JDM patients who had been diagnosed between 1970 and 2006 previously described in detail [22]. Briefly, JDM patients were identified from hospital records and all could be tracked through the national population register. In the overall study, inclusion criteria for patients were: a probable or definite diagnosis of DM, disease onset before 18 y of age, age >6 y and a minimum of 24 months of disease duration at inclusion. Fifty-nine patients were included and age- and sex-matched controls (1:1 with patients) were randomly drawn from the National Population Register. At the time of inclusion, 39/59 patients were ≥18 y old. We consider VAT as an essential variable which was only possible to measure in adult study participants age ≥18 y. Therefore, we only included all adult study participants (39 patients and 39 controls) in the present study.

Ethics

As required under the Declaration of Helsinki, written informed consent was obtained from all patients and controls, and from parents in the cases of participants who were <16 y of age. The current study was specifically approved by The Regional Committees for Medical Research Ethics South-East Norway, REC south-east B, approval number S-05144.

Data collection and clinical measurements

Study participants were clinically examined over the period 2005–2009 by a single physician (HS) during a follow-up (FU) programme that was conducted at Oslo University Hospital (OUS). This included systolic and diastolic blood pressure. In patients, disease activity was measured by DAS for JDM (DAS) (0–20) including DAS skin (0–9) and DAS muscle (0–11) [23]. Cumulative organ damage including lipodystrophy was measured through use of the MDI (0–40) [24]. All study participants completed self-reported questionnaires at FU to assess their daily smoking levels at that time and their average weekly physical activity over the last year [25]. We categorized activities as those that induced sweat or breathlessness as frequencies: < or ≥ twice a week.

Blood samples were taken from participants when in a non-fasting state and were analysed for levels of glucose, total cholesterol, triglycerides (TG), high density lipoproteins (HDL), low density lipoproteins (LDL) and lipoproteins (a), and erythrocyte sedimentation rate (ESR were all measured consecutively at the accredited medical biochemistry laboratory at OUS Rikshospitalet according to standard protocols). High-sensitivity CRP (hsCRP) was assayed (Cobas c702, Roche Diagnostics, Indianapolis, IN, USA) in a single run at the same medical laboratory. Samples were taken at approximately the same time point (early in the morning and non-fasting) from both patients and controls.

To identify study participants who had metabolic syndrome, we used the definition set by the US national cholesterol education program adult treatment panel III [11]. These require the presence of three or more of the following risk factors: waist circumference >102 cm in men and >88 cm in women; TG ≥1.7 mmol/l; HDL ≤1.04 mmol/l in men and ≤1.29 mmol/l in women; fasting blood glucose ≥5.6 mmol/l; and elevated SBP and DBP ≥130/85 mmHg. For this study, no waist circumference measurements were available. However, a BMI of >30 kg/m^2 was used as a surrogate estimate of central obesity. The World Health Organization [12] and others [26] have included BMI in their definition of the metabolic syndrome. Although blood samples for TG and glucose measurement had been drawn during non-fasting periods, we used standard fasting reference values.

Cardiac function measures

Two-dimensional M-mode and Doppler echocardiography were performed, using a Vivid 7 ultrasound scanner, (GE-Vingmed Ultrasound, Horten, Norway), as previously described [20]. In brief, to assess left ventricular (LV) systolic function we calculated long axis strain (LAS) as the average septal and mitral annulus displacement expressed as a percentage of LV end-diastolic length. LV diastolic cardiac function was assessed as early diastolic tissue velocity (e'). We defined systolic dysfunction as LAS $\leq$13.7% and diastolic dysfunction as e' $\leq$8.2 cm/second, which are median−2SD of control values [27]. LV cardiac dysfunction was defined as occurrence of systolic and/or diastolic dysfunction.

When both metabolic syndrome and cardiac dysfunction are mentioned together, we used the term 'cardiometabolic syndrome'.

Adipose tissue distribution

Adipose tissue distribution was determined in all study participants through use of DXA. The total mass of fat (FM) was measured by application of a narrow fan-beam densitometer scan according to the manufacturer's protocol (GE Healthcare Lunar Prodigy, Madison, WI, USA). Android and gynoid fat was measured in regions of interest through use of the DXA enCORE software (version 16 from GE Healthcare). VAT was computed by subtraction of SAT from the total amount of android fat (which had been analysed in 2014) [28] and the android : gynoid ratio was calculated. Complete VAT data were obtained in 38 patients and 36 controls, and are presented as weight and percentage of total body fat.

Statistics

Differences between patients and controls were tested by independent sample t-tests, Mann–Whitney *U* tests or χ^2 tests, as appropriate. Correlations were determined by the Pearson or Spearman correlation coefficients when appropriate. Associations with sex, time factors, blood pressure and adipose phenotypic values, and the composite variables 'metabolic syndrome' and 'cardiac dysfunction', were assessed for the patients only. Strengths of correlations were defined as weak $r_{sp} = 0.1–0.3$, moderate as $r_{sp} = 0.3–0.6$ and strong $r_{sp} = 0.6–1.0$. *P*-values $\leq$0.05 were considered statistically significant. Statistical analysis was only performed when $n > 4$. Correlations between variables that were included in composite variables were not assessed.

Determinants contributing to decreased cardiac function and occurrence of metabolic syndrome as outcome measures was assessed using logistic regression analyses. First, explanatory variables were tested in univariate models. If they showed associations with ($P \leq 0.05$) or were known from the literature to be associated with the outcome variables, these variables were included in the multivariate models (using enter).

The significance level was set at 5% ($P \leq 0.05$) for our primary aims. In order to correct for multiple comparisons, the significance level was set at 1% ($P \leq 0.01$) for our secondary aims. All statistical analyses were performed SPSS version 26.0 (SPSS, Chicago, IL, USA).

Results

Characteristics and disease variables in patients

In patients, mean disease duration was 22.7 y (S.D. 8.9 y) at FU (Table 1). Approximately half of the patients (i)

Table 1 Characteristics and disease variables in study participants

Characteristics	Patients (*n* = 39)	Controls (*n* = 39)	*P*
Female, *n* (%)	18 (51.4)	18 (51.4)	NA
Age at FU, y[a]	31.7 (10.3)	31.8 (10.2)	NA
Weight, kg[a]	71.9 (16.2)	72.9 (14.7)	0.78
Height, m[a]	1.73 (0.1)	1.74 (0.1)	0.46
PRINTO inactive, *n* (%)	20 (47.4)	NA	NA
Disease duration, y[a]	22.7 (8.9)	NA	NA
DAS total FU[b]	4.5 (3.0–6.5)	NA	NA
MDI total at FU[b]	5.0 (2.0–7.0)	NA	NA
Lipodystrophy, *n* (%)	10 (25.6)	NA	NA
ESR, mm/h[b]	6.0 (4.0–10.0)	4 (3.0–8.0)	0.81
hs-CRP, mg/l[b]	1.1 (0.2–3.1)	0.7 (0.3–1.3)	0.46
Prednisolone treatment at FU, *n* (%)	4 (10.3)	NA	NA
Years of prednisolone use during disease course[a]	2.8 (0.8–6.5)	NA	NA
Cumulative prednisolone at FU, g[b]	9.0 (3.5–16.7)	NA	NA
Physical activity frequencies $\geq$2 times/week, *n* (%)	23 (59.0)	27 (69.2)	0.35
Smokers daily at FU, *n* (%)	11 (28.2)	7 (17.9)	0.28

Values are n (%), [a]mean (S.D.) or [b]median (IQR). FU: follow-up; hs-CRP: high sensitive CRP; MDI: myositis damage index; NA: not applicable. Independent samples *t* test and χ^2 were used to compare differences between patients and controls, when appropriate.

Table 2 Body composition in study participants

	Patients ($n = 39$)	Controls ($n = 39$)	*P*
Total body fat mass, kg[c]	22.6 (8.7)	20.3 (7.6)	0.21
VAT, g[d]	557[a] (178–1072)	232[b] (72–751)	**0.04**
VAT % of total body fat mass[d]	2.5[a] (1.0–4.7)	1.2[b] (0.4–2.3)	**0.009**
SAT, g[d]	19.7[a] (14.7–29.2)	17.7[b] (14.5–24.5)	0.27
SAT % of total body fat mass[d]	2.6[a] (1.0–4.8)	1.3[b] (0.5–2.3)	**0.02**
Appendicular fat mass, kg[c]	10.0 (4.3)	9.3 (3.2)	0.45
Android fat mass, kg[c]	2.0 (1.1)	1.6 (1.0)	0.10
Gynoid fat mass, kg[c]	3.9 (1.7)	3.8 (1.4)	0.92
Android: Gynoid fat mass ratio[d]	0.42 (0.35–0.70)	0.36 (0.29–0.49)	**0.01**

Values are [a]$n = 38$, [b]$n = 35$, [c]mean (S.D.) or [d]median (IQR). VAT: visceral adipose tissue. Independent samples *t* tests were used to compare differences between patients and controls. Values in bold: $P \leq 0.05$.

Table 3 Cardio-metabolic risk factors and cardiac function in study participants

	Patients	Controls	*P*
Triglycerides, mmol/l	1.8 (1.63)	1.1 (1.0)	0.03
LDL-cholesterol[a], mmol/l	2.42 (0.76)	2.90 (1.4)	0.02
HDL-cholesterol in women, mmol/l	1.25 (0.28)	1.62 (0.41)	**0.002**
HDL-cholesterol in men, mmol/l	0.92 (0.31)	1.24 (0.30)	**0.005**
Total cholesterol[b], mmol/l	4.44 (0.83)	4.86 (0.96)	0.06
Lipoprotein(a), mg/l	351.0 (246.7)	398.7 (409.2)	0.64
Glucose[c], mmol/l	5.11 (0.93)	4.93 (0.58)	0.44
SBP, mmHg	121.3.0 (22.7)	115.3 (13.0)	0.16
DBP, mmHg	72.4 (14.0)	70.3 (7.9)	0.40
LAS, %	15.6 (2.4)	17.2 (1.7)	**0.001**
e', cm/s	10.2 (2.6)	11.8 (2.1)	**0.005**
BMI, kg/m^2	24.1 (4.4)	24.0 (3.9)	0.92

Values are mean (S.D.). Unless otherwise stated, *n* in both patients/controls = 39, [a]$n = 32$, [b]$n = 31$, [c]$n = 30$. DBP: diastolic blood pressure; e': early diastolic tissue velocity; HDL: high-density lipoprotein; LAS: long axis strain; LDL: low-density lipoprotein; SBP: systolic blood pressure. Independent samples *t* test and χ^2 were used to compare differences between patients and controls, when appropriate. Values in bold: $P \leq 0.01$.

were female ($n = 18$, 51.4%) and (ii) had inactive disease ($n = 20$, 47.4%) (Table 1). Median MDI was 5.0 (2.0–7.0) and lipodystrophy was found in 10 patients (26%). The median total DAS was 4.5 (3.0–6.5) (Table 1). At FU, four patients (10%) were treated with prednisolone.

Body fat composition in study participants

Patients had 2.4 times more VAT and approximately twice as much VAT as a percentage of their total body FM compared with controls (*P*'s 0.04 and 0.009, respectively). Further, the android : gynoid ratio was 1.2 times higher than that of the controls (Table 2, $P = 0.01$). Also, SAT % of total body fat mass was higher in the patient group (Table 2, $P = 0.02$).

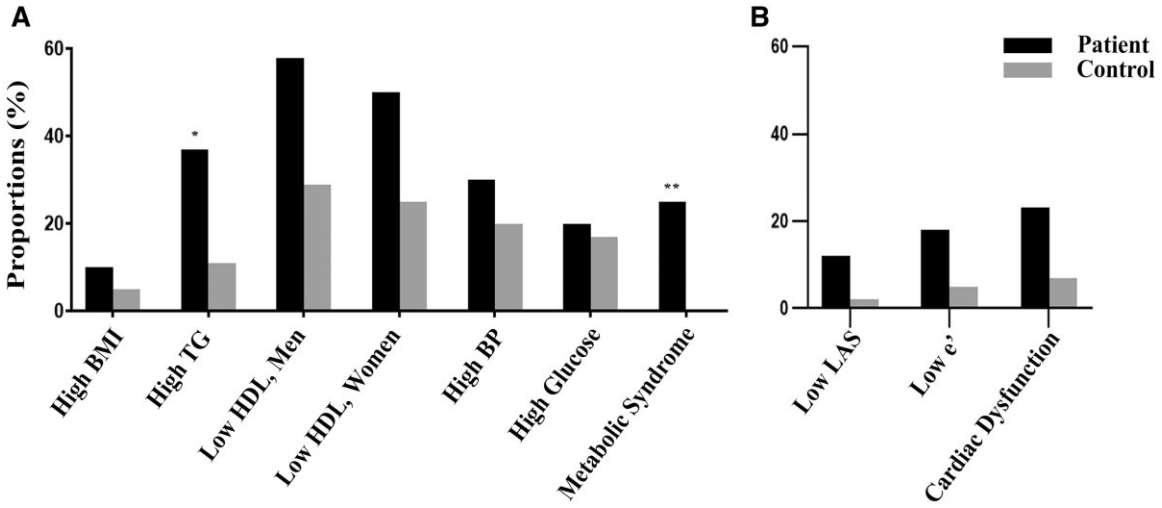
Metabolic risk factors and cardiac function in study participants

Both female and male patients had lower HDL-cholesterol levels than the controls of the same sex (0.37 mmol/l and 0.34 mmol/l, $P = 0.002$ and 0.005, respectively) (Table 3). Glucose levels and blood pressure were not significantly different between patients and controls. In patients, both systolic function (LAS) and diastolic function (e') were reduced compared with controls by 9% ($P = 0.005$) and 1.6 cm/second ($P = 0.001$). BMI was not significantly different between patients and controls (Table 3).

Occurrence of cardio-metabolic risk factors, metabolic syndrome and cardiac dysfunction in patients compared with controls

TG levels $\geq$1.7 mmol/l were found in 37.1% of the patients and in 11.4% of the controls ($P = 0.01$) (Fig. 1A). It was found that 26% of patients had metabolic syndrome, whereas no controls did ($P = 0.02$) (Fig. 1A). Also, 24% of the patients had cardiac dysfunction, which was almost three times as many as the controls; however, this did not reach significance ($P = 0.07$) (Fig. 1B). Three patients had coexisting metabolic syndrome and cardiac dysfunction; none of these patients used glucocorticoids at follow-up.

FIG. 1 Occurrence (%) of cardio-metabolic risk factors, metabolic syndrome and cardiac dysfunction in patients compared with controls.



(**A**) Occurrence (%) of the cardio-metabolic risk factors: body mass index (BMI), lipids, blood pressure and glucose at levels exposing risk for the metabolic syndrome, and occurrence of metabolic syndrome. (**B**) Data for systolic and diastolic dysfunction, and occurrence of cardiac dysfunction when one or both systolic and diastolic dysfunction were present. High BMI: >30 kg/m^2; high TG: triglycerides ≥1.7 mmol/l; low HDL: high density lipoprotein ≤1.04 mmol/l in men and 1.29 mmol/l in women; high BP: systolic and diastolic blood pressure ≥130/85 mmHg; high glucose: blood glucose ≥5.6 mmol/l; low LAS: long axis strain ≤13.7%; low e': early diastolic tissue velocity ≤8.2 cm/s; cardiac dysfunction: presence of low LAS and/or low e'. *$P \leq 0.05$; **$P \leq 0.01$.

TABLE 4 Correlations between visceral adipose tissue, metabolic syndrome, cardiac dysfunction and relevant explanatory variables

	Visceral adipose tissue		Metabolic syndrome	Cardiac dysfunction
	Patients (n = 38–39)	Controls (n = 37–39)	Patients (n = 38–39)	Patients (n = 38–39)
Cumulative prednisolone	0.21	NA	–0.29	0.40
Male gender	0.30	0.33	0.28	0.46*
Age at first symptoms	0.28	NA	0.11	0.14
Age at FU	0.47	0.19	0.20	0.31
Disease duration to FU	0.44*	NA	0.17	0.28
SBP	0.43*	0.47*	NA	NA
DBP	0.50*	0.34	NA	NA
VAT	NA	NA	0.75*	0.43*
Lipodystrophy	0.27	NA	–0.17	0.51*
Android : gynoid fat mass ratio	0.75*	0.85*	0.30	0.40

DBP: diastolic blood pressure; FU: follow-up; NA: not applicable; SBP: systolic blood pressure; VAT: visceral adipose tissue. Values are Pearson's or Spearman's correlation coefficient when appropriate; *$P \leq 0.01$.

Correlations between visceral adipose tissue, metabolic syndrome, cardiac dysfunction and relevant explanatory variables

In patients, VAT was strongly associated with occurrence of metabolic syndrome and moderately associated with cardiac dysfunction, disease duration and diastolic blood pressure (Table 4). Cardiac dysfunction was moderately associated with both higher amounts of VAT, male gender and the occurrence of lipodystrophy (Table 4).

Determinants of cardiac dysfunction and metabolic syndrome in patients

Lipodystrophy and male sex tended to be associated with cardiac dysfunction (Table 5), but did not reach

Table 5 Determinants of cardiac dysfunction in patients

	Univariate analyses		Multivariate analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Cardiac dysfunction				
Lipodystrophy	12.5 (2.19, 71.36)	**0.004**	20.11 (1.61, 251.50)	**0.02**
Male gender	15.2 (1.66, 139.31)	0.16	21.50 (1.18, 393.08)	**0.04**
VAT	1.00 (1.000, 1.003)	0.28	1.00 (0.999, 1.003)	0.16
Disease duration	1.09 (0.99, 1.21)	0.10	0.99 (0.85, 1.16)	0.90

Results from univariate and multivariate logistic regression analyses. OR: odds ratio; VAT: visceral adipose tissue. Values in bold are $P \leq 0.05$.

statistical significance for our *P*-values adjusted for multiple comparisons; both increased the odds ratio of cardiac dysfunction by ≈20%. VAT and disease duration were not significantly associated with that outcome. No determinants for metabolic syndrome were found (data not shown).

Discussion

In our study of JDM patients, assessed after mean disease duration 22.7 years, VAT was increased by 2.4 times compared with controls. Patients had poorer cardiac outcomes as diastolic and systolic functions, and more frequent occurrence of metabolic syndrome, both compared with controls. In patients, VAT correlated positively with metabolic syndrome and cardiac dysfunction (Table 4). Further, lipodystrophy and male sex tended to be independently associated with cardiac dysfunction (Table 5).

We found higher VAT masses and higher android: gynoid ratios in patients compared with controls, although total FM and BMIs were comparable between groups. We have previously described body composition as assessed by DXA in children and adults with JDM [29]. Similarly, in adult patients with SLE and RA, VAT has been found to be expanded whereas other adipose tissues were comparable between patients and controls [30–32]. These studies suggested that the reported increases in VAT might be due to disease-related factors rather than the weight gain that is often induced by glucocorticoid treatment. It is of note that only 10% of our patients were on prednisolone at FU.

A quarter of our patient group had lipodystrophy. Of all autoimmune diseases, JDM is the most frequent associated with lipodystrophy, a complication rarely described in adult-onset DM [33]. Both lipodystrophy and high VAT mass have been associated with metabolic abnormalities [9, 10, 13], as discussed below. A potential reason for the metabolic implications of both lipodystrophy and increased VAT mass might be a common lack of subcutaneous lipid-storing cells. This storage-cell shortage causes lipids to accumulate instead in the metabolically active visceral adipocytes in the abdomen and/or in the liver [9]. However, in visceral adipocytes, the molecular mechanism that leads to development of metabolic syndrome might differ in patients with autoimmune diseases, such as JDM [9], compared with the general population [10].Of the risk factors for metabolic syndrome, HDL-cholesterol levels in our patients were lower than those of the controls.

Also in patients, there was a tendency towards higher TG and lower LDL cholesterol levels compared with the controls (although not reaching our adjusted *P*-values). Decreased rather that increased cholesterol levels are commonly reported in inflammatory diseases such as RA, SLE and JDM [26, 31, 34], including long-term JDM [35]. A lipid lowering effect from pro-inflammatory cytokines is a potential explanation for the lower levels of cholesterol in rheumatic patients [36]. Still, this dyslipidemic profile constitutes—similarly to a high lipid profile in non-rheumatic patients—a risk of developing metabolic syndrome, cardiovascular disease, and eventually heart failure [34, 36].

Patients more frequently had cardiac dysfunction (systolic and/or diastolic dysfunction) than controls (albeit mostly sub-clinically), as we have reported previously in both children and adults with JDM [20]. Cardiac abnormalities and the degree of dysfunction vary according to the underlying autoimmune disease [37]. In other words, both types of autoimmunity, along with disease-related myocarditis and inflamed cardiac vasculature, might be primary causes of the cardiac dysfunction that is found in idiopathic inflammatory myopathy (IIM) including JDM [20, 38].

The metabolic syndrome was observed in around a quarter of our patient and none of the controls. Three patients had coexisting metabolic syndrome and cardiac dysfunction, none of these patients were using prednisolone at follow-up. Prevalence of metabolic syndrome has been found more commonly in autoimmune diseases when compared with controls, and has been observed in almost 50% of patients with adult-onset IIM [18, 39]. The prevalence of metabolic syndrome in JDM and in other paediatric rheumatic diseases is unknown; however, an increased risk (OR: 5.2) of metabolic syndrome has been described in adults with juvenile-onset arthritis [40]. The inflammatory state of IIM, which

involves increased ESR and levels of hsCRP and raised levels of various cytokines that are produced by activated immune cells, is a probable promoter of the syndrome. Also, increased levels of VAT would further escalate the inflammatory state and metabolic alterations leading to metabolic syndrome in IIM [10] also in JDM. In patients, higher amounts of VAT were moderately associated with disease duration. Similarly, VAT has been found to increase with disease duration in female SLE patients; this is thought to be due to long-term use of low doses of corticosteroids [31]. However, we found no correlation between VAT and cumulative prednisolone dosage. Thus, we might speculate that the association with disease duration that was found in our patients was due to autoimmune damage to subcutaneous fat. Still, we have no evidence of such damage to support this explanation.

Occurrence of the metabolic syndrome was not surprisingly associated with increased levels of VAT. Expansion of VAT has been found to increase the risk of development of metabolic syndrome in the general population [13]. However, after adjustments for sex, lipodystrophy and disease duration, the metabolic syndrome among our patients was no longer significantly associated with levels of VAT; this may have been related to the relatively small sample size (Type 2 error). A larger study found a strong association between levels of VAT and metabolic syndrome in RA patients even after several adjustments [30]. This finding shows the impact of VAT on the development of metabolic syndrome, also in rheumatic patients.

Cardiac dysfunction was associated with male sex, and with measures of adipose distribution, which were: levels of VAT and occurrence of lipodystrophy. Diastolic and systolic dysfunctions represent different functional impairments in cardiac function [41, 42]. Whereas obesity is associated with both systolic and diastolic dysfunction [15], male sex and autoimmune alteration to the myocardium are associated with systolic dysfunction [41, 43]. Also, dysfunctional microvasculature has been found to be associated with a reduction in cardiac contractility in obese people [15]. Therefore, JDM patients can have microvasculature abnormalities due to their vasculopathy and might be at higher risk of suffering from cardiac dysfunction. However, in a previous study we found no such association in our patients [44]. Moreover, cardiac alterations in patients with acquired lipodystrophy have been found to involve both diastolic and systolic dysfunctions [45, 46]. There was a tendency towards associations between cardiac dysfunction and lipodystrophy and male sex when adjusted for disease duration, age and amounts of VAT. However, the study might be underpowered to detect important associations.

A strength of this study was that the results were less biased towards serious cases than other outcome studies have been [47], as 95% of all the tracked and identified JDM patients participated in the study. Also, the controls, who were randomly selected from the Norwegian national registry, were representative of the cardio-metabolic status of the general population. This feature contributed to the strength of the validity of our study. One limitation was the availability of measurements taken from non-fasting blood samples only; another limitation was that we had no waist circumference measurements for the study participants. However, the android: gynoid ratio has been reported to be a good substitute measure [13].

Conclusion

In this cross-sectional study, adults with juvenile-onset DM, presents adipose tissue distribution most frequently as central adiposity and lipodystrophy. Increased levels of VAT were associated with disease duration and the development of metabolic syndrome and cardiac dysfunction. The results of this study support the hypothesis that there is a disease-related cause of altered adipose tissue distribution and of development of metabolic alterations, which adds an extra burden to the risk of development of cardio-metabolic syndrome in JDM. However, and importantly, the cardiac dysfunction found was mostly subclinical and longitudinal studies are needed in order to follow the progression of cardio-metabolic alterations in long-term JDM.

Acknowledgements

The authors would like to thank Anita Tollisen for help with patient inclusion, and Ellen Nordal and Marite Rygg for patient recruitment.

Funding: The study was supported by the Anders Jahres fund for promotion of science and the Olav Raagholt and Gerd Meidel Raagholt Research Foundation.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

The data that underlie this article cannot be shared publicly due to the privacy of individuals who participated in the study. The data will be shared if a reasonable request is made to the corresponding author.

References

1 Papadopoulou C, McCann LJ. The vasculopathy of juvenile dermatomyositis. Front Pediatr 2018;6:284.

2 Bingham A, Mamyrova G, Rother KI *et al.* Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. Medicine 2008;87:70–86.

3 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.

4 Verma S, Singh S, Bhalla AK, Khullar M. Study of subcutaneous fat in children with juvenile dermatomyositis. Arthritis Rheum 2006;55:564–8.

5 Akinci B, Sahinoz M, Oral E. Lipodystrophy syndromes: presentation and treatment. Endotext: MDText. com, Inc.; 2018. https://www.ncbi.nlm.nih.gov/books/NBK513130/.

6 Pope E, Janson A, Khambalia A, Feldman B. Childhood acquired lipodystrophy: a retrospective study. J Am Acad Dermatol 2006;55:947–50.

7 Sharma A, Gupta A, Rawat A, Suri D, Singh S. Long-term outcome in children with juvenile dermatomyositis: A single-center study from north India. Int J Rheum Dis 2020;23:392–96.

8 Kavanagh GM, Colaco CB, Kennedy CT. Juvenile dermatomyositis associated with partial lipoatrophy. J Am Acad Dermatol 1993;28:348–51.

9 Garg A. Adipose tissue dysfunction in obesity and lipodystrophy. Clin Cornerstone 2006;8(Suppl 4):S7–13.

10 Guzik TJ, Skiba DS, Touyz RM, Harrison DG. The role of infiltrating immune cells in dysfunctional adipose tissue. Cardiovascular Res 2017;113:1009–23.

11 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.

12 Alberti KG, Zimmet PZ; WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–53.

13 Fox CS, Massaro JM, Hoffmann U *et al.* Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation 2007;116: 39–48.

14 Sowers JR. Update on the cardiometabolic syndrome. Clin Cornerstone 2001;4:17–23.

15 Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. Transl Res 2017;183:57–70.

16 Eimer MJ, Brickman WJ, Seshadri R *et al.* Clinical status and cardiovascular risk profile of adults with a history of juvenile dermatomyositis. J Pediatr 2011;159:795–801.

17 Coyle K, Rother KI, Weise M *et al.* Metabolic abnormalities and cardiovascular risk factors in children with myositis. J Pediatr 2009;155:882–7.

18 de Moraes MT, de Souza FH, de Barros TB, Shinjo SK. Analysis of metabolic syndrome in adult dermatomyositis with a focus on cardiovascular disease. Arthritis Care Res 2013;65:793–9.

19 Lundberg IE. The heart in dermatomyositis and polymyositis. Rheumatology 2006;45:iv18–21.

20 Schwartz T, Sanner H, Husebye T, Flato B, Sjaastad I. Cardiac dysfunction in juvenile dermatomyositis: a case-control study. Ann Rheum Dis 2011;70:766–71.

21 Sanner H, Gran JT, Sjaastad I, Flato B. Cumulative organ damage and prognostic factors in juvenile dermatomyositis: a cross-sectional study median 16.8 years after symptom onset. Rheumatology 2009;48: 1541–7.

22 Sanner H, Aalokken TM, Gran JT *et al.* Pulmonary outcome in juvenile dermatomyositis: a case-control study. Ann Rheum Dis 2011;70:86–91.

23 Bode RK, Klein-Gitelman MS, Miller ML, Lechman TS, Pachman LM. Disease activity score for children with juvenile dermatomyositis: reliability and validity evidence. Arthritis Rheum 2003;49:7–15.

24 Rider LG, Werth VP, Huber AM *et al.* Measures of adult and juvenile dermatomyositis, polymyositis, and inclusion body myositis: physician and Patient/Parent Global Activity, Manual Muscle Testing (MMT), Health Assessment Questionnaire (HAQ)/Childhood Health Assessment Questionnaire (C-HAQ), Childhood Myositis Assessment Scale (CMAS), Myositis Disease Activity Assessment Tool (MDAAT), Disease Activity Score (DAS), Short Form 36 (SF-36), Child Health Questionnaire (CHQ), physician global damage, Myositis Damage Index (MDI), Quantitative Muscle Testing (QMT), Myositis Functional Index-2 (FI-2), Myositis Activities Profile (MAP), Inclusion Body Myositis Functional Rating Scale (IBMFRS), Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), Dermatomyositis Skin Severity Index (DSSI), Skindex, and Dermatology Life Quality Index (DLQI). Arthritis Care Res 2011;63(Suppl 11): S118–57.

25 Sanner H, Kirkhus E, Merckoll E *et al.* Long-term muscular outcome and predisposing and prognostic factors in juvenile dermatomyositis: a case-control study. Arthritis Care Res 2010;62:1103–11.

26 Kozu KT, Silva CA, Bonfá E *et al.* Dyslipidaemia in juvenile dermatomyositis: the role of disease activity. Clin Exp Rheumatol 2013;31:638–44.

27 Ibrahim IM, Hafez H, Al-Shair MHA, El Zayat A. Echocardiographic parameters differentiating heart failure with preserved ejection fraction from asymptomatic left ventricular diastolic dysfunction. Echocardiography 2020;37:247–52.

28 Olarescu NC, Jørgensen AP, Godang K *et al.* Dual-energy X-ray absorptiometry is a valid method to estimate visceral adipose tissue in adult patients with Prader-Willi syndrome during treatment with growth hormone. J Clin Endocrinol Metab 2014;99:E1727–31.

29 Witczak BN, Bollerslev J, Godang K *et al.* Body composition in longstanding juvenile dermatomyositis; Associations with disease activity, muscle strength and cardiometabolic measures. Rheumatology (Oxford) 2022; 61:2959–68.

30 Giles JT, Allison M, Blumenthal RS *et al.* Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. Arthritis Rheum 2010;62:3173–82.

31 Li Z, Shang J, Zeng S *et al.* Altered body composition and increased visceral adipose tissue in premenopausal and late postmenopausal patients with SLE. Clin Rheumatol 2019;38:3117–27.

32 Seguro LPC, Paupitz JA, Caparbo VF, Bonfa E, Pereira RMR. Increased visceral adipose tissue and altered adiposity distribution in premenopausal lupus patients: correlation with cardiovascular risk factors. Lupus 2018; 27:1001–6.

33 Pretel M, Navedo M, Marqués L, Aguado L. Adult dermatomyositis associated with lipodystrophy. Actas Dermosifiliogr 2013;104:724–5.

34 Myasoedova E, Crowson CS, Kremers HM *et al.* Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70:482–7.

35 Schwartz T, Sjaastad I, Flato B *et al.* In active juvenile dermatomyositis, elevated eotaxin and MCP-1 and cholesterol levels in the upper normal range are associated with cardiac dysfunction. Rheumatology 2014;53: 2214–22.

36 Venetsanopoulou AI, Pelechas E, Voulgari PV, Drosos AA. The lipid paradox in rheumatoid arthritis: the dark horse of the augmented cardiovascular risk. Rheumatology Int 2020;40:1181–91.

37 Diederichsen LP, Simonsen JA, Diederichsen AC *et al.* Cardiac abnormalities in adult patients with polymyositis or dermatomyositis as assessed by noninvasive modalities. Arthritis Care Res 2016;68: 1012–20.

38 Zhong Y, Bai W, Xie Q *et al.* Cardiac function in patients with polymyositis or dermatomyositis: a three-dimensional speckle-tracking echocardiography study. Int J Cardiovasc Imaging 2018;34:683–93.

39 De Souza F, Shinjo SK. The high prevalence of metabolic syndrome in polymyositis. Clin Exp Rheumatol 2014;32:82–7.

40 Sule S, Fontaine K. Metabolic syndrome in adults with a history of juvenile arthritis. Open Access Rheumatol 2018;10:67–72.

41 Simmonds SJ, Cuijpers I, Heymans S, Jones EAV. Cellular and molecular differences between HFpEF and HFrEF: a step ahead in an improved pathological understanding. Cells 2020;9:242.

42 Seferović PM, Polovina M, Bauersachs J *et al.* Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019;21:553–76.

43 Zhang L, Wang GC, Ma L, Zu N. Cardiac involvement in adult polymyositis or dermatomyositis: a systematic review. Clin Cardiol 2012;35:686–91.

44 Barth Z, Schwartz T, Flato B *et al.* Association between nailfold capillary density and pulmonary and cardiac involvement in medium to longstanding Juvenile dermatomyositis. Arthritis Care Res 2019;71:492–7.

45 Bjørnstad PG, Foerster A, Ihlen H. Cardiac findings in generalized lipodystrophy. Acta Pædiatrica 1996; 85(s413;413:):39–43.

46 Lupsa BC, Sachdev V, Lungu AO, Rosing DR, Gorden P. Cardiomyopathy in congenital and acquired generalized lipodystrophy: a clinical assessment. Medicine 2010;89: 245–50.

47 Tsaltskan V, Aldous A, Serafi S *et al.* Long-term outcomes in Juvenile Myositis patients. Semin Arthritis Rheum 2020; 50:149–55.