Body composition in longstanding juvenile dermatomyositis; Associations with disease activity, muscle strength and cardiometabolic measures

Birgit Nomeland Witczak[1], Jens Bollerslev[2,3], Kristin Godang[3], Thomas Schwartz[1,4], Berit Flatø[2,5], Øyvind Molberg[2,5], Ivar Sjaastad[1,6], Helga Sanner[4,5]

[1]Institute for Experimental Medical Research and KG Jebsen center for cardiac research, Oslo University Hospital-Ullevål, and University of Oslo, Oslo, Norway

[2]Institute for Clinical Medicine, Medical Faculty, University of Oslo, Oslo, Norway

[3]Section of Specialized Endocrinology, Department of Endocrinology, Preventive Medicine and Morbid Obesity, Oslo University Hospital Rikshospitalet, Oslo, Norway

[4]Bjørknes University College, Oslo, Norway

[5]Department of Rheumatology, Oslo University Hospital-Rikshospitalet, Oslo, Norway

[6]Department of Cardiology, Oslo University Hospital-Ullevål, Oslo, Norway

Correspondence to: Birgit Nomeland Witczak, Oslo University Hospital, Institute for Experimental Medical Research, Ullevål PB 4956 Nydalen. NO-0424 Oslo, Norway.

E-mail: b.n.witczak@medisin.uio.no

ORCiD ID: https://orcid.org/0000-0002-3136-4283

ABSTRACT

Objective: To (i) compare body composition parameters in patients with longstanding juvenile dermatomyositis (JDM) and controls and (ii) explore associations between body composition and disease activity/inflammation, muscle strength, health-related quality of life (HRQL) and cardiometabolic measures.

Methods: In a cross-sectional study, we included 59 patients (median disease duration 16.7y; median age 21.5y) and 59 age- and sex-matched controls. Active/inactive disease were defined by the PRINTO criteria. Body composition was assessed by total body dual-energy absorptiometry (DXA), inflammation by hs-CRP and cytokines, muscle strength by manual muscle test (MMT-8), HRQL by 36-item short form survey physical component score (SF-36 PCS) and cardiometabolic function by echocardiography (systolic and diastolic function) and serum-lipids.

Results: DXA analyses revealed lower appendicular lean mass index (ALMI) (reflecting limb skeletal muscle mass), higher body fat percentage (BF%) and higher android:gynoid fat ratio (A:G ratio) (reflecting central fat distribution) in patients than controls, despite similar BMI. Patients with active disease had lower ALMI and higher BF% than those with inactive disease; lower ALMI and higher BF% were associated with inflammation (elevated monocyte attractant protein-1 (MCP-1) and hs-CRP). Lower ALMI was associated with reduced muscle strength; higher BF% was associated with impaired HRQL. Central fat distribution (higher A:G ratio) was associated with impaired cardiac function and unfavorable serum-lipids.

Conclusion: Despite normal BMI, patients with JDM, especially those with active disease, had unfavorable body composition, which was associated with impaired HRQL/muscle strength and cardiometabolic function. The association between central fat distribution and cardiometabolic alterations is a novel finding in JDM.

Key words: juvenile dermatomyositis, body composition, central fat distribution, muscle strength, health-related quality of life, cardiometabolic.

Rheumatology key messages:

- Unfavourable body composition in longstanding JDM includes lower muscle mass, higher bodyfat% and central adiposity
- Lower muscle mass and higher body fat % is associated with active disease, inflammation and muscle weakness
- Central body fat distribution was associated with cardiometabolic alterations including dyslipidaemia and impaired cardiac function

Introduction

Juvenile dermatomyositis (JDM) is the most common juvenile onset idiopathic inflammatory myopathy (IIM), and typically presents with skin rash, proximal (and sometimes distal) muscle weakness and impaired physical function (1). While underlying pathophysiological mechanisms of JDM are still not clear (2), it is apparent that involvement of skeletal muscles often causes damage, evident as atrophy, fibrosis and fat infiltration by imaging (3, 4). Although the long-term functional outcome of JDM has improved, a high proportion of patients still develop cardiometabolic dysfunction (hypertension, dyslipidemia, insulin resistance (IR) and mostly subclinical cardiac dysfunction), even at young age and with normal Body Mass Index (BMI) (4-9).

Total body dual-energy x-ray absorptiometry (DXA) is a validated technique to measure body composition and bone mineral content (BMC) as well as soft tissue mass: fat mass (FM) and lean mass (LM). In the general population, unfavorable DXA assessed body composition (low skeletal muscle mass accompanied by higher body fat percentage (BF%) and central fat distribution), is a strong risk factor for a variety of adverse clinical outcomes. These outcomes include impaired physical function, insulin resistance, cardiovascular events

and all-cause mortality (10-13). Only two previous studies in JDM have assessed body composition using DXA. These studies provided somewhat conflicting results, possibly due to limited sample sizes and relatively short disease duration (5, 14).

Unfavorable body composition, comprising DXA-derived low muscle mass with or without fat accumulation, is commonly reported in other juvenile and adult rheumatic diseases, both in early and late disease stage (15-18). Central fat distribution often occurs concurrently (15, 19). These adverse changes are associated with impaired physical function (18) and increased cardiometabolic risk (15, 16).

Recent studies in the general population, stress that skeletal muscle and adipose tissue are major metabolic and endocrine organs secreting cytokines and chemokines involved in crosstalk with other organs (20). Hence, it appears that skeletal muscle inflammation, a hallmark of JDM, may influence body composition and metabolic functions through increased secretion of pro-inflammatory cytokines. We and others have reported that patients with JDM have higher circulating pro-inflammatory cytokine levels than controls (21, 22), but no previous JDM studies investigated the potential association between cytokines and body composition.

Aiming for increased understanding of body composition in patients with JDM, we investigated DXA assessed muscle and fat mass distribution in patients with longstanding JDM compared with age- and sex-matched controls. Further, we performed explorative analyses of associations between body composition, disease activity/inflammation, muscle strength, health-related quality of life (HRQL) and cardiometabolic measures.

Methods

Study population and study design

The present study is part of a larger cross-sectional study conducted at Oslo University Hospital (OUS) between September 2005 and May 2009, where details on the design of the Norwegian JDM study have been described previously (3). The inclusion criteria were disease onset before 18 years, minimum disease duration 24 months from disease onset to follow-up visit and probable or definite diagnosis of dermatomyositis according to the Bohan and Peter criteria (23). The study population included 59 patients diagnosed with JDM and 59 sex- and age matched controls; all participants were ≥6 years at time of study entry.

The study was approved by the Norwegian South East Regional Committee for Medical and Health Research Ethics (S-05144). All participants ≥16 years, or guardians of participants <16 years, provided written informed consent according to the Declaration of Helsinki.

Demographics, clinical data, muscle strength and HRQL

Data on demographics and clinical parameters were obtained directly from study participants at the follow-up visit by a single study physician (HS) as previously described (3). Disease activity was measured by the Disease Activity Score (DAS) (0-20) (24). The PRINTO criteria for clinically inactive disease were applied to identify patients with active and inactive disease (25). Information on current and cumulative prednisolone use was extracted from medical records. In all study participants, self-reported physical activity inducing sweating or breathlessness (hours/week) was assessed; subjectively assessed muscle strength was measured by the unilateral manual muscle test (MMT-8) (0-80) and HRQL was assessed in patients >13 years by the 36-Item Short Form Survey (SF-36) physical component score (PCS) (0-100) (24).

Body composition

Total and regional body composition measurements were obtained by a narrow fanbeam densitometer scan DXA-Lunar Prodigy with software version 16 (GE Healthcare, Madison, WI, USA), operated by a certified densitometry technologist (KG). Standard imaging and positioning protocols were used to measure and estimate BMC, LM (kg) and FM (kg) for total body and regional sites (trunk, arms and legs). The total body LM includes skeletal muscle mass and the mass of all other organs. We also estimated FM in android and gynoid regions of interest (ROI) and calculated the ratio between them: A:G ratio. ROI of android was defined as the region from pelvis cut (lower boundary) to above the pelvis cut by 20 % of the distance from pelvis cut line to neck cut line (upper boundary). ROI of gynoid was defined as the region among the 2× Android height, beginning at a distance of 1.5× Android height below pelvis cut (26). Appendicular LM (ALM) was the sum of LM in arms and legs; ALM is an estimate of appendicular skeletal muscle mass, as the LM in the extremities consists mainly of muscle tissue (27). LM indexed by height^2 (LMI), and especially appendicular LM index (ALMI) has been used as a surrogate marker of skeletal muscle mass. FM was indexed by height^2 (FMI). Total body fat percentage (BF%) was defined as the ratio between total FM and total body mass (sum of BMC, LM and FM) multiplied by 100.

We used data sets from the age- and sex-matched control group to define cut-offs for high and low values of the selected body composition measures. Low ALMI was defined as <mean ALMI value in controls -2 SD, high BF% as >mean BF% in controls +2 SD and high A:G ratio >95th percentile of control group values.

Laboratory analyses

Serum samples were collected from the participants at follow-up and stored at -80^{0}C until analysis. A total of 26 cytokines were previously analyzed by Luminex (21). For the current study, we included three cytokines whose levels were significantly elevated compared with

controls: monocyte chemoattractant protein (MCP-1; CCL2), interferon gamma-induced protein-10 (IP-10; CXCL10) and interleukin-6 (IL-6). Tumor necrosis factor-α (TNF-α) was also included due to the general clinical relevance in muscle biology (28). High sensitivity C-reactive protein (hs-CRP) and lipids (high density lipoprotein (HDL) and triglycerides (TG)) were all analyzed consecutively at accredited medical biochemistry laboratory OUS Rikshospitalet according to standard protocols. All samples were non-fasting.

Cardiovascular measures

Left ventricular (LV) cardiac function was evaluated with echocardiography. Early tissue doppler velocity (e') was used as a measure of diastolic function, and long axis strain (LAS) as a measure of systolic function, as previously described in detail (7, 8).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0 (Armonk, NY: IBM Corp.). Mean and SD were used to describe continuous parametric data; median and IQRs were used to describe continuous non-parametric data. Comparisons between patients and matched controls were tested by the two-tailed paired sample t-test or Wilcoxon's rank sum test for continuous variables, as appropriate, and McNemar's test for dichotomous variables. For comparison of patients with active and inactive disease, the independent sample Student t-test or the Mann-Whitney U-test were used, as appropriate.

In patients, univariable linear regression analyses were used to investigate the associations between the following body composition variables: ALMI, BF% and A:G ratio (dependent variables) and measures of JDM disease activity and inflammation (independent variables). Subsequent multivariable linear regression analyses were performed, highly intercorrelated independent variables were avoided ($r > 0.7$); thus, disease duration was not

included due to the strong correlation with age (r >0.9). All multivariable regression analysis were adjusted for age and sex using blockwise entry. Then four explanatory variables (listed in Table 1) considered clinically relevant correlates for ALMI, BF% and A:G ratio were entered in a forward stepwise manner. Data on the strength of the associations were given as unstandardized beta (β) with 95% confidence intervals. No collinearity existed in the multivariable models.

Additionally, multivariable linear regression models were used to explore the age and sex adjusted associations between ALMI, BF% and A:G ratio (independent variables) and cardiometabolic measures, muscle strength and HRQL (dependent variables), using the entry method. In these models, strength of the associations was given as standardized beta (β).

All tests were two sided, and $p<0.05$ was considered statistically significant. Due to the hypothesis-generating nature of our study, we did not correct for multiple comparisons.

Results

General and clinical characteristics of study participants

Table 2 shows characteristics of all participants. The 59 patients with JDM had median 16.8 years disease duration at time of follow-up; 36 (61.0%) were female, and 20 (33.9%) of these were females ≥18 years. At follow-up, 29 (49.2%) patients had inactive disease (Table 2). We found no significant differences in body weight and BMI, neither between patients and matched controls, nor between patients with active and inactive disease (Table 2). As expected, more patients with active disease used prednisolone and/or DMARDs compared to those with inactive disease (Table 2). Markers of cardiometabolic function differed between patients and controls, as previously shown in the same cohort (6-8), but we found no significant difference between patients with active or inactive disease. While patients had

higher circulating levels of pro-inflammatory cytokines than controls, the levels were not significantly different in patients with active and inactive disease (Table 2).

DXA-derived body composition parameters in patients and controls

DXA-derived body-composition measures are summarized in Table 3. All LM parameters, including ALM, were lower in the patients than in the controls (Table 3). The patients had 10.4% lower ALM and 8.6% lower ALMI compared with controls ($p<0.01$ for both parameters) (Table 3). Correspondingly, low ALMI (<4.0 kg/m^2) was present in 1 patient (1.7%) and in 1 control (1.7%). Total and regional FM did not differ between patients and controls, but BF% was 11.1% higher in patients compared with controls ($p=0.018$) (Table 3). High BF% (>41.7%) was present in 6 patients (10.2%) and in 1 control (3.4%) ($p=0.29$). Additionally, the patients had 18.8% higher A:G ratio than the controls ($p=0.005$) (Table 3). High A:G ratio (>0.74) was present in 8 patients (13.6%) and 2 controls (3.4%) ($p=0.070$).

DXA-derived body composition parameters stratified according to disease activity, sex and age

We found that the patients with active disease had 13.2% lower ALMI than patients with inactive disease ($p=0.013$) (Table 3). Total LM and regional LM in arms and legs and LMI were 15.4%, 24.5%, 17.6% and 9.1% lower (all p-values<0.05) while regional BF% in arms and legs were 28.6% and 18.0% higher (both p-values<0.05) in patients with active than inactive disease (Table 3).

In all study participants, ALMI was higher in males vs. females (Figure 1A) and in those ≥18 vs. <18 years of age (Figure 1B) (both p-values<0.001). In both males and in those ≥18 years of age, ALMI was lower in patients vs. their respective controls ($p=0.008$ and $p=0.024$, respectively) (Figure 1A and 1B). In all study participants, BF% was higher in

females vs. males (both p-values <0.001) (Figure 1A). In both females and in those ≥18 years of age, BF% was higher in patients vs. their respective controls (both p-values<0.05) (Figure 1A and 1B). Also, in all study participants, A:G ratio was higher in males than females (Figure 1A), and in those ≥18 vs. those <18 years of age (Figure 1B) (all p-values ≤0.004). In both sexes as well as in those ≥18 years of age, A:G ratio was higher in patients vs. their respective controls (in male p=0.044, female p=0.033 and age≥18 p=0.004) (Figure 1A and 1B).

Body composition and associations with disease characteristics in patients

Table 4 presents age and sex adjusted correlates of body composition and measures of disease activity/inflammation. ALMI was negatively associated with MCP-1 (unstandardized ß -0.019, 95% CI (-0.035, -0.002), p=0.029); both age and male sex were positively and independently associated with the outcome. BF% was independently associated with hs-CRP (unstandardized ß 0.360, 95% CI (0.29, 1.36), p=0.003); male sex was negatively associated (Table 4). For A:G ratio as an outcome, only age and no disease activity/inflammation parameters were associated. None of the body composition measures were independently associated with cumulative prednisolone dose (Table 4).

Associations between body composition and cardiometabolic measures, muscle strength and HRQL in patients

Table 4 shows age and sex adjusted correlates of body composition with cardiometabolic parameters, muscle strength and HRQL. Lower ALMI was associated with higher LV systolic function and lower MMT-8. Higher BF% was associated with lower SF-36 PCS (Table 1). A higher A:G ratio was associated with both lower LV diastolic and systolic cardiac function and also with lower HDL and higher TG levels (Table 1).

Discussion

Aiming to map and understand body composition in JDM, we performed DXA analyses of patients with JDM at median 16.7 years disease duration. Main findings were that patients, compared to matched controls, had lower lean mass, higher BF% and more central fat distribution (A:G ratio) despite similar BMI. Additionally, the results indicated associations between the patients' unfavorable body composition and a number of disease-relevant parameters, such as active disease, inflammation markers, impaired muscle strength and HRQL as well as cardiometabolic measures.

To our knowledge, there are only two previous studies on DXA assessed body composition in JDM. These controlled studies included 20 (only females) and 25 patients, respectively, with median disease duration of 3.2 and 5.5 years (5, 14). While one of the studies showed lower skeletal muscle mass in (female) patients than in controls (14), no differences in body fat between patients and controls were found (5, 14). For comparison, studies in juvenile onset SLE and JIA have demonstrated lower muscle mass and higher BF% in patients with both early (17, 29) and longstanding disease (16, 30).

The finding of lower ALMI in our JDM cohort, is in line with our previous studies showing MRI assessed muscle damage of thigh muscles (atrophy, fatty-infiltration and/or calcinosis) in the same cohort (3) as well as reduced cross-sectional area of thigh muscles in patients with JDM assessed after mean 21.8 years disease duration (31). Accordingly, in the present study we found that lower ALMI was associated with impaired muscle strength assessed by MMT-8. Moreover, we observed associations between inflammatory chemokine MCP-1 and lower ALMI. This finding is in line with the notion that systemically elevated pro-inflammatory cytokines may contribute to skeletal muscle damage in JDM (31, 32). However, it is not possible to conclude on causal relationships in a cross-sectional design.

Our patients with active disease had lower ALMI compared with those with inactive disease. In contrast to studies in other rheumatic diseases (14, 15, 17, 29, 33), we found most pronounced ALMI reduction in male patients. This sex specific impact on ALMI (that reflects skeletal muscle mass) may reflect a more severe disease course among male patients with JDM. Further studies are needed to elaborate this finding.

We found higher BF% in female vs. male patients and in patients ≥ vs < 18years. These results differ from controlled studies in other rheumatic diseases which have reported increased BF%, in both sexes compared with controls (33), and also among young patients with JIA and SLE (16, 17, 29). The age and sex differences in BF% may be JDM specific or related to study sample size.

Also, higher BF% was associated with hs-CRP in the current study, in line with results from studies on adult-onset rheumatic diseases (34, 35). Hs-CRP is an established biomarker and predictor of cardiovascular disease (36) associated with metabolic abnormalities including adiposity, hyperinsulinemia, IR, elevated TG, low HDL. This is of importance for patients with JDM, possibly linking increased BF% and inflammation.

To our knowledge, associations between DXA-derived measures of body fat and physical function have never previously been examined in JDM, but one adult IIM study (37) reported that high BF%, total FM and FMI were associated with impaired physical function (muscle fatigability). The association between higher BF% and impaired HRQL demonstrated in our JDM cohort has previously been shown in children with obesity from the general population (38). Increased adiposity creates low-grade inflammation, with elevated proinflammatory cytokines including TNF-α and IL-6 (39) that may contribute to impaired HRQL

This study is the first to assess A:G ratio as a measure of central fat distribution in patients with JDM. Fat distribution is of importance to assess risk of cardiovascular disease.

Accumulation of fat in the abdominal region is associated with an increased risk of type 2 diabetes and cardiovascular disease (40). Our finding of increased A:G ratio in patients vs. controls is in line with studies in adult-onset IIM (37) and with the central fat distribution reported in other rheumatic inflammatory disorders (19, 41). However, even though patients with longstanding JDM show alterations in body composition similar to adult-onset rheumatic disease populations, the findings are present at a significantly younger age. Further studies are needed to see if this eventually leads to cardiovascular disease.

A novel finding of our study was the association of central fat distribution and impaired LV cardiac function (systolic and diastolic) in patients with JDM. This is supported by studies in the general population (42, 43), but has neither been investigated in JDM, nor in any other connective tissue diseases. Our finding is interesting because subclinical LV cardiac dysfunction is associated with cardiovascular morbidity and mortality (44-46). Also, central fat distribution was associated with increased cardiometabolic risk (dyslipidemia), in accordance with findings in studies in both juvenile- and adult-onset SLE and RA (15, 16, 19, 41), and in children and adolescents in the general population (47). Although patients with JDM have higher risk of cardiovascular- and cerebrovascular disease and metabolic abnormalities (high TG, low LDL, IR) (4-9), further studies are required to confirm a link between subclinical LV cardiac dysfunction and adverse clinical outcomes in JDM.

Our patients with active disease had more unfavourable body composition than those with inactive disease. Studying patients after long-term follow-up, many were diagnosed in a period where treatment regimens (included use of biologics) where less aggressive than current practice (48). Also, our patients reported to be less physically active compared to controls. It is known that physical activity can improve body composition in the general population (49). However, no body composition changes were found after a 12-week aerobic exercise program in a small (n=8) Danish JDM study with patients who had recovered from

JDM (50). Hopefully, body composition in patients with JDM can improve with personalized multidisciplinary disease management, including optimized exercise and medical treatment. The shown association between impaired body composition and both muscle weakness and lower HRQL support a clinical relevance of our findings. However, due to the cross-sectional study design, we cannot ascertain any causal relationships.

Strengths of our study include that our patient cohort includes 95% of all trackable patients with JDM in Norway diagnosed in the given time period. The inclusion of age-and sex matched controls from the National Registry also represents a strength. Limitations include the cross-sectional design (which makes causal relationships challenging), the relatively small study sample size and the wide age-range. We have no data on disease flare or puberty stage (of the younger participants), and suboptimal data on physical activity. The study consisted mainly of Caucasians, and one should be careful about extrapolating results to other populations.

Conclusion

Despite normal BMI, patients with JDM, especially those with active disease, had unfavorable body composition, which was associated with impaired muscle strength, HRQL, metabolic and cardiac function. The mechanisms underlying the unfavourable body composition in JDM have yet to be explored. Our results suggest associations between central fat distribution and cardiometabolic alterations, especially left ventricular cardiac dysfunction. This is a novel and potentially modifiable finding in patients with JDM. However, further studies are warranted to explore the clinical relevance of impaired body composition.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

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

Ethics: All authors state that this study complies with the Declaration of Helsinki, and is approved by the locally appointed ethics committee and that informed consent has been obtained from the subjects or their legally authorized representative.

Data Availability Statement: The data underlying this article cannot be shared publicly for the privacy of the individuals that participated in the study.

References

1. Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. Lancet. 2008;371(9631):2201-12.
2. Wienke J, Deakin CT, Wedderburn LR, van Wijk F, van Royen-Kerkhof A. Systemic and Tissue Inflammation in Juvenile Dermatomyositis: From Pathogenesis to the Quest for Monitoring Tools. Front Immunol. 2018;9:2951.
3. Sanner H, Kirkhus E, Merckoll E, Tollisen A, Roisland M, Lie BA, et al. Long-term muscular outcome and predisposing and prognostic factors in juvenile dermatomyositis: A case-control study. Arthritis Care Res (Hoboken). 2010;62(8):1103-11.
4. Coyle K, Rother KI, Weise M, Ahmed A, Miller FW, Rider LG. Metabolic abnormalities and cardiovascular risk factors in children with myositis. J Pediatr. 2009;155(6):882-7.
5. Kozu KT, Silva CA, Bonfa E, Sallum AM, Pereira RM, Viana VS, et al. Dyslipidaemia in juvenile dermatomyositis: the role of disease activity. Clin Exp Rheumatol. 2013;31(4):638-44.
6. Schwartz T, Sjaastad I, Flato B, Vistnes M, Christensen G, Sanner H. In active juvenile dermatomyositis, elevated eotaxin and MCP-1 and cholesterol levels in the upper normal range are associated with cardiac dysfunction. Rheumatology (Oxford). 2014;53(12):2214-22.
7. Schwartz T, Sanner H, Gjesdal O, Flato B, Sjaastad I. 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(10):1805-10.
8. Schwartz T, Sanner H, Husebye T, Flato B, Sjaastad I. Cardiac dysfunction in juvenile dermatomyositis: a case-control study. Ann Rheum Dis. 2011;70(5):766-71.
9. Silverberg JI, Kwa L, Kwa MC, Laumann AE, Ardalan K. Cardiovascular and cerebrovascular comorbidities of juvenile dermatomyositis in US children: an analysis of the National Inpatient Sample. Rheumatology. 2018;57(4):694-702.
10. Lee DH, Giovannucci EL. Body composition and mortality in the general population: A review of epidemiologic studies. Exp Biol Med (Maywood). 2018;243(17-18):1275-85.
11. Gomez-Ambrosi J, Silva C, Galofre JC, Escalada J, Santos S, Gil MJ, et al. Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. Obesity. 2011;19(7):1439-44.
12. Wiklund P, Toss F, Weinehall L, Hallmans G, Franks PW, Nordstrom A, et al. Abdominal and gynoid fat mass are associated with cardiovascular risk factors in men and women. The Journal of clinical endocrinology and metabolism. 2008;93(11):4360-6.

13. Borga M, West J, Bell JD, Harvey NC, Romu T, Heymsfield SB, et al. Advanced body composition assessment: from body mass index to body composition profiling. J Investig Med. 2018;66(5):1-9.
14. Santiago RA, Silva CA, Caparbo VF, Sallum AM, Pereira RM. Bone mineral apparent density in juvenile dermatomyositis: the role of lean body mass and glucocorticoid use. Scand J Rheumatol. 2008;37(1):40-7.
15. Turk SA, van Schaardenburg D, Boers M, de Boer S, Fokker C, Lems WF, et al. An unfavorable body composition is common in early arthritis patients: A case control study. PloS one. 2018;13(3):e0193377.
16. Lilleby V, Haugen M, Morkrid L, Frey Froslie K, Holven KB, Forre O. Body composition, lipid and lipoprotein levels in childhood-onset systemic lupus erythematosus. Scand J Rheumatol. 2007;36(1):40-7.
17. Lien G, Selvaag AM, Flato B, Haugen M, Vinje O, Sorskaar D, et al. A two-year prospective controlled study of bone mass and bone turnover in children with early juvenile idiopathic arthritis. Arthritis and rheumatism. 2005;52(3):833-40.
18. Giles JT, Bartlett SJ, Andersen RE, Fontaine KR, Bathon JM. Association of body composition with disability in rheumatoid arthritis: impact of appendicular fat and lean tissue mass. Arthritis Rheum. 2008;59(10):1407-15.
19. Li Z, Shang J, Zeng S, Wu H, Zhou Y, Xu H. Altered body composition and increased visceral adipose tissue in premenopausal and late postmenopausal patients with SLE. Clin Rheumatol. 2019;38(11):3117-27.
20. Li F, Li Y, Duan Y, Hu CA, Tang Y, Yin Y. Myokines and adipokines: Involvement in the crosstalk between skeletal muscle and adipose tissue. Cytokine & growth factor reviews. 2016.
21. Sanner H, Schwartz T, Flato B, Vistnes M, Christensen G, Sjaastad I. Increased levels of eotaxin and MCP-1 in juvenile dermatomyositis median 16.8 years after disease onset; associations with disease activity, duration and organ damage. PLoS One. 2014;9(3):e92171.
22. Bilgic H, Ytterberg SR, Amin S, McNallan KT, Wilson JC, Koeuth T, et al. Interleukin-6 and type I interferon-regulated genes and chemokines mark disease activity in dermatomyositis. Arthritis and rheumatism. 2009;60(11):3436-46.
23. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292(7):344-7.
24. Rider LG, Werth VP, Huber AM, Alexanderson H, Rao AP, Ruperto N, 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 (Hoboken). 2011;63 Suppl 11:S118-57.
25. Lazarevic D, Pistorio A, Palmisani E, Miettunen P, Ravelli A, Pilkington C, et al. The PRINTO criteria for clinically inactive disease in juvenile dermatomyositis. Annals of the rheumatic diseases. 2013;72(5):686-93.
26. Bouchi R, Nakano Y, Ohara N, Takeuchi T, Murakami M, Asakawa M, et al. Clinical relevance of dual-energy X-ray absorptiometry (DXA) as a simultaneous evaluation of fatty

liver disease and atherosclerosis in patients with type 2 diabetes. Cardiovasc Diabetol. 2016;15:64.
27. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. The American journal of clinical nutrition. 1990;52(2):214-8.
28. Thoma A, Lightfoot AP. NF-kB and Inflammatory Cytokine Signalling: Role in Skeletal Muscle Atrophy. Adv Exp Med Biol. 2018;1088:267-79.
29. Regio P, Bonfa E, Takayama L, Pereira R. The influence of lean mass in trabecular and cortical bone in juvenile onset systemic lupus erythematosus. Lupus. 2008;17(9):787-92.
30. Brabnikova Maresova K, Jarosova K, Pavelka K, Stepan JJ. The association between lean mass and bone mineral content in the high disease activity group of adult patients with juvenile idiopathic arthritis. BMC musculoskeletal disorders. 2014;15:51.
31. Berntsen KS, Raastad T, Marstein H, Kirkhus E, Merckoll E, Cumming KT, et al. Functional and Structural Adaptations of Skeletal Muscle in Long-Term Juvenile Dermatomyositis: A Controlled Cross-Sectional Study. Arthritis & rheumatology (Hoboken, NJ). 2020;72(5):837-48.
32. Miller FW, Lamb JA, Schmidt J, Nagaraju K. Risk factors and disease mechanisms in myositis. Nat Rev Rheumatol. 2018;14(5):255-68.
33. Muller R, Kull M, Polluste K, Valner A, Lember M, Kallikorm R. Factors Associated With Low Lean Mass in Early Rheumatoid Arthritis: A Cross- Sectional Study. Medicina (Kaunas). 2019;55(11).
34. Santos MJ, Vinagre F, Canas da Silva J, Gil V, Fonseca JE. Body composition phenotypes in systemic lupus erythematosus and rheumatoid arthritis: a comparative study of Caucasian female patients. Clin Exp Rheumatol. 2011;29(3):470-6.
35. Giles JT, Bartlett SJ, Andersen R, Thompson R, Fontaine KR, Bathon JM. Association of body fat with C-reactive protein in rheumatoid arthritis. Arthritis Rheum. 2008;58(9):2632-41.
36. Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. International journal of cardiology. 2013;168(6):5126-34.
37. Cleary LC, Crofford LJ, Long D, Charnigo R, Clasey J, Beaman F, et al. Does computed tomography-based muscle density predict muscle function and health-related quality of life in patients with idiopathic inflammatory myopathies? Arthritis Care Res (Hoboken). 2015;67(7):1031-40.
38. Tsiros MD, Buckley JD, Olds T, Howe PR, Hills AP, Walkley J, et al. Impaired Physical Function Associated with Childhood Obesity: How Should We Intervene? Child Obes. 2016;12(2):126-34.
39. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. The Journal of clinical investigation. 1995;95(5):2409-15.
40. Karpe F, Pinnick KE. Biology of upper-body and lower-body adipose tissue--link to whole-body phenotypes. Nature reviews Endocrinology. 2015;11(2):90-100.
41. Giles JT, Allison M, Blumenthal RS, Post W, Gelber AC, Petri M, et al. Abdominal adiposity in rheumatoid arthritis: association with cardiometabolic risk factors and disease characteristics. Arthritis Rheum. 2010;62(11):3173-82.
42. Sawada N, Nakanishi K, Daimon M, Yoshida Y, Ishiwata J, Hirokawa M, et al. Influence of visceral adiposity accumulation on adverse left and right ventricular mechanics in the community. European journal of preventive cardiology. 2020;27(18):2006-15.

43. Sawada N, Daimon M, Kawata T, Nakao T, Kimura K, Nakanishi K, et al. The Significance of the Effect of Visceral Adiposity on Left Ventricular Diastolic Function in the General Population. Sci Rep. 2019;9(1):4435.
44. Russo C, Jin Z, Elkind MS, Rundek T, Homma S, Sacco RL, et al. Prevalence and prognostic value of subclinical left ventricular systolic dysfunction by global longitudinal strain in a community-based cohort. European journal of heart failure. 2014;16(12):1301-9.
45. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC, Jr., et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. Jama. 2011;306(8):856-63.
46. Playford D, Strange G, Celermajer DS, Evans G, Scalia GM, Stewart S, et al. Diastolic dysfunction and mortality in 436 360 men and women: the National Echo Database Australia (NEDA). European heart journal cardiovascular Imaging. 2021;22(5):505-15.
47. Daniels SR, Morrison JA, Sprecher DL, Khoury P, Kimball TR. Association of body fat distribution and cardiovascular risk factors in children and adolescents. Circulation. 1999;99(4):541-5.
48. Bellutti Enders F, Bader-Meunier B, Baildam E, Constantin T, Dolezalova P, Feldman BM, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. Annals of the rheumatic diseases. 2017;76(2):329-40.
49. Silva B, Silva I, Ekelund U, Brage S, Ong KK, De Lucia Rolfe E, et al. Associations of physical activity and sedentary time with body composition in Brazilian young adults. Sci Rep. 2019;9(1):5444.
50. Riisager M, Mathiesen PR, Vissing J, Preisler N, Orngreen MC. Aerobic training in persons who have recovered from juvenile dermatomyositis. Neuromuscul Disord. 2013;23(12):962-8.

Table 1. Associations between body composition and cardiometabolic measures, muscle strength and HRQL in patients with JDM

	e' (n=56)	LAS	HDL (n=57)	TG (n=54)	MMT-8	SF 36 PCS (n=51)
ALMI, kg/m^2	0.083	-0.261*	-0.214	0.045	0.638**	0.286
BF%	-0.187	-0.072	-0.246	-0.045	-0.314	-0.362*
A:G ratio	-0.298**	-0.314**	-0.580**	0.649**	0.063	-0.197

Values are standardized ß, adjusted for age and sex. N= 59 if otherwise not stated. *p<0.05, **p<0.01. ALMI, appendicular lean mass index; BF%, body fat percentage of total body mass; A:G fat ratio, android:gynoid fat mass ratio; e', early diastolic tissue velocity (marker of diastolic function); LAS, long axis strain (marker of systolic function); HDL, high density lipoprotein cholesterol; TG, triglyceride; MMT-8, manual muscle test-8; SF 36 PCS, 36 item short form health survey, physical component score.

Table 2. Characteristics of patients with JDM, including active and inactive disease-groups, and matched controls at follow-up

	JDM active (n=30)	JDM inactive (n=29)	JDM total (n=59)	Controls (n=59)
Characteristics and disease measures				
Female, n (%)	21 (70.0)	15 (51.7)	36 (61.0)	36 (61.0)
Age, y	21.5 (13.7-36.3)	21.5 (16.9-33.6)	21.5 (15.4-34.8)	21.6 (15.1-34.8)
Disease duration, y	16.8 (7.0-28.1)	16.7 (6.8-24.8)	16.8 (6.9-27.0)	NA
BMI, kg/m^2	21.9 (5.1)	22.7 (4.5)	22.3 (4.8)	22.5 (4.5)
Physical activity, h/w	4 (3-5)	4 (3-4)	4 (3-4)	5 (4-5) *
DAS total at FU	6 (5-8)	3 (1-5) **	5 (3-6)	NA
SF36 PCS > 13 y	47.3 (39.1-54.7)	56.9 (52.3-59.7) **	53.9 (46.4-58.2)	56.9 (52.8-59.7) *
MMT-8	75 (73-77)	79 (79-80) *	78 (75-80)	80 (80-80) **
Medication				
Prednisolone				
Cumulative dose, g	8.9 (5.7-15.6)	6.0 (0.9-10.4) *	7.9 (3.6-12.6)	NA
Current use, n (%)	9 (30.0)	1 (3.4)	10 (16.9)	NA
DMARD and/or Prednisolone				
Current user, n (%)	14 (46.7)	3 (10.3) *	17 (28.8)	NA
Markers of cardiometabolic function				
Echocardiography				
e', cm/s	10.9 (2.8)	11.6 (2.7)	11.3 (2.8)	12.4 (2.1) *
LAS, %	16.7 (2.7)	16.4 (2.4)	16.6 (2.5)	17.7 (2.0) **
Blood lipids				

HDL, mmol/L	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.5 (0.4) *
TG, mmol/L	1.0 (0.8-1.4)	0.9 (0.7-1.9)	0.9 (0.7-1.7)	0.8 (0.6-1.3) *
Circulating inflammation markers				
hs-CRP, mg/L	1.4 (0.4-4.0)	0.8 (0.3-2.0)	1.0 (0.3-2.5)	0.6 (0.2-1.3)
IP-10, pg/mL	1014 (940-1462)	1002 (876-1617)	1009 (918-1569)	963 (751-1174) *
MCP-1, pg/mL	33.5 (19.6-47.3)	23.8 (15.7-43.8)	28.5 (18.7-46.3)	23.7 (15.3-32.2) *
IL-6, pg/mL	4.3 (3.3-7.3)	3.6 (3.1-5.2)	3.9 (3.2-5.7)	3.6 (2.5-4.5) *
TNF-α, pg/mL	17.4 (12.5-23.6)	16.6 (12.9-23.1)	16.8 (12.8-23.3)	15.3 (11.4-18.5)

Values are mean (SD), median (IQR) or number (%); HDL, n= 57 pairs, JDM active n= 28; e', n= 56 pairs, JDM active n = 29; TG, n= 54 pairs, JDM active n= 26; Cytokines, n = 54 pairs, JDM active n=28; Physical activity, hours/week (h/w) n=51 pairs; SF-36 PCS >13 y, n=51 pairs. *p <0.05, **p ≤0.001, when comparing patients and controls or JDM active and JDM inactive. BMI, body mass index; DAS total at FU, disease activity score at follow-up; SF 36 PCS, 36 item short form health survey, physical component score; MMT-8, manual muscle test-8; DMARD, disease- modifying antirheumatic drug; e', early diastolic tissue velocity; LAS, long axis strain; HDL, high density lipoprotein cholesterol; TG, triglyceride; hs-CRP, high sensitive c-reactive protein; IP-10, Interferon gamma-induced protein-10; MCP-1, Monocyte attractant protein-1; IL-6, Interleukine-6; TNF-α, tumour necrosis factor-alpha.

Table 3. Body composition in patients with JDM, including active and inactive disease-groups, and controls at follow-up

	JDM active (n=30)	JDM inactive (n=29)	*p*-value	JDM total (n=59)	Controls (n=59)	*p*-value
Lean mass, kg						
Total LM	38.0 (14.7)	44.9 (9.7)	**0.036**	41.4 (12.9)	44.9 (13.6)	**0.008**
Trunk LM	19.0 (7.2)	22.1 (4.9)	0.057	20.5 (6.3)	21.8 (6.5)	**0.032**
Arms LM	3.7 (1.9)	4.9 (1.5)	**0.030**	4.2 (1.8)	4.7 (1.8)	**0.007**
Legs LM	12.6 (7.3)	15.3 (3.6)	**0.027**	13.9 (4.9)	15.6 (5.2)	**0.006**
ALM	16.2 (7.3)	20.0 (4.9)	**0.024**	18.1 (6.5)	20.2 (6.9)	**0.004**
Fat mass, kg						
Total FM	17.5 (13.3-28.6)	16.4 (13.0-21.9)	0.81	16.6 (13.0-24.7)	16.8 (13.2-22.2)	0.22
Trunk FM	8.2 (5.5-13.3)	8.2 (5.6-11.9)	0.98	8.2 (5.5-12.2)	7.5 (5.5-10.2)	0.15
Arms FM	1.8 (1.4-2.7)	1.5 (1.3-2.2)	0.35	1.8 (1.3-2.4)	1.8 (1.4-2.3)	0.37
Legs FM	6.4 (4.9-9.3)	6.1 (4.9-8.5)	0.72	6.3 (4.9-8.9)	6.4 (5.0-8.4)	0.44
AFM	8.1 (6.6-11.6)	7.8 (6.3-10.8)	0.66	8.0 (6.4-10.9)	8.1 (6.5-10.6)	0.42
Android	1.3 (0.8-2.1)	1.2 (0.8-2.1)	0.87	1.2 (0.8-2.1)	1.1 (0.7-1.5)	0.097
Gynoid	3.0 (2.2-4.6)	3.0 (2.2-4.3)	0.93	3.0 (2.2-4.6)	3.1 (2.3-4.2)	0.76
Total mass $_{(LM+FM+BMC)}$, kg						
Total Mass	59.6 (22.7)	66.8 (16.4)	0.17	63.1 (20.0)	65.4 (19.8)	0.37
Trunk TM	29.3 (12.9)	32.4 (9.0)	0.29	30.8 (11.2)	31.2 (10.4)	0.79
Arms TM	5.9 (2.5)	6.8 (1.9)	0.13	6.4 (2.2)	6.8 (2.2)	0.099
Legs TM	20.3 (7.5)	23.4 (6.3)	0.092	21.9 (7.0)	23.2 (7.1)	0.17
Body Fat %						
Total BF %	32.0 (6.9)	28.1 (8.1)	0.052	30.1 (7.7)	27.1 (7.3)	**0.018**
Trunk BF %	30.6 (9.3)	27.9 (9.6)	0.28	29.3 (9.5)	26.4 (8.9)	0.080
Arms BF %	35.1 (9.1)	27.3 (9.3)	**0.002**	31.3 (10.0)	28.3 (8.5)	**0.019**
Legs BF %	34.8 (8.5)	29.5 (9.2)	**0.025**	32.2 (9.2)	29.1 (7.7)	**0.011**
AFM BF %	34.9 (8.6)	29.0 (9.2)	**0.014**	32.0 (9.3)	28.9 (7.9)	**0.011**
Indices (kg/m^2) or ratio						
LMI	14.0 (2.9)	15.4 (1.8)	**0.029**	14.7 (2.5)	15.6 (2.6)	**0.014**
ALMI	5.9 (1.6)	6.8 (1.1)	**0.013**	6.4 (1.4)	7.0 (1.5)	**0.006**
FMI	6.4 (4.8-9.4)	6.0 (4.3-7.5)	0.32	6.1 (4.5-8.5)	5.7 (4.7-7.8)	0.12
AFMI	3.2 (2.6-4.2)	2.7 (2.1-3.7)	0.21	3.0 (2.3-3.8)	2.8 (2.3-3.6)	0.24
A:G ratio	0.37 (0.32-0.66)	0.39 (0.26-0.49)	0.93	0.38 (0.26-0.62)	0.32 (0.24-0.44)	**0.005**

Values are mean (SD), median (IQR) or number (%); *p*-values between patients with JDM and controls and between JDM active and JDM inactive. Significant *p*-values are marked in bold. LM, lean mass; ALM,

appendicular lean mass; FM, fat mass; AFM, appendicular fat mass; BF%, body fat percentage of total body mass; TM, total body mass; BMC, bone mineral content; LMI, LM index; ALMI, ALM index; FM%, FM percentage; FMI, FM index; AFMI, AFM index; A:G ratio, android:gynoid fat mass ratio.

Table 4. Associations between body composition measures and disease variables in patients with JDM

	Univariable analysis			Multivariable analysis		
	β	95% CI	*p*-value	β	95% CI	*p*-value
ALMI, kg/m^2						
Age, y	0.05	0.02, 0.08	**<0.001**	0.06	0.03, 0.09	**<0.001**
Male sex	1.30	0.62, 1.99	**<0.001**	1.26	0.61, 1.91	**<0.001**
Cumulative prednisolone dose, g	0.00	-0.03, 0.03	0.99			
IL-6, pg/mL	0.00	-0.05, 0.04	0.88			
MCP-1, pg/mL	0.008	-0.010, 0.026	0.37	-0.019	-0.035, -0.002	**0.029**
DAS total at FU	-0.13	-0.25, 0.00	0.050			
BF%						
Age, y	0.11	-0.05, 0.27	0.17	0.10	-0.05, 0.24	0.17
Male sex	-7.92	-11.51, -4.32	**<0.001**	-6.93	-10.48, -3.38	**<0.001**
hs-CRP, mg/L	1.15	0.60, 1.71	**<0.001**	0.83	0.29, 1.36	**0.003**
Cumulative prednisolone dose, g	0.08	-0.09, 0.25	0.36			
IL-6, pg/mL	0.04	-0.16, 0.24	0.67			
MCP-1, pg/L	0.03	-0.06, 0.13	0.49			
A:G ratio						
Age, y	0.02	0.01, 0.02	**<0.001**	0.01	0.01, 0.02	**<0.001**
Male sex	0.21	0.03, 0.40	**0.026**	0.15	-0.03, 0.33	0.092
Cumulative prednisolone dose, g	0.01	0.00, 0.02	**0.004**			
IL-6, pg/mL	0.00	-0.01, 0.01	0.85			
MCP-1, pg/mL	0.006	0.001, 0.010	**0.016**			
DAS total at FU	0.02	-0.01, 0.05	0.22			

Univariable and multivariable linear regression analysis with ALMI, BF% and A:G ratio as dependent variables; Values are unstandardized ß (ß) and 95% confidence interval (CI); significant *p*-values are marked in bold. ALMI, appendicular lean mass index; BF %, body fat percentage of total body mass; A:G ratio, android:gynoid fat mass ratio; hs-CRP, high sensitivity c-reactive protein; IL-6, interleukin 6; MCP-1, monocyte attractant protein; DAS total, disease activity score.

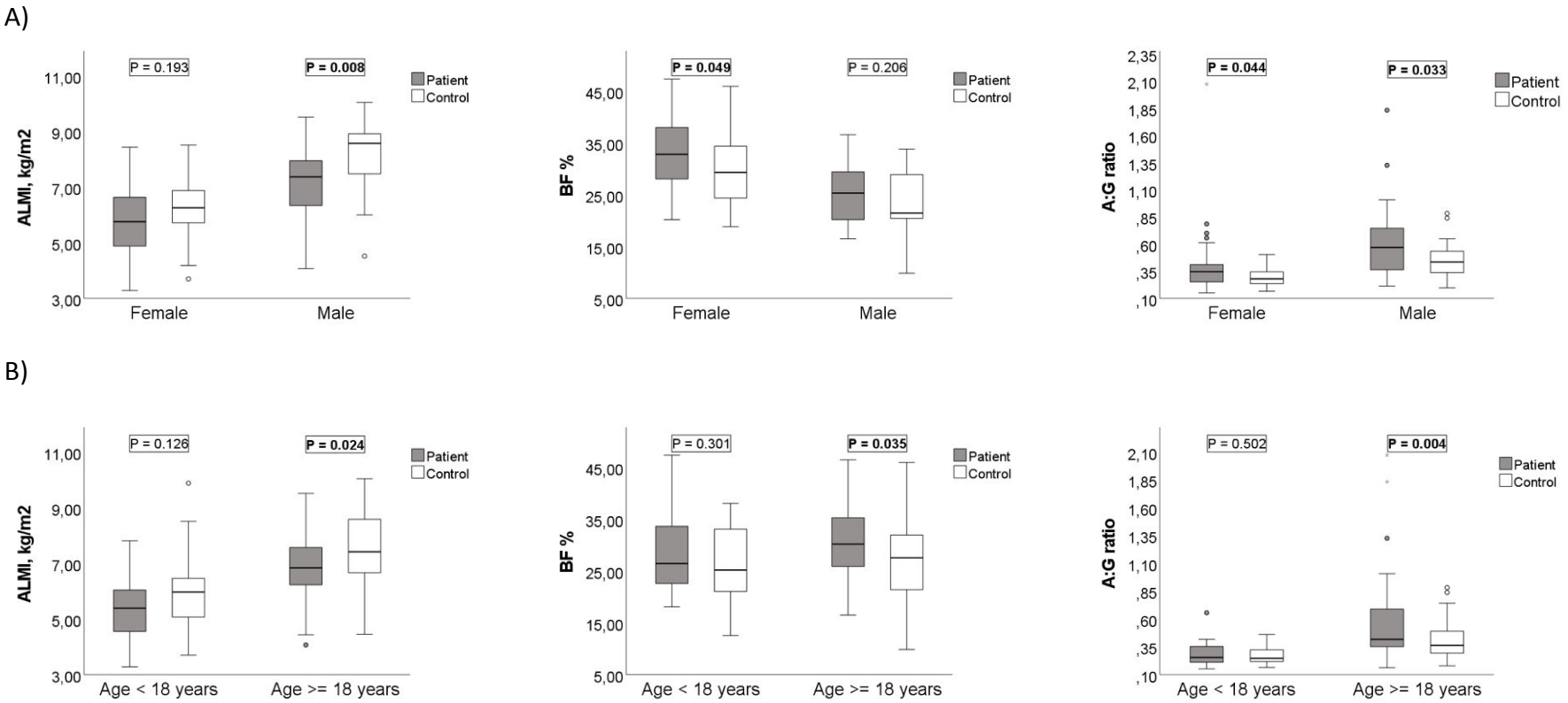

Figure 1. Body composition in patients with JDM and controls stratified by sex and age at follow-up.

A: body composition variables (ALMI (left panel), BF% (middle panel) and A:G ratio (right panel)) in study participants (patients with JDM and age- and sex matched controls), stratified by sex. B: body composition variables (ALMI (left panel), BF% (middle panel) and A:G ratio (right panel)) in study participants (patients with JDM and age- and sex matched controls), stratified by age < 18 versus >= age 18 years .

ALMI, appendicular lean mass index; BF%, Body fat percentage; A:G ratio, android fat mass:gynoid fat mass ratio.