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Predictors of Acquired Lipodystrophy in Juvenile-Onset Dermatomyositis and a Gradient of Severity

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Abstract

We describe the clinical features of 28 patients with juvenile dermatomyositis (JDM) and 1 patient with adult-onset dermatomyositis (DM), all of whom developed lipodystrophy (LD) that could be categorized into 1 of 3 phenotypes, generalized, partial, or focal, based on the pattern of fat loss distribution. LD onset was often delayed, beginning a median of 4.6 years after diagnosis of DM. Calcinosis, muscle atrophy, joint contractures, and facial rash were DM disease features found to be associated with LD. Panniculitis was associated with focal lipodystrophy while the anti-p155 autoantibody, a newly described myositis-associated autoantibody, was more associated with generalized LD. Specific LD features such as acanthosis nigricans, hirsutism, fat redistribution, and steatosis/nonalcoholic steatohepatitis were frequent in patients with LD, in a gradient of frequency and severity among the 3 sub-phenotypes. Metabolic studies frequently revealed insulin resistance and hypertriglyceridemia in patients with generalized and partial LD. Regional fat loss from the thighs, with relative sparing of fat loss from the medial thighs, was more frequent in generalized than in partial LD and absent from DM patients without LD. Cytokine polymorphisms, the C3 nephritic factor, insulin receptor antibodies, and lamin mutations did not appear to play a pathogenic role in the development of LD in our patients. LD is an under-recognized sequela of JDM, and certain DM patients with a severe, prolonged clinical course and a high frequency of calcinosis appear to be at greater risk for the development of this complication. High-risk JDM patients should be screened for

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metabolic abnormalities, which are common in generalized and partial LD and result in much of the LD-associated morbidity. Further study is warranted to investigate the pathogenesis of acquired LD in patients with DM.

INTRODUCTION

Dermatomyositis (DM) is a chronic systemic autoimmune disease characterized by proximal weakness and characteristic skin rashes that can begin in children under 18 years of age as juvenile dermatomyositis (JDM) or in adults⁵². Although patients with JDM may experience resolution of the illness over several years with few sequelae, a significant proportion of patients have residual weakness, muscle atrophy, joint contractures, and/or calcinosis³⁰. A less frequently recognized but clinically important complication of JDM is lipodystrophy (LD).

LD, which may be congenital or acquired, is a condition in which patients lose subcutaneous fat in a localized or generalized distribution, frequently with resultant metabolic abnormalities such as insulin resistance (IR) and hyperlipidemia²¹. These patients have a loss of mature, functional adipocytes, as opposed to an absence of lipid in otherwise normal adipocytes⁵⁰. Acquired LD has been reported in connection with infections, antiretroviral therapy used to treat patients with human immunodeficiency virus (HIV), and a number of autoimmune diseases, including JDM, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and Sjögren syndrome^{40,46}. A proposed classification of acquired generalized LD includes an autoimmune subgroup³⁹.

Of the autoimmune diseases, JDM is one of the more well established in its association with LD, and possibly the most frequent⁴⁶. Several small studies have highlighted the occurrence of LD in JDM patients, with a prevalence of 10%–40%^{31,37,56,62}. Metabolic abnormalities such as IR, diabetes, and dyslipidemia accompany the fat loss in many of these patients. However, the specific characteristics of JDM or LD in this patient population have not been systematically studied.

Although the pathogenesis of acquired LD is unknown, several theories exist regarding its development. Tumor necrosis factor alpha (TNF- α) and interleukin-1 (IL-1) have been shown to inhibit adipogenesis¹⁹. TNF- α is known to induce IR¹². These cytokines, which are also important in the pathogenesis of DM, may play a role in the development of LD³⁶. Mutations in specific genes regulating adipocyte differentiation, fat metabolism, and other aspects of adipogenesis have been associated with specific clinical phenotypes of congenital LD¹. Mutations in A-type lamins are responsible for lipodystrophic diseases such as Dunnigan-type familial partial LD, Emery-Dreifuss muscular dystrophy, and Hutchinson-Gilford progeria syndrome¹⁴. Over-expression of lamin A has been shown to inhibit adipocyte differentiation⁷. Delta-like 1 (dlk 1) protein, an epidermal growth factor-like protein, also controls adipocyte differentiation³⁵. Such an adipocyte differentiation factor may be altered in patients with LD. Low levels of C3 due to the C3 nephritic factor are frequently seen in patients with acquired partial LD and may play a role in its pathogenesis⁴⁰.

Because acquired LD in patients with JDM has not been systematically studied, we made use of a large national myositis registry to perform a detailed and multidisciplinary examination of the prevalence of the major LD phenotypes, the spectrum of clinical and metabolic abnormalities, and the characteristics of DM that are predictive of development of LD. Based on the metabolic and genetic data summarized, we also examined possible pathogenic factors for development of LD in patients with DM.

METHODS

Patients

The Childhood Myositis Heterogeneity Collaborative Study, conducted by the National Institutes of Health (NIH) (Bethesda, MD), and the United States Food and Drug Administration (Bethesda, MD), enrolled 411 patients with juvenile idiopathic inflammatory myopathy from 1994 to December 2006. Of these patients, 353 had JDM, either alone or in overlap with another autoimmune disease. All patients completed a clinical questionnaire and provided a blood sample.

Twenty-eight patients with JDM who had LD, based on physician recognition of body fat loss, were identified in this cohort. One additional patient with adult-onset DM was identified from an ongoing natural history study at the NIH in which 692 patients with inflammatory and other myopathies have enrolled since 1994. Nineteen of the DM patients with LD were examined at the NIH Clinical Center (Bethesda, MD) and evaluated by both a pediatric rheumatologist conducting myositis research and an endocrinologist performing LD research. All patients or their legal guardians gave informed consent for these studies.

Patients with generalized loss of fat in the face, trunk, abdomen, and all extremities were classified as having generalized LD³⁹. Patients with loss of fat from the upper and/or lower extremities, with a relative sparing of fat loss from the abdomen and trunk⁴³, were categorized as having partial LD. Patients with fat loss from localized areas, often resulting in skin surface depression or dimpling, were diagnosed with localized or focal lipoatrophy (LA)²¹.

DM disease course was classified as monocyclic if the patient experienced full recovery without relapses and discontinued all medications within 2 years of diagnosis; polycyclic if the patient had recurrence of active disease after a definite remission; and chronic continuous if disease activity and/or medication use persisted beyond 2 years³⁰. Disease activity at most recent follow-up was assessed based on a physician's global activity rating⁵¹, as well as on the presence of typical signs of active DM, including the presence of rashes, weakness, and elevated muscle enzymes.

Fat Distribution

Eighteen patients with DM and LD had T1-weighted thigh (n = 18) and/or abdominal (n = 9) magnetic resonance imaging (MRI) examinations obtained on a 1.5 Tesla scanner (General Electric Medical Systems, Milwaukee, WI). MRIs were obtained to assess muscle disease or to determine areas of fat loss. Fat distributions on axial images of the right midthigh and the L2–L3 vertebral body level were compared to those for 18 sex- and age-matched DM patients without LD and to 9 sex-matched healthy control subjects, respectively, by a single radiologist who was blinded to diagnosis.

Dual-energy X-ray absorptiometry (DXA) scans using a Hologic 4500 machine (Hologic QDR 4500; Hologic, Bedford, MA) were used to quantify percentage total body fat. Adult lower limit of normal for total body fat was determined by subtracting 2 standard deviations from published mean values⁹. For children, a body fat percentage less than the second percentile of published values was used to define an abnormally low value³⁸. Ovarian volumes greater than 3 mL in premenarchal and 9.8 mL in menarchal girls/women, as measured by pelvic ultrasound, were considered abnormally increased¹⁰.

Laboratory Studies of Metabolic Features

For all fasting laboratory studies, insulin or lipid altering medications were held the morning of the test. A fasting plasma glucose of 100–125 mg/dL (5.6–6.9 mmol/L) was considered to

be impaired, and a level of ≥ 126 mg/dL (7 mmol/L) was considered consistent with diabetes mellitus²². Plasma glucose values at 2 hours following a 1.75 g/kg (maximally 75 g) oral glucose challenge were considered impaired when ≥ 140 mg/dL (7.8 mmol/L), and diabetic if ≥ 200 mg/dL (11.1 mmol/L)^{4a,22}. A fasting insulin of >27 μ U/mL (187.5 pmol/L) was indicative of IR in the NIH Clinical Center laboratory. A homeostasis model assessment of IR (HOMA-IR) of ≥ 4 was considered indicative of IR, and a value of ≥ 8 was consistent with diabetes⁴⁹.

In adults, levels of fasting cholesterol ≥ 200 mg/dL (5.2 mmol/L), low-density lipoprotein (LDL) ≥ 130 mg/dL (3.4 mmol/L), triglyceride ≥ 150 mg/dL (1.7 mmol/L), and a high-density lipoprotein (HDL) <50 mg/dL (1.3 mmol/L) in women or <40 mg/dL (1.04 mmol/L) in men were considered abnormal²⁴. For individuals aged 19 years or younger, we defined elevated triglyceride, total cholesterol, and LDL as greater than the 95th percentile and low HDL as less than the 5th percentile for age- and sex-matched controls⁴. In prepubertal girls, leptin levels <2.08 ng/mL were considered low³. For postpubertal women, leptin levels below the 5th percentile for healthy women were considered abnormal⁵³.

Hepatic Involvement

Hepatic involvement was assessed in 16 patients who had liver imaging by ultrasound or computerized tomography (CT). Liver biopsies were performed in 9 patients with abnormal liver imaging and/or elevated transaminases. Eight of 9 biopsies were reviewed at the NIH by a single pathologist. Hematoxylin-eosin stained sections of liver were examined for features of nonalcoholic steatohepatitis (NASH). Masson trichrome and ubiquitin stains were also examined for features of fibrosis and Mallory hyaline, respectively. A pathologic diagnosis of NASH was made if zone 3 ballooning degeneration and hepatocellular injury in the presence of steatosis and spotty lobular inflammation were present⁴⁸. Steatosis, lobular inflammation, portal inflammation, ballooning hepatocellular injury, Mallory hyaline, and fibrosis were scored semiquantitatively on a scale from 0 to 4⁴⁸.

Myositis-Associated Antibody and Myositis-Specific Antibody Testing

Patients were tested for the presence of myositis-associated and myositis-specific autoantibodies by protein and RNA immunoprecipitation as previously reported⁵⁸.

Insulin Receptor Antibodies

Three patients were screened for insulin receptor antibodies as previously described⁵.

HLA Typing

Purified genomic DNA was utilized for high-resolution HLA typing using commercial reagents for polymerase chain reaction (PCR)-mediated sequence-specific oligonucleotide probe hybridization and sequence-specific primer techniques (GenoVison, West Chester, PA and Dynal Biotech, Lafayette Hill, PA), as previously described⁴². High-resolution DRB1 and DQA1 alleles were examined in 16 and 19 white JDM patients with LD, respectively, and were compared to 93 and 177 race-matched JDM patients without LD, respectively.

Cytokine Polymorphisms

IL-1 α ⁻⁸⁸⁹(C-T), IL-1 α ⁺⁴⁸⁴⁵(C-T), IL-1 β ⁻⁵¹¹(C-T), IL-1 β ⁺³⁹⁵³(C-T) and TNF- α promoter polymorphisms at positions -238 (A-G) and -308 (A-G) were determined by PCR of DNA isolated from peripheral blood lymphocytes followed by restriction enzyme digestion and polyacrylamide gel electrophoresis^{44,45}. DNA samples were examined in 14 white patients with JDM and LD and in 141 JDM patients without LD.

Tristetraprolin (TTP) Polymorphisms

Genomic DNA was assayed for quality using an RNase P assay kit (Applied Biosystems [ABI], Foster City, CA). Genotyping for ZFP36 polymorphisms was performed in 10 JDM patients with LD and in 35 without LD using high-throughput matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (BioServe Biotechnologies, Laurel, MD)⁸. Each set of study samples was processed with 4 positive and 4 negative control samples. Allele calls for all polymorphisms were greater than 88%.

Lamin A (LMNA) Gene Analysis

DNA samples from 3 JDM patients with partial LD underwent sequence analysis for the coding region of the LMNA gene (www.progeriaresearch.org/diagnostic_testing.html; The Progeria Research Foundation, Peabody, MA). PCR amplification of indicated exons, plus about 100 flanking base pairs, was followed by cycle sequencing using the ABI Big Dye Terminator v. 3.0 kit (ABI, Foster City, CA) and using 1 of the PCR primers as a sequencing primer. Sequencing products were resolved by electrophoresis on an ABI 3130xl capillary sequencer. ABI base calling software was used to help interpret the electropherograms. Sequencing was performed separately in both the forward and reverse directions. Nomenclature for reporting sequence variants was taken from den Dunnen and Antonarakis¹¹.

Western Blot for dlk 1 Protein Expression Analysis

Western blots for the analysis of dlk 1 expression in the sera were performed according to standard procedures²⁶. One hundred µg of total serum proteins from each sample were used. A 1:200 dilution of rabbit polyclonal anti-Extldk (ImClone Systems Inc., New York, NY) was used as the primary antibody. Detection was performed with enhanced chemiluminescence (Amersham Biosciences, Piscataway, NJ). Quantitation was done using ImageQuant software following densitometry scanning on a FluorImager SI (Molecular Dynamics, Sunnyvale, CA). Albumin was used as control for protein loading.

Statistical Analysis

GraphPad Instat v. 3.00 (GraphPad Software, San Diego, CA), Sigma Stat for Windows v. 3.0.1 (Systat Software, Inc., Richmond, CA), and SAS Enterprise Guide 8.02 (SAS Institute Inc., Cary, NC) were used for statistical analyses. Data were expressed as median and interquartile ranges, and p values for differences between patient groups were obtained by the Mann-Whitney test. When comparing proportions between groups, p values were calculated by the Fisher exact test or analysis of variance. A p value less than or equal to 0.05 was considered significant. For HLA and cytokine polymorphisms, p values were adjusted for multiple comparisons using the Holm procedure²⁸. Alleles that were of higher or lower frequency in DM patients with LD compared to DM patients without LD before correction for multiple comparisons were termed possible risk or protective factors when the confidence interval (CI) on the odds ratio (OR) was appropriate. For TTP polymorphisms, haplotypes were inferred using PHASE 2.0.2 (Seattle, WA, <http://www.stat.washington.edu/stephens/software.html>). The exact test was used to determine deviations from Hardy-Weinberg equilibrium. Random Forests classification analysis was performed using the statistical language, R (http://www.stat.berkeley.edu/users/breiman/RandomForests/cc_home.htm). For each Random Forests analysis, 500 trees were drawn and the variables were randomly chosen at each tree split. To account for differences in sample sizes in JDM cases with and without LD, the number of observations used in bootstrap sampling was kept equal⁴².

RESULTS

Patient Demographics and Clinical Features

LD was noted in 28 of 353 (7.9%) patients with JDM, but was not reported in any patients with juvenile polymyositis (n = 50). One JDM patient with LD had another immune-mediated disease, ulcerative colitis. LD was present in only 1 adult-onset DM patient of 692 adult myositis patients enrolled in the adult natural history study.

Of the 29 DM patients with LD described in the current study, 8 had generalized LD, 16 had partial LD, and 5 had focal LA. The median age of the DM patients with LD at initial assessment was 17.1 years [25% 9.5 yr, 75% 25 yr]. The median follow-up after diagnosis of DM was 8.5 years.

We compared the features of DM in patients with LD with those in JDM patients without LD (Table 1). Patients with LD more often had a chronic continuous course of DM compared to those without LD, and they more often developed malar or facial erythema, erythroderma, panniculitis, calcinosis, muscle atrophy, and joint contractures (see Table 1, $p \leq 0.02$ for all). Notably, panniculitis was reported in 4 of 5 patients with focal LA, less frequently in patients with partial LD, and not reported in patients with generalized LD ($p = 0.012$). Patients with focal LA uniformly had dysphonia, which was increased in frequency compared to JDM patients without LD ($p < 0.001$).

Because multiple clinical characteristics were associated with the development of LD, we performed Random Forests classification analysis to determine the relative importance of the clinical features and characteristics in discriminating DM patients with LD from those without LD (Table 2). From this analysis, the most important clinical features in discriminating DM patients with LD from those without LD were muscle atrophy, joint contractures, malar rash, calcinosis, and a chronic continuous illness course. We then examined which characteristics best predicted the development of LD in JDM by logistic regression modeling. Malar rash resulted in a complete separation of the groups with an infinite likelihood ratio and was dropped from the models. Table 3 demonstrates 2 multiple regression models, each consisting of 3 variables, which had the highest likelihood ratios and resulted in significant contributing features. Joint contractures and calcinosis were strong predictors for the development of LD in JDM patients in both models; and panniculitis and muscle atrophy was each predictive of LD in 1 model.

The most common subtype of calcinosis in patients with JDM and LD was superficial plaques and nodules, present in 21 of 23 LD patients who developed calcinosis. Thirteen of 23 had tumorous deposits, and 11 of 23 had calcinosis along fascial planes. Two patients had calcinosis universalis. All patients had some disease damage based on the physician's global assessment⁵¹, and 20 of 29 had moderate or severe global disease damage at most recent follow-up.

Patients with DM and LD had a similarly high rate of antinuclear antibody positivity compared to those without LD (Table 1). The newly recognized anti-p155 myositis-associated autoantibody was present more often in patients with generalized LD than in JDM patients without LD (6 of 7 [86%] vs. 27 of 76 [36%]; $p = 0.014$), and more frequently in generalized than in partial or focal LD (ANOVA $p = 0.012$). Other myositis-associated autoantibodies present in the LD patients included anti-Ro in 3 patients and anti-U1RNP in 1 patient. None of the LD patients had myositis-specific autoantibodies. Anti-insulin receptor antibodies were not detected in 3 patients tested. Serum C3 level was normal in 18 LD patients tested, including 11 with partial LD.

The clinical features of LD in patients with DM are presented in Table 4. Acanthosis nigricans, muscle prominence, hepatomegaly, and hypertrichosis were frequent examination findings in LD patients, and there was no difference in the frequency of these features among LD subgroups. Hyperpigmentation was a less frequent manifestation in our patients. Two JDM patients with LD had focal segmental glomerulosclerosis, which is rarely observed in patients with DM.

Patients reported that the onset of fat loss preceded a physician's diagnosis of LD by a median of 2.6 years [25% 0.5 yr, 75% 5.8 yr; $n = 7$]. The onset of LD occurred before 20 years of age in all but 1 JDM patient. Physician diagnosis of LD, or patient recollection of LD onset if physician diagnosis date was unavailable, followed the diagnosis of DM by a median of 4.6 years (see Table 4). There was no difference in the delay in diagnosis of LD or in the time to onset of LD after the diagnosis of DM among the LD subgroups.

Distribution of Fat Loss

Figure 1–Figure 3 illustrate the pattern of fat loss seen in each of the 3 LD subtypes based on clinical documentation. Patients with generalized LD invariably had fat loss from all extremities and buccal fat loss (Fig. 1 A–C), as well as fat loss from the abdomen and trunk. Patients with partial LD universally had fat loss in the arms, and the majority (12 of 16) had buccal fat loss. Although the majority of patients with partial LD had fat loss from the lower extremities, others had increased fat deposition (Fig. 2 A and B). Patients with focal LA had fat loss in the buttocks (in 2 of 5 focal LA patients) or thigh, at a site of calcinosis (Fig. 3 A and B). Fat loss in the palms and soles was noted in 2 patients, although this was not systematically documented. Of the 8 patients with generalized LD, 1 presented with partial LD and later progressed to generalized LD. We did not see progression to partial or generalized LD in 3 patients with focal LA who had follow-up evaluations for a median of 6.4 years [25% 5.9 yr, 75% 7.0 yr].

Fat redistribution, with increased fat deposition in certain areas, was a common feature in the generalized (3 of 8) and partial (11 of 16) LD patients, but was not observed in focal LA patients. Nine of 14 patients had fat redistribution in the parotid and submandibular glands, and this was more common in patients with generalized LD than in those with partial LD (3 of 3 patients with generalized LD vs. 6 of 11 with partial LD ($p = 0.26$)). Three patients were noted to have exophthalmos due to increased fat deposition in the retro-orbital space. Other areas of increased fat deposition in partial LD patients included the abdomen and/or trunk, and the lower extremities. No patient had increased fat deposition in the upper extremities.

Two of 3 generalized LD patients had a low total body fat percentage measured by DXA. The median percentage total body fat was 9.7% in patients with generalized LD (range, 7.9%–17.5%). One of 6 partial LD patients had a low total body fat percentage measured by DXA. The median percentage total body fat for partial LD patients was 25.5% (range, 11.9%–49.8%). Generalized LD patients had lower leptin levels than partial LD patients ($p = 0.048$), and patients with focal LA did not have low leptin levels (Table 4). DXA percentage body fat and leptin values highly correlated ($r_s = 0.964$, $p < 0.001$).

MRI showed subcutaneous fat loss in both the thighs and the abdomen (Table 5). A unique pattern of greater medial relative to lateral thigh subcutaneous fat was present in DM patients with LD compared to age- and sex-matched DM patients without LD (Table 5 and Fig. 4A). Five of 7 LD patients with subcutaneous fat loss in all 4 compartments of the thigh also had relatively less fat loss medially. Three patients did not have fat loss medially, but had fat loss in the other 3 thigh compartments. One patient had fat gain medially accompanied by fat loss in the other 3 compartments. Patients with focal LA did not have detectable subcutaneous fat loss on thigh MRI. In fact, 1 focal LA patient had fat gain in all 4 compartments of the thigh.

Edema in the subcutaneous fat was not evident on STIR MRI exams. Bone marrow fat was preserved in all patients.

Abdominal MRI often revealed subcutaneous fat loss, intraabdominal fat gain, and greater intraabdominal fat relative to subcutaneous fat in LD patients compared to healthy control subjects (Table 5 and Fig. 4B). Three of 3 patients with DM without LD had abdominal subcutaneous fat gain instead of fat loss on MRI, as compared to only 1 of 9 patients with DM and LD ($p = 0.018$). All 3 patients with generalized LD had a decrease in abdominal subcutaneous fat on MRI, as compared to only 2 of 6 with partial LD ($p = 0.167$).

Two biopsies including the subcutaneous fat from sites of LD were available from a patient with DM and partial LD. One from the thigh demonstrated adipocyte loss without associated inflammation, while the other showed calcinosis associated with the adipocytes, and no panniculitis (Fig. 5 A and B).

Metabolic Features

Nine of 24 (38%) LD patients had impaired glucose tolerance and/or diabetes based on fasting glucose, while 13 of 21 (62%) had an elevated fasting insulin value (Table 6). Fifty percent of patients had HOMA-IR levels consistent with type 2 diabetes (HOMA-IR value ≥ 8), while 70% were insulin resistant (HOMA-IR value ≥ 4). There was no difference in prednisone dose between patients with metabolic impairments and those without. The median prednisone dose was 0.18 mg/kg per day [25% 0.09 mg/kg per day, 75% 0.44 mg/kg per day] for the 13 of 22 (59%) patients who were receiving oral prednisone when glucose and insulin values were checked.

Oral glucose tolerance tests (OGTT) were performed in 13 patients (5 with generalized, 7 with partial, and 1 with focal LD). Testing was performed in most cases due to fasting metabolic abnormalities. The median 2-hour glucose for the overall group was 210 mg/dL [25% 105 mg/dL, 75% 271 mg/dL] (11.7 mmol/L [25% 5.8 mmol/L, 75% 15.0 mmol/L]), and 269 mg/dL (14.9 mmol/L) and 166 mg/dL (9.2 mmol/L) in the generalized and partial groups, respectively ($p = 0.34$). Two patients with partial LD had impaired glucose tolerance, and 7 patients (4 with generalized and 3 with partial LD) had evidence of diabetes on the OGTT. There was no difference in the median prednisone dose between those with an abnormal OGTT and those with a normal OGTT. Two patients received insulin and 3 were taking oral hypoglycemic agents, but these were held the morning of glucose and insulin testing.

An elevated fasting triglyceride level was the predominant lipid abnormality in the LD patients (Table 6). Nine of 19 (47%) LD patients had elevated LDL (median, 119 mg/dL [25% 83 mg/dL, 75% 155 mg/dL]) (3.1 mmol/L [25% 2.1 mmol/L, 75% 4.0 mmol/L]). Twelve of 20 (60%) LD patients had a low HDL (median, 36 mg/dL [25% 22 mg/dL, 75% 45 mg/dL]) (0.9 mmol/L [25% 0.6 mmol/L, 75% 1.2 mmol/L]). With the exception of triglycerides, the differences between generalized, partial, and focal LD patients were not significant in terms of lipid profiles. There was no difference in the median prednisone dose in patients with normal compared with abnormal lipid profile results. Patients with a normal HDL were on a higher median corticosteroid dose than patients with a low HDL (0.29 vs. 0.00 mg/kg per day, respectively, $p = 0.052$).

Another common finding was elevated serum testosterone levels (Table 6). In addition, patients frequently had menstrual irregularity and ovarian enlargement by ultrasound (Table 4). Right ovarian volumes (median, 12.8 cm³) were greater than left (7.5 cm³, $p = 0.03$), for unclear reasons. Five of the 6 patients with an enlarged right ovary had IR. Four patients had all 3 findings simultaneously: an enlarged ovary, IR, and menstrual irregularity.

Hepatic Findings

Hepatomegaly and steatosis on ultrasound or CT imaging were frequently present in the LD patients, to a similar extent in patients with generalized and partial LD (Table 4). By ultrasound, 10 patients had steatosis and 6 had normal liver imaging. Liver CT and MRI results were concordant with ultrasound results (n = 6). In 9 patients who underwent a liver biopsy, findings included definite steatohepatitis in 4 patients and steatosis in 4 patients. One patient had only mild inflammation and no steatosis. There was no evidence of autoimmune hepatitis or other liver diseases. Median NASH pathologic semiquantitative scores were 1.0 [25% 0.5, 75% 2.5] for portal inflammation, 2.0 [25% 1.0, 75% 4.0] for parenchymal inflammation, 3.0 [25% 1.5, 75% 4.0] for steatosis, 0.5 [25% 0.0, 75% 2.0] for cellular injury, 0.0 [25% 0.0, 75% 1.0] for Mallory bodies, 3.0 [25% 1.5, 75% 3.0] for fat, and 0.5 [25% 0.0, 75% 2.0] for fibrosis. Two patients underwent serial liver biopsies. One had regression of steatosis over 5 years without medications that would have improved her liver status. The other patient showed progression over 3 years from simple steatosis to NASH with fibrosis.

Serum levels of lactate dehydrogenase, transaminases, and the aspartate aminotransferase (AST)/alanine amino-transferase (ALT) ratio did not discriminate between LD patients with and without NASH, likely due to frequent elevation of these liver-associated enzymes in patients with active myositis. Corticosteroid and methotrexate doses at the time of liver biopsy or imaging did not differ in patients with and without objective liver disease (p = 0.25 and p = 0.69, respectively). There was no relationship between liver abnormalities and the duration of the treatment, creatine kinase levels, or myositis global disease activity. Fasting glucose, insulin, cholesterol, and triglyceride levels also did not differ in those with or without objective liver abnormalities.

Immunogenetic Risk Factors

The HLA alleles DRB1*0801 (25% in JDM patients with LD vs. 3% in JDM patients without LD, OR, 10.0; 95% CI, 2.0–50.2; p = 0.009) and DQA1*0201 (32% vs. 14%, respectively, OR, 2.9; 95% CI, 1.02–8.5; p = 0.049) were increased in white JDM patients with LD compared to ethnically matched JDM patients without LD, but were not significantly different after correction for multiple comparisons. White JDM patients with LD possibly had a higher frequency of the IL-1 β ⁻⁵¹¹ TT polymorphism (36% vs. 14%, OR, 3.3; 95% CI, 1.03–10.5; p = 0.05) and a lower frequency of the IL-1 β ⁻⁵¹¹ C allele (64% vs. 86%, OR, 0.31; 95% CI, 0.096–0.97; p = 0.05) compared to ethnically matched JDM patients without LD. P values after Holm adjustment for multiple comparisons using family wise error rates of 5% were not significant in these analyses. There were no differences in the frequency of other HLA alleles, IL-1 α ⁻⁸⁸⁹, IL-1 α ⁺⁴⁸⁴⁵, IL-1 β ⁺³⁹⁵³, TNF- α ⁻³⁰⁸, TNF- α ⁻²³⁸ in white JDM patients with versus without LD (unadjusted p values ranged from 0.08 to 1.0).

The ZFP36 variant allele frequencies for TTP were similar between JDM patients with and without LD for ZFP36*2, ZFP36*8, and ZFP36*10. Other ZFP36 alleles were absent in JDM patients with and without LD. The ZFP36 TTP haplotype frequencies were also similar between JDM cases with and without LD.

LMNA Mutations

In a white male JDM patient with partial LD, 2 polymorphisms in LMNA were found. One was in exon 1 (51 C>T Ser17Ser, a documented SNP [rs 11549668]) and the other in exon 10 (1698 C>T His566His, also a documented SNP [rs 4641]). A Hispanic female patient with partial LD and JDM had only the exon 10 SNP described above. The third sample, from an African American female patient with partial LD and JDM, had 5 documented polymorphisms, exon 5 861 T>C Ala287Ala (rs17847240); exon 6+16 G>A intronic (rs534807); exon 7 1338 T>C Asp446Asp (rs17847243); exon 9 –41 C>T intronic (rs17847245); and a G>C

polymorphism 79 bases beyond the coding region of exon 12, also a known SNP (rs7339). In all these samples, the polymorphisms seen were documented SNPs with high frequencies in the general population and resulted in synonymous amino acid changes when found within the coding region.

dlk 1 Protein Levels

The mean ratio of dlk/actin in plasma, as detected by Western blot, was 4.5 ± 2.3 in 21 healthy controls, 5.0 ± 2.8 in 9 JDM patients without LD, 3.8 ± 2.5 in 9 patients with generalized LD, and 3.0 ± 3.0 in 9 patients with partial LD. There were no significant differences in dlk/actin plasma levels between patients with LD and either healthy controls or JDM patients without LD, confirmed in 3 independent experiments.

DISCUSSION

We found that LD is a late complication of JDM and is associated with more severe, chronic disease and with other disease sequelae such as calcinosis, IR, overt diabetes, and hypertriglyceridemia were common metabolic findings, particularly in patients with generalized and partial LD, and this was independent of steroid use. We discovered a number of distinct features associated with the 3 LD phenotypes suggesting a gradient of sequelae, with the most severe and greatest number of findings in the generalized LD phenotype (Table 7). To our knowledge, the current study is the most comprehensive review of these patients ever published; it required significant multidisciplinary collaboration to examine these patients adequately.

Acquired LD has been reported in a number of systemic and organ-specific autoimmune diseases other than JDM^{39,40}. However, JDM patients may develop LD more frequently than patients with other autoimmune diseases⁴⁶. Reported prevalence rates for acquired LD associated with JDM vary from 12% to 40%^{31,37,56,62}, whereas we observed acquired LD in almost 8% of a large registry of patients with JDM. The most likely reason for this lower frequency of LD in our registry is referral bias, with an overestimation of LD in other reports that have included small cohorts from tertiary centers. Our study may be more generalizable due to the broader referral base of the nationwide registry of juvenile myositis in our study. Our study may also underestimate the prevalence, however, due to the under-recognition of LD in JDM.

Although LD is associated with JDM, LD has been infrequently reported in adult DM. The reasons for this lack of association with adult myositis are unclear. We found several features of DM to be associated with the development of LD, including joint contractures, muscle atrophy, panniculitis, and calcinosis. If LD is related to panniculitis or calcinosis of the adipocytes, as we observed in this study, differences in pathogenesis between JDM and adult DM may also be responsible. Of note, polymyositis is not associated with acquired LD in either adults or children.

DM patients with the generalized LD phenotype had more LD disease features compared to DM patients with the partial or focal LD phenotype. These features include buccal fat loss, acanthosis nigricans, hypertrichosis, hyperpigmentation, menstrual irregularity, and decreased leptin levels. In addition, abnormalities of glucose and lipid metabolism, as well as hyperandrogenism, were more prevalent. Patients with focal LA tended not to have metabolic sequelae and appear to represent a distinct group. However, the frequency distribution of many of these LD features did not differ between the LD subgroups, possibly due to small sample sizes.

Our definition of acquired generalized LD is similar to that of Misra and Garg³⁹. However, our definition of acquired partial LD differs from both Misra and Garg and the Barraquer-Simons phenotype, which involves abdominal fat loss but sparing of fat loss from the thighs⁴⁰. The majority of our patients with partial LD had no abdominal fat loss, but a little over half lost fat in the thighs. Our patients with focal LA had fat loss limited to sites of dystrophic calcification, most often in the extremities, but occasionally involving the trunk. Buccal fat loss occurred in all of our patients with generalized LD and in the majority of patients with partial LD, but not in focal LA. Patients in the current series were similar to other acquired LD patients in that bone marrow fat was preserved. This differs from congenital LD, where there is loss of bone marrow fat. Although many of our patients were treated with corticosteroids, we observed a different pattern of fat distribution from corticosteroid-induced LD. Corticosteroids typically cause subcutaneous fat accumulation in the face (“moon facies”), dorsocervical region (“buffalo hump”), and abdomen while subcutaneous fat is often decreased in the limbs¹⁷. Our patients did not demonstrate increased fat in the face or posterior neck/upper back region, thus differentiating them from patients with corticosteroid-induced LD.

Some of the patients in the current series had a normal total percentage body fat measured by DXA. This may seem inconsistent with a diagnosis of LD, but may be explained by the observed redistribution of fat. No difference in total percentage body fat on DXA is found between HIV patients with LD and HIV controls¹³. Normal percentage body fat on DXA has been reported in a patient with familial partial LD associated with mandibuloacral dysplasia⁵⁵ and in a patient with acquired generalized LD³⁹. A 2007 study⁶¹ found a total percentage body fat by DXA ranging from 16.6% to 27.6% in 3 female patients with Dunnigan familial partial LD, 23.1% in 1 female with Barraquer-Simons acquired partial LD, and 5.1% in a patient with congenital generalized LD. Two of these patients with Dunnigan partial LD had normal total percentage body fat. It may be that acquired LD associated with DM is a less severe form of LD than congenital generalized LD, thus explaining why fewer LD patients with DM had low DXA scores. Nevertheless, average values for total percentage body fat by DXA in an LD population are unknown and clearly differ based on the subtype of LD. Long-term corticosteroid usage in these DM patients with long-standing active disease may also be contributing to higher total body fat content despite the presence of these regional losses¹⁷.

While DXA is excellent for measuring total body fat mass, MRI is superior to DXA for measuring regional fat, which is of special importance in LD⁵⁴. The pattern of fat loss and redistribution varies between congenital and acquired LD and between generalized and partial LD^{39,47}. We observed a loss of subcutaneous fat in the thigh in generalized and partial LD patients compared to patients with DM without LD. While LD patients clearly lost fat from anterior, posterior, and lateral compartments of the thigh, they had less clear fat loss medially and thus had a pattern of greater medial to lateral subcutaneous fat in the thigh. Thus, MRI may be a useful tool to diagnose LD or to monitor a patient’s response to therapy.

We found disease-associated dyslipidemia in DM patients with all 3 subgroups of LD. The majority of our patients developed hypertriglyceridemia along with low HDL, including the 2 patients with focal LA. Although corticosteroids are known to increase triglycerides, they usually cause concurrent elevation in HDL cholesterol^{16,32}. Previous studies have shown that total cholesterol, LDL, and triglycerides correlate with prednisone dose in lupus patients and that these lipids are higher in lupus patients on steroids compared to those not on steroids^{15, 20}. Elevated serum total and LDL cholesterol were seen in some of our LD patients, but not in the majority. Hence, the lipid profile present in our cohort of LD patients, namely that of hypertriglyceridemia and low HDL, is not consistent with steroid-induced dyslipidemia.

IR and overt diabetes were frequent metabolic sequelae in our patients with generalized and partial LD, but not focal LA. Misra and colleagues^{39,40} reported similar results in their

autoimmune subgroup of acquired generalized LD, but a low frequency of these metabolic abnormalities in acquired partial LD patients with a number of different autoimmune diseases. Another report of 8 patients with JDM and LD found a similar frequency of hypertriglyceridemia, but did not examine glucose or insulin metabolism⁶². Further, in a series of 23 patients with acquired LD in which JDM was the underlying diagnosis in the majority, none of the patients had diabetes and the frequency of hyperlipidemia was low⁴⁶. The reason for the higher frequency of glucose metabolic abnormalities in our patients may be related to more in-depth testing in our cohort and possible referral bias.

Loss of adipose tissue, IR, and hypertriglyceridemia play a critical role in the pathogenesis of fatty liver disease. Thus, it is not surprising that NASH was present in some of our patients. Some patients may have clinically asymptomatic hepatomegaly or evidence of steatosis on liver imaging. Only 2 of our 8 generalized LD patients had hepatomegaly, compared to 100% of another series of patients with acquired generalized LD associated with autoimmunity³⁹. We found liver ultrasound to be useful in detecting liver pathology and identifying those patients who require biopsy.

The etiology of acquired LD following JDM remains unknown. It has been hypothesized that an immune-mediated destruction of adipocytes or pre-adipocytes occurs. LA has been reported in association with panniculitis, and a “panniculitis variety” of acquired generalized LD has been described³⁹. While Misra and Garg³⁹ differentiate the panniculitis variety from the autoimmune variety of acquired LD, there is clearly some overlap. Panniculitis was frequent in our patients with focal LA and may have been under-reported in our patients with JDM. In our patients, panniculitis and calcification typically predated the development of LA and occurred at the site of the focal LA. The skin biopsies of 1 patient showed calcification of the adipocytes and fat atrophy but did not demonstrate panniculitis; however, the biopsies were performed 1–4 months after LD was clinically appreciated.

Another potential mechanism for the development of LD is decreased fat uptake by adipocytes due to autoantibodies interfering with adipocyte function. Auto-antibodies to the cell surface insulin receptor have been reported to occur frequently in the presence of other auto-immune diseases, such as systemic lupus erythematosus⁵. However, anti-insulin receptor antibodies were not present in the 3 patients tested, nor in 3 patients tested from another group of JDM patients³¹. While antinuclear antibodies were present in similar frequencies in JDM patients with and without LD, the p155 myositis-associated autoantibody was more prevalent in our patients with generalized LD. The p155 autoantibody is directed to transcriptional intermediary factor 1 gamma, a transcription factor known to be present in erythroid, mesenchymal, and epithelial cells which regulates differentiation through a TGF β -dependent pathway by binding Smad2/3^{27,59}. Interestingly, in patients with Dunnigan familial partial LD, Smad-2 abnormally co-localizes on the nuclear membrane with lamin A/C, which differs from healthy individuals or patients with limb girdle muscular dystrophy⁵⁷. It is unclear if the p155 autoantibody is related to the development of LD or the transcription of adipocyte or muscle specific genes, but, in any case, generalized LD is a newly described phenotype associated with the anti-p155 autoantibody.

Cytokines might also play a role in the immunopathogenesis of LD. The increased levels of IL-1 and TNF- α that occur in DM may contribute to the development of IR or LD^{19,36}. A mouse knockout model of TTP deficiency results in systemic autoimmunity and subcutaneous fat loss related to an excess of TNF- α ⁶⁰. TNF- α may act by decreasing leptin production^{18, 23} or by preventing production of adiponectin and other adipocyte genes¹². We examined TNF- α promoter and TTP polymorphisms to determine if certain alleles might lead to increased susceptibility to LD, but did not find any associations with the development of LD in JDM patients. This may in part be due to our small sample size. Other genetic polymorphisms were

possibly increased in frequency in white JDM patients with LD compared to those without LD, including HLA alleles DRB1*0801, DQA1*0201, and IL-1 β ⁻⁵¹¹ TT. Interestingly, this IL-1 genotype is associated with higher stimulated levels of IL-1 β in vitro²⁵.

Several previously studied mechanisms of LD appeared not to be operative in our patients. C3 nephritic factor, an IgG antibody that breaks down C3 and lyses adipocytes, has been associated with acquired partial LD⁴⁰. Misra and colleagues⁴⁰ found that 12 of their 18 (67%) patients with acquired partial LD had a low C3 level, and 72 of 87 (83%) reported patients with acquired partial LD had a C3 nephritic factor. However, the majority of patients in the current series had normal C3 levels, including all of those tested with partial LD, and this is similar to previous reports^{29,34}.

Another possible cause of LD might be disrupted differentiation of adipocytes. Mutations in the nuclear lamin A gene, critical for adipocyte development, are associated with Dunnigan-type familial partial LD, as well as with Emery-Dreifuss muscular dystrophy^{1,33}. Lamin A mutations were not found in 3 patients with acquired partial LD associated with DM. We also analyzed the dlk 1 protein, an epidermal growth-factor-like protein that is highly expressed by pre-adipocytes and inhibits adipocyte differentiation³⁵. We did not find any abnormalities in dlk 1 serum levels in our patients. However, adipogenesis may depend on the equilibrium between dlk 1 and the newly described dlk 2 protein⁴¹. It is possible that other genes regulating adipocyte differentiation, such as PPAR γ and 1-acylglycerol-3-phosphate-*O*-acyltransferase 2 (AGPAT2), which have been associated with congenital LD phenotypes², are implicated, but these have not been examined in our patients.

The optimal treatment of DM-associated LD is not known. The metabolic aberrations in other forms of LD respond to metabolic therapies such as thiazolidinediones and leptin replacement⁶. Further research is needed to study the safety and efficacy of these and other metabolic therapies for LD in JDM patients.

Conclusion

Physicians should monitor JDM patients closely for evolving LD and the accompanying metabolic abnormalities, particularly several years after the onset of DM in patients with continuing disease activity. Three phenotypes of LD, generalized LD, partial LD, and focal LA, exist in patients with JDM and these have diverse patterns of fat loss and associated features of LD (summarized in Table 7). In particular, JDM patients with calcinosis, joint contractures, and muscle atrophy are at highest risk of developing LD. Furthermore, a chronic continuous disease course, malar rash or erythroderma, and the p155 autoantibody are also associated with LD or its subsets. Panniculitis is associated with focal LA, which develops at sites of calcinosis. These 3 subphenotypes of LD have a gradient in the frequency and severity of associated metabolic sequelae, apparently related to the extent of fat loss. Glucose intolerance, hypertriglyceridemia, NASH, and other features of LD are frequent in patients with generalized and partial LD. Thigh MRI is useful in demonstrating patterns of fat loss and relative sparing of the medial thigh that may help in confirming a diagnosis of LD, particularly in patients with generalized or partial LD. The increased morbidity in JDM incurred by having these coexisting metabolic problems necessitates proper identification and treatment.

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Abbreviations

CI, confidence interval
 CT, computerized tomography
 dlk, delta-like
 DM, dermatomyositis
 DXA, dual-energy X-ray absorptiometry
 HDL, high-density lipoprotein
 HIV, human immuno-deficiency virus
 HOMA-IR, homeostasis model assessment of insulin resistance
 IL, interleukin
 IR, insulin resistance
 JDM, juvenile dermatomyositis
 LA, lipoatrophy
 LD, lipodystrophy
 LDL, low-density lipoprotein
 LMNA, lamin A
 MRI, magnetic resonance imaging
 NASH, nonalcoholic steatohepatitis
 NIH, National Institutes of Health
 OGTT, oral glucose tolerance test
 OR, odds ratio
 PCR, polymerase chain reaction
 TNF, tumor necrosis factor
 TTP, tristetraprolin

APPENDIX

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REFERENCES

1. Agarwal AK, Garg A. Genetic basis of lipodystrophies and management of metabolic complications. *Annu Rev Med* 2006;57:297–311. [PubMed: 16409151]
2. Agarwal AK, Garg A. Genetic disorders of adipose tissue development, differentiation, and death. *Annu Rev Genomics Hum Genet* 2006;7:175–199. [PubMed: 16722806]

3. Ahmed ML, Ong KK, Morrell DJ, Cox L, Drayer N, Perry L, Preece MA, Dunger DB. Longitudinal study of leptin concentrations during puberty: sex differences and relationship to changes in body composition. *J Clin Endocrinol Metab* 1999;84:899–905. [PubMed: 10084568]
4. American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics* 1992;89:525–584. [PubMed: 1538956]
- 4a. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus [Position Statement]. *Diabetes Care* 2007;30:S42–S47. [PubMed: 17192378]
5. Arioglu E, Andewelt A, Diabo C, Bell M, Taylor SI, Gorden P. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective. *Medicine (Baltimore)* 2002;81:87–100. [PubMed: 11889410]
6. Arioglu E, Duncan-Morin J, Sebring N, Rother KI, Gottlieb N, Lieberman, Herion D, Kleiner DE, Reynolds J, Premkumar A, Sumner AE, Hoofnagle J, Reitman ML, Taylor SI. Efficacy and safety of troglitazone in the treatment of lipodystrophy syndromes. *Ann Intern Med* 2000;133:263–274. [PubMed: 10929166]
7. Boguslavsky RL, Stewart CL, Worman HJ. Nuclear lamin A inhibits adipocyte differentiation: implications for Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet* 2006;15:653–663. [PubMed: 16415042]
8. Carrick DM, Chulada P, Donn R, Fabris M, McNicholl J, Whitworth W, Blackshear PJ. Genetic variations in ZFP36 and their possible relationship to autoimmune diseases. *J Autoimmun* 2006;26:182–196. [PubMed: 16546352]
9. Chumlea WC, Guo SS, Kuczmarski RJ, Flegal KM, Johnson CL, Heymsfield SB, Lukaski HC, Friedl K, Hubbard VS. Body composition estimates from NHANES III bioelectrical impedance data. *Int J Obes Relat Metab Disord* 2002;26:1596–1609. [PubMed: 12461676]
10. Cohen HL, Tice HM, Mandel FS. Ovarian volumes measured by US: bigger than we think. *Radiology* 1990;177:189–192. [PubMed: 2204964]
11. den Dunnen JT, Antonarakis SE. Nomenclature for the description of human sequence variations. *Hum Genet* 2001;109:121–124. [PubMed: 11479744]
12. Diehl AM. Tumor necrosis factor and its potential role in insulin resistance and nonalcoholic fatty liver disease. *Clin Liver Dis* 2004;8:619–638. [PubMed: 15331067]
13. Dinges WL, Chen D, Snell PG, Weatherall PT, Peterson DM, Garg A. Regional body fat distribution in HIV-infected patients with lipodystrophy. *J Investig Med* 2005;53:15–25.
14. Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS. Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. *Nature* 2003;423:293–298. [PubMed: 12714972]
15. Ettinger WH, Goldberg AP, Applebaum-Bowden D, Hazzard WR. Dyslipoproteinemia in systemic lupus erythematosus. Effect of corticosteroids. *Am J Med* 1987;83:503–508. [PubMed: 3661587]
16. Ettinger WH Jr, Hazzard WR. Prednisone increases very low density lipoprotein and high density lipoprotein in healthy men. *Metabolism* 1988;37:1055–1058. [PubMed: 3185288]
17. Fardet L, Cabane J, Kettaneh A, Lebbe C, Flahault A. Corticosteroid-induced lipodystrophy is associated with features of the metabolic syndrome. *Rheumatology* 2007;46:1102–1106. [PubMed: 17409127]
18. Fawcett RL, Waechter AS, Williams LB, Zhang P, Louie R, Jones R, Inman M, Huse J, Considine RV. Tumor necrosis factor- α inhibits leptin production in subcutaneous and omental adipocytes from morbidly obese humans. *J Clin Endocrinol Metab* 2000;85:530–535. [PubMed: 10690850]
19. Feve B. Adipogenesis: cellular and molecular aspects. *Best Pract Res Clin Endocrinol Metab* 2005;19:483–499. [PubMed: 16311213]
20. Formiga F, Meco JF, Pinto X, Jacob J, Moga I, Pujol R. Lipid and lipoprotein levels in premenopausal systemic lupus erythematosus patients. *Lupus* 2001;10:359–363. [PubMed: 11403267]
21. Garg A. Acquired and inherited lipodystrophies. *N Engl J Med* 2004;350:1220–1234. [PubMed: 15028826]
22. Genuth S, Alberti KG, Bennett P, Buse J, DeFronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J,

- Zimmet P. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–3167. [PubMed: 14578255]
23. Gottschling-Zeller H, Birgel M, Scriba D, Blum WF, Hauner H. Depot-specific release of leptin from subcutaneous and omental adipocytes in suspension culture: effect of tumor necrosis factor-alpha and transforming growth factor-beta1. *Eur J Endocrinol* 1999;141:436–442. [PubMed: 10526261]
 24. Grundy SM. Approach to lipoprotein management in 2001 National Cholesterol Guidelines. *Am J Cardiol* 2002;90(8A):11i–21i.
 25. Hall SK, Perregaux DG, Gabel CA, Woodworth T, Durham LK, Huizinga TW, Breedveld FC, Seymour AB. Correlation of polymorphic variation in the promoter region of the interleukin-1 beta gene with secretion of interleukin-1 beta protein. *Arthritis Rheum* 2004;50:1976–1983. [PubMed: 15188375]
 26. Harlow, E.; Lane, D. *Antibodies: A Laboratory Manual*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 1988.
 27. He W, Dorn DC, Erdjument-Bromage H, Tempst P, Moore MA, Massague J. Hematopoiesis controlled by distinct TGF β 1 gamma and Smad4 branches of the TGF β pathway. *Cell* 2006;125:929–941. [PubMed: 16751102]
 28. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Statist* 1979;6:65–70.
 29. Huang JL. Juvenile dermatomyositis associated with partial lipodystrophy. *Br J Clin Pract* 1996;50:112–113. [PubMed: 8731651]
 30. Huber AM, Lang B, LeBlanc CM, Birdi N, Bolaria RK, Malleson P, MacNeil I, Momy JA, Avery G, Feldman BM. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. *Arthritis Rheum* 2000;43:541–549. [PubMed: 10728746]
 31. Huemer C, Kitson H, Malleson PN, Sanderson S, Huemer M, Cabral DA, Chanoine JP, Petty RE. Lipodystrophy in patients with juvenile dermatomyositis—evaluation of clinical and metabolic abnormalities. *J Rheumatol* 2001;28:610–615. [PubMed: 11296968]
 32. Ilowite NT, Samuel P, Ginzler E, Jacobson MS. Dyslipoproteinemia in pediatric systemic lupus erythematosus. *Arthritis Rheum* 1988;31:859–863. [PubMed: 3134897]
 33. Jacob KN, Garg A. Laminopathies: multisystem dystrophy syndromes. *Mol Genet Metab* 2006;87:289–302. [PubMed: 16364671]
 34. Kavanagh GM, Colaco CB, Kennedy CT. Juvenile dermatomyositis associated with partial lipodystrophy. *J Am Acad Dermatol* 1993;28:348–351. [PubMed: 8436656]
 35. Laborda J. The role of the epidermal growth factor-like protein dlk in cell differentiation. *Histol Histopathol* 2000;15:119–129. [PubMed: 10668203]
 36. Lundberg I, Ulfgren AK, Nyberg P, Andersson U, Klareskog L. Cytokine production in muscle tissue of patients with idiopathic inflammatory myopathies. *Arthritis Rheum* 1997;40:865–874. [PubMed: 9153548]
 37. McCann LJ, Juggins AD, Maillard SM, Wedderburn LR, Davidson JE, Murray KJ, Pilkington CA. The Juvenile Dermatomyositis National Registry and Repository (UK and Ireland)—clinical characteristics of children recruited within the first 5 yr. *Rheumatology* 2006;45:1255–1260. [PubMed: 16567354]
 38. McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. *Int J Obes* 2006;30:598–602.
 39. Misra A, Garg A. Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. *Medicine (Baltimore)* 2003;82:129–146. [PubMed: 12640189]
 40. Misra A, Peethambaram A, Garg A. Clinical features and metabolic and autoimmune derangements in acquired partial lipodystrophy: report of 35 cases and review of the literature. *Medicine (Baltimore)* 2004;83:18–34. [PubMed: 14747765]
 41. Nueda ML, Baladron V, Garcia-Ramirez JJ, Sanchez-Solana B, Ruvira MD, Rivero S, Ballesteros MA, Monsalve EM, Diaz-Guerra MJ, Ruiz-Hidalgo MJ, Laborda J. The novel gene EGFL9/Dlk2, highly homologous to Dlk1, functions as a modulator of adipogenesis. *J Mol Biol* 2007;367:1270–1280. [PubMed: 17320102]
 42. O’Hanlon TP, Carrick DM, Arnett FC, Reveille JD, Carrington M, Gao X, Oddis CV, Morel P, Malley JD, Malley K, Dreyfuss J, Shamim EA, Rider LG, Chanock SJ, Foster CB, Bunch T, Plotz PH, Love

- LA, Miller FW. Immunogenetic risk and protective factors for the idiopathic inflammatory myopathies: distinct HLA-A, -B, -Cw, -DRB1 and -DQA1 allelic profiles and motifs define clinicopathologic groups in caucasians. *Medicine (Baltimore)* 2005;84:338–349. [PubMed: 16267409]
43. Park JY, Javor ED, Cochran EK, DePaoli AM, Gorden P. Long-term efficacy of leptin replacement in patients with Dunnigan-type familial partial lipodystrophy. *Metabolism* 2007;56:508–516. [PubMed: 17379009]
 44. Parks CG, Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS, Pandey JP. Systemic lupus erythematosus and genetic variation in the interleukin 1 gene cluster: a population based study in the southeastern United States. *Ann Rheum Dis* 2004;63:91–94. [PubMed: 14672899]
 45. Parks CG, Pandey JP, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS, Feghali-Bostwick CA, Cooper GS. Genetic polymorphisms in tumor necrosis factor (TNF)-alpha and TNF-beta in a population-based study of systemic lupus erythematosus: associations and interaction with the interleukin-1alpha-889 C/T polymorphism. *Hum Immunol* 2004;65:622–631. [PubMed: 15219382]
 46. Pope E, Janson A, Khambalia A, Feldman B. Childhood acquired lipodystrophy: a retrospective study. *J Am Acad Dermatol* 2006;55:947–950. [PubMed: 17097389]
 47. Premkumar A, Chow C, Bhandarkar P, Wright V, Koshy N, Taylor S, Arioglu E. Lipoatrophic-lipodystrophic syndromes: the spectrum of findings on MR imaging. *AJR Am J Roentgenol* 2002;178:311–318. [PubMed: 11804885]
 48. Promrat K, Lutchman G, Uwaifo GI, Freedman RJ, Soza A, Heller T, Doo E, Ghany M, Premkumar A, Park Y, Liang TJ, Yanovski JA, Kleiner DE, Hoofnagle JH. A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis. *Hepatology* 2004;39:188–196. [PubMed: 14752837]
 49. Quon MJ. Limitations of the fasting glucose to insulin ratio as an index of insulin sensitivity. *J Clin Endocrinol Metab* 2001;86:4615–4617. [PubMed: 11600512]
 50. Reitman ML, Arioglu E, Gavrilova O, Taylor SI. Lipoatrophy revisited. *Trends Endocrinol Metab* 2000;11:410–416. [PubMed: 11091118]
 51. Rider LG, Feldman BM, Perez MD, Rennebohm RM, Lindsley CB, Zemel LS, Wallace CA, Ballinger SH, Bowyer SL, Reed AM, Passo MH, Katona IM, Miller FW, Lachenbruch PA. Juvenile Dermatomyositis Disease Activity Collaborative Study Group. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies: I. Physician, parent, and patient global assessments. *Arthritis Rheum* 1997;40:1976–1983. [PubMed: 9365086]
 52. Rider, LG.; Pachman, LM.; Miller, FW. *Myositis and You: A Guide to Juvenile Dermatomyositis for Patients, Families and Health Care Providers*. Vol. 1st ed. Washington, DC: The Myositis Association; 2007.
 53. Ruhl CE, Everhart JE. Leptin concentrations in the United States: relations with demographic and anthropometric measures. *Am J Clin Nutr* 2001;74:295–301. [PubMed: 11522551]
 54. Schwenk A. Methods of assessing body shape and composition in HIV-associated lipodystrophy. *Curr Opin Infect Dis* 2002;15:9–16. [PubMed: 11964900]
 55. Simha V, Garg A. Body fat distribution and metabolic derangements in patients with familial partial lipodystrophy associated with mandibuloacral dysplasia. *J Clin Endocrinol Metab* 2002;87:776–785. [PubMed: 11836320]
 56. Singh S, Bansal A. Twelve years experience of juvenile dermatomyositis in North India. *Rheumatol Int* 2006;26:510–515. [PubMed: 16163542]
 57. Spuler S, Kalbhenn T, Zabojszcza J, van Landeghem FK, Ludtke A, Wenzel K, Koehnlein M, Schuelke M, Ludemann L, Schmidt HH. Muscle and nerve pathology in Dunnigan familial partial lipodystrophy. *Neurology* 2007;68:677–683. [PubMed: 17325275]
 58. Targoff IN, Mamyrova G, Trieu EP, Perurena O, Koneru B, O'Hanlon TP, Miller FW, Rider LG. A novel autoantibody to a 155-kd protein is associated with dermatomyositis. *Arthritis Rheum* 2006;54:3682–3689. [PubMed: 17075819]
 59. Targoff IN, Trieu EP, Levy-Neto M, Prasertsuntarasai T, Miller FW. Autoantibodies to transcriptional intermediary factor 1-gamma (TIF1-g) in dermatomyositis. *Arthritis Rheum* 2006;54:S1241.
 60. Taylor GA, Carballo E, Lee DM, Lai WS, Thompson MJ, Patel DD, Schenkman DI, Gilkeson GS, Broxmeyer HE, Haynes BF, Blackshear PJ. A pathogenetic role for TNF alpha in the syndrome of

cachexia, arthritis, and autoimmunity resulting from tristetraprolin (TTP) deficiency. *Immunity* 1996;4:445–454. [PubMed: 8630730]

61. Valerio CM, Godoy-Matos A, Moreira RO, Carraro L, Guedes EP, Moises RS, Mory PB, de Souza LL, Russo LA, Melazzi AC. Dualenergy X-ray absorptiometry study of body composition in patients with lipodystrophy. *Diabetes Care* 2007;30:1857–1859. [PubMed: 17384343]
62. Verma S, Singh S, Bhalla AK, Khullar M. Study of subcutaneous fat in children with juvenile dermatomyositis. *Arthritis Rheum* 2006;55:564–568. [PubMed: 16874777]

FIGURE 1.

A., B., C. Features of the generalized lipodystrophy (LD) phenotype in a patient with juvenile dermatomyositis. Loss of subcutaneous fat from the entire lower and upper extremity, buccal fat loss, and acanthosis nigricans are typical features of generalized LD. Figure **A** demonstrates dystrophic calcification in the thighs in the region of the LD, as well as possible muscle hypertrophy. Generalized hyperpigmentation is evident, as well as parotid enlargement in Figure **C**.

FIGURE 2.

A. and **B.** Features of the partial LD phenotype in a patient with juvenile onset-dermatomyositis. Increased fat deposition in the thighs and abdomen of a partial LD patient, accompanied by a loss of fat from the calves and feet.

FIGURE 3.

Features of focal LA in 2 patients with juvenile-onset dermatomyositis. Localized skin LA and subcutaneous dimpling is seen in the right buttock (**A**) and left mid-thigh (**B**), in regions of calcinosis.

FIGURE 4.

A. Thigh MRI from a DM patient with generalized LD showing loss of anterior, lateral, and posterior subcutaneous fat. There is increased medial relative to lateral subcutaneous fat. **B.** Abdominal MRI from the same patient showing loss of subcutaneous abdominal fat and increase in intraabdominal fat.

FIGURE 5.

A. A biopsy from the thigh at a site of LD showing atrophic changes in the subcutaneous fat from an adult DM patient with partial LD. There is shrinkage of individual adipocytes associated with increased capillary vascularity. There was no significant inflammation at this site. This biopsy was taken 2.3 years after onset of DM and 4 months after onset of LD (hematoxylin-eosin, original magnification $\times 200$). **B.** A biopsy from the left upper arm at a site of subcutaneous fat loss from the same patient. There are deep dermal changes associated with calcinosis of the subcutaneous adipose tissue. The upper dermis and the epidermis were normal. This biopsy was obtained 2 years after onset of DM and 1 month after onset of LD (hematoxylin-eosin, original magnification $\times 100$).

TABLE 1
Dermatomyositis Disease Characteristics Associated With Lipodystrophy Phenotypes

	DM With Any LD Phenotype	DM With Generalized LD		DM With Partial LD		DM With Focal LA		DM Without LD		All LD vs. DM Without LD	
Disease Characteristic	No. of Patients (%)	N	No. of Patients (%)	N	No. of Patients (%)	N	No. of Patients (%)	N	No. of Patients (%)	p Value	
Female	22 (76)	29	6 (75)	8	12 (75)	16	4 (80)	5	61 (73)	83	1.0
Median delay to diagnosis of DM, mo [25%, 75%]	3.6 [2.4, 10.8]	26	3.6 [3.0, 3.6]	8	3.6 [2.1, 11.3]	13	3.0	5	5.0 [3.0, 8.0]	83	0.41
DM disease course											
Monocyclic	2 (7)	29	0 (0)	8	1 (6)	16	1 (20)	5	30 (36)	83	0.01
Polycyclic	6 (21)	29	1 (13)	8	4 (25)	16	1 (20)	5	18 (22)	83	0.88
Chronic continuous	21 (72)	29	7 (88)	8	11 (69)	16	3 (60)	5	25 (30)	83	<0.001
Undefined	0 (0)	29	0 (0)	8	0 (0)	16	0 (0)	5	10 (12)	83	0.11
Myalgia	12 (46)	26	4 (50)	8	5 (38)	13	3 (60)	5	35 (45)	77	0.87
Arthritis	16 (57)	28	3 (38)	8	10 (67)	15	3 (60)	5	29 (35)	83	0.06
Dysphagia	10 (37)	27	4 (50)	8	4 (29)	14	2 (40)	5	28 (34)	83	0.94
Dysphonia	10 (37)	27	1 (13)	8	4 (29)	14	5 (100)*	5	17 (20)*	83	0.14
Malar rash/facial erythema	26 (96)	27	8 (100)	8	13 (93)	14	5 (100)	5	52 (63)	83	0.002
Erythroderma	7 (26)	27	3 (38)	8	4 (29)	14	0 (0)	5	6 (7)	83	0.02
Cutaneous ulceration	1 (3)	29	0 (0)	8	1 (6)	16	0 (0)	5	16 (19)	83	0.08
Panniculitis	9 (31)	29	0 (0) [†]	8	5 (31) [†]	16	4 (80) [†]	5	2 (2)	82	<0.001
Calcinosis	23 (79)	29	8 (100)	8	10 (63)	16	5 (100)	5	24 (29)	83	<0.001
Joint contractures	27 (93)	29	7 (88)	8	15 (94)	16	5 (100)	5	31 (37)	83	<0.001
Muscle atrophy	24 (83)	29	7 (88)	8	14 (88)	16	3 (60)	5	26 (31)	83	<0.001
Wheelchair use	4 (14)	28	2 (25)	8	2 (13)	15	0 (0)	5	9 (11)	81	0.91
Highest CK level, U/L, median [25%, 75%]	356 [149, 677]	25	446 [300, 2158]	6	374 [139, 756]	14	277 [157, 479]	5	529 [252, 2470]	81	0.16

Disease Characteristic	DM With Any LD Phenotype		DM With Generalized LD		DM With Partial LD		DM With Focal LA		DM Without LD		All LD vs. DM Without LD	
	No. of Patients (%)	N	No. of Patients (%)	N	No. of Patients (%)	N	No. of Patients (%)	N	No. of Patients (%)	N	p Value	
Elevated CK level	15 (60)	29	5 (83)	8	7 (50)	16	3 (60)	5	58 (72)	81		0.40
ANA positive	23 (79)	28	7 (88)	8	12 (75)	16	4 (80)	5	165 (66)	75		1.0
Anti-p155 autoantibody	13 (46)	28	6 (86) ^{‡§}	7	6 (38) [§]	16	1 (20) [§]	5	27 (36) [‡]	76		0.23

Abbreviations: CK = creatine kinase, ANA = antinuclear antibody.

* p < 0.001 for DM with focal LA vs. DM without LD.

[†] ANOVA p = 0.012.

[‡] p = 0.014 for DM with generalized LD vs. DM without LD.

[§] ANOVA p = 0.049.

TABLE 2

Relative Importance of Features Used to Discriminate JDM Patients With LD (n = 28) From Those Without LD (n = 76) by Random Forests Classification Analysis*

Variable	Relative Importance % (GINI impurity rank)
Muscle atrophy	100 (2.67)
Joint contractures	99 (2.63)
Malar rash	77 (2.06)
Calcinosis	76 (2.04)
Chronic continuous disease course	59 (1.58)
Panniculitis	52 (1.40)
Cutaneous ulcerations	44 (1.17)
Dysphonia	35 (0.93)
Anti-p155 autoantibody	33 (0.87)
Arthritis	29 (0.77)
Elevated serum CK level	28 (0.76)
Myalgia	25 (0.66)
Dysphagia	21 (0.56)
Erythroderma	14 (0.37)
Wheelchair use	12 (0.32)

* The "out of bag" error rate was 11.1%.

Abbreviations: See previous table.

TABLE 3
Two Logistic Regression Models of Predictors of LD in Patients With JDM

Variable	Coefficient	Standard Error	p Value	OR	95% Wald Confidence Limits
Joint contractures	2.53	0.90	0.005	12.6	2.2–73.2
Panniculitis	2.58	1.00	0.010	13.2	1.9–93.8
Calcinosis	1.20	0.66	0.070	3.3	0.91–12.2
Likelihood ratio chi square 34.7, $p < 0.001$; percent concordant 81.6.					
Variable	Coefficient	Standard Error	p Value	OR	95% Wald Confidence Limits
Calcinosis	1.50	0.64	0.019	4.5	1.3–15.6
Muscle atrophy	1.49	0.71	0.037	4.4	1.1–18.0
Joint contractures	1.62	0.88	0.067	5.0	0.89–28.3
Likelihood ratio chi square 30.67, $p < 0.001$; percent concordant 80.3.					

TABLE 4

Characteristics of Acquired LD Phenotypes in DM Patients

Disease Characteristic	DM With Any LD Phenotype		DM With Generalized LD		DM With Partial LD		DM With Focal L/A	
	No. of Patients (%) or Median [25%, 75%]	N	No. of Patients (%) or Median [25%, 75%]	N	No. of Patients (%) or Median [25%, 75%]	N	No. of Patients (%) or Median [25%, 75%]	N
Median age (yr) at diagnosis of LD	12.3 [9.7, 17.0]	29	13.8 [11.3, 17.2]	8	12.2 [10.0, 16.8]	16	9.4 [6.9, 18.9]	5
Median delay (yr) from diagnosis of DM to LD	4.6 [2.5, 7.5]	29	7.4 [2.8, 8.2]	8	5.0 [1.4, 7.4]	16	3.3 [2.3, 4.6]	5
Race								
White	21 (72.4)	29	6 (75)	8	11 (69)	16	4 (80)	5
Hispanic	5 (17.2)	29	2 (25)	8	2 (13)	16	1 (20)	5
Other (African American, Native American, mixed)	3 (10.3)	29	0 (0)	8	3 (19)	16	0 (0)	5
Acanthosis nigricans	11 (38)	29	4 (50)	8	6 (38)	16	1 (20)	5
Buccal fat loss	20 (69)	29	8 (100)*	8	12 (75)*	16	0 (0)*	5
Muscle prominence	10 (34)	29	3 (38)	8	6 (38)	16	1 (20)	5
Hypertrichosis	16 (55)	29	6 (75)	8	8 (50)	16	2 (40)	5
Hyperpigmentation	4 (14)	29	3 (38)	8	1 (6)	16	0 (0)	5
Hepatomegaly	11 (38)	29	2 (25)	8	9 (56) [†]	16	0 (0) [†]	5
Steatosis on ultrasound or CT	10 (63)	16	3 (50)	6	7 (70)	10	NA	0
Steatohepatitis	4 (44)	9	1 (33)	3	3 (50)	6	NA	0
Menstrual irregularity [‡]	8 (57)	14	3 (60)	5	4 (50)	8	1 (100)	1
Median right ovarian volume (cm ³)	12.8 [10.5, 39.4]	7	27.5 [10, 45]	2	12.8 [9.3, 31.8]	5	NA	0
Right ovarian enlargement by ultrasound	6 (86)	7	2 (100)	2	4 (80)	5	NA	0
Median leptin level (ng/mL)	4.1 [2.3, 9.5]	10	2.2 [1.8, 3.2]	4	9.5 [3.7, 17.1]	5	8.3	1
Low leptin level	5 (50)	10	4 (100) [§]	4	1 (20) [§]	5	0 (0)	1

Abbreviations: NA = not available.

* p < 0.0001 by ANOVA.

⁷ $p = 0.045$ for DM with partial LD vs. focal LA.

[#] Patients excluded if male ($n = 7$), premenarchal ($n = 4$), or data unknown ($n = 4$).

[§] $p = 0.048$ for DM with generalized LD vs. partial LD.

TABLE 5
Distribution of Thigh and Abdominal Fat Loss Detected by MRI

Thigh MRI	DM With Any LD Phenotype	N	No. of Patients (%)	DM With Generalized LD	N	No. of Patients (%)	DM With Partial LD	N	No. of Patients (%)	DM With Focal LA	N	No. of Patients (%)	DM Without LD*	N	No. of Patients (%)	All LD vs. DM Without LD	McNemar p Value
Thigh subcutaneous fat loss from multiple compartments	7 (39)	18	5 (100) [†]	5	2 (22) [†]	9	0 (0) [†]	4	0 (0)					18	0 (0)		0.02
Greater medial relative to lateral subcutaneous fat	10 (56)	18	3 (60)	5	6 (67)	9	1 (25)	4	1 (6)					18	1 (6)		0.008
Medial compartment fat loss	7 (39)	18	5 (100) [†]	5	2 (22) [†]	9	0 (0) [†]	4	0 (0)					18	0 (0)		0.02
Lateral compartment fat loss	11 (61)	18	5 (100) [‡]	5	6 (67) [‡]	9	0 (0) [‡]	4	1 (6)					18	1 (6)		0.004
Anterior compartment fat loss	11 (61)	18	5 (100) [‡]	5	6 (67) [‡]	9	0 (0) [‡]	4	1 (6)					18	1 (6)		0.004
Posterior compartment fat loss	11 (61)	18	5 (100) [‡]	5	6 (67) [‡]	9	0 (0) [‡]	4	1 (6)					18	1 (6)		0.004
Bone marrow fat present	18 (100)	18	5 (100)	5	9 (100)	9	4 (100)	4	18 (100)					18	18 (100)		1.0
Abdominal MRI	DM With Any LD Phenotype	N	DM With Generalized LD	N	DM With Partial LD	N	DM With Focal LD	N	Healthy Controls [§]	N	All LD vs. Healthy Controls						
Subcutaneous fat loss	5 (56)	9	3 (100)	3	2 (33)	6	NA	0	0 (0)	9	0.07						
Subcutaneous fat gain	1 (11)	9	0 (0)	3	1 (17)	6	NA	0	0 (0)	0	0.32						
Intraabdominal fat loss	1 (11)	9	0 (0)	3	1 (17)	6	NA	0	0 (0)	9	1.0						
Intraabdominal fat increase	4 (44)	9	2 (67)	3	2 (33)	6	NA	0	0 (0)	9	0.13						
Greater intraabdominal fat relative to subcutaneous fat	6 (67)	9	3 (100)	3	3 (50)	6	NA	0	0 (0)	9	0.04						

* These patients were matched for sex and age.

[†] ANOVA p = 0.004.

[‡] ANOVA p = 0.011.

[§] These patients were matched for sex only.

TABLE 6
Metabolic Characteristics of LD Phenotypes in Patients With DM

Metabolic Characteristic	DM With Any LD Phenotype		DM With Generalized LD		DM With Partial LD		DM With Focal LA	
	No. of Patients (%) or Median [25%, 75%]	N	No. of Patients (%) or Median [25%, 75%]	N	No. of Patients (%) or Median [25%, 75%]	N	No. of Patients (%) or Median [25%, 75%]	N
Median highest fasting glucose (mg/dL)	96 [82, 108]	24	104 [90, 199]	8	96 [83, 108]	12	81 [75, 85]	4
Impaired fasting glucose (≥ 100 mg/dL)	9 (38)	24	5 (63)	8	4 (34)	12	0 (0)	4
Diabetes (glucose ≥ 126 mg/dL)	5 (21)	24	3 (38)	8	2 (17)	12	0 (0)	4
Corresponding median fasting insulin (μ U/mL)								
Prepubertal	26 [14, 83]	6	83	1	29 [11, 73]	3	19 [14, 24]	2
Postpubertal	36 [21, 49]	15	30 [24, 64]	4	38 [22, 52]	9	26 [15, 37]	2
Elevated fasting insulin	13 (62)	21	5 (100)*	5	8 (67)	12	1 (25)*	4
Median HOMA	7.8 [3.2, 18.8]	20	19.9 [6.0, 23.6]	5	8.7 [4.1, 16.0]	12	3.1 [3.0, 4.3]	3
Insulin resistance defined by HOMA value >4	14 (70)	20	4 (80)	5	9 (75)	12	1 (33)	3
Diabetes defined by HOMA value ≥ 8	10 (50)	20	3 (60)	5	7 (58)	12	0 (0)	3
Median Hemoglobin A1c (%)	6.0 [5.3, 7.4]	13	6.4 [4.5, 7.1]	5	5.6 [5.1, 7.3]	6	6.2 [4.8, 7.6]	2
Elevated Hemoglobin A1c ($>6.4\%$)	5 (38)	13	2 (40)	5	2 (33)	6	1 (50)	2
Median fasting triglyceride (mg/dL)	232 [147, 351]	24	337 [266, 904] [†]	6	218 [110, 351]	13	181 [150, 212] [†]	5
Elevated fasting triglyceride	17 (71)	24	6 (100)	6	7 (54)	13	4 (80)	5
Median fasting cholesterol (mg/dL)	204 [158, 229]	25	204 [180, 215]	7	173 [141, 244]	13	215 [203, 229]	5
Elevated cholesterol	12 (48)	25	4 (57)	7	5 (38)	13	3 (60)	5
Median total testosterone (ng/dL) [†]								
Prepubertal	41 [28, 52]	3	23	1	41	1	56	1
Postpubertal	34 [21, 61]	10	34 [24, 54]	3	33 [17, 68]	7	NA	0
Elevated testosterone	5 (38)	13	2 (50)	4	2 (25)	8	1 (100)	1

* p = 0.048 for DM with generalized LD vs. focal LA.

[†] p = 0.009 for DM with generalized LD vs. focal LA.

[#]All patients with testosterone values checked were female.

TABLE 7

Features Associated With the 3 Major LD Phenotypes in JDM

	Generalized LD	Partial LD	Focal LA
JDM features associated with LD	Joint contractures, calcinosis, muscle atrophy, chronic continuous illness course, malar/facial erythema, erythroderma, p155 autoantibody	Joint contractures, calcinosis, muscle atrophy, chronic continuous illness course, malar/facial erythema, erythroderma	Joint contractures, calcinosis, muscle atrophy, chronic continuous illness course, malar/facial erythema, panniculitis, dysphonia
Fat loss distribution	Face, all extremities, abdomen/trunk, buccal fat loss, SQ fat loss on MRI of thighs with relative sparing of medial thigh, SQ fat loss and intraabdominal fat gain on abdominal MRI	Face, upper > lower extremities, buccal fat loss, SQ fat loss on MRI of thighs with relative sparing of medial thigh	Isolated area on extremity or buttock at site of calcinosis
LD clinical features	Steatosis/NASH, ovarian enlargement, acanthosis nigricans, hypertrichosis, low leptin level	Hepatomegaly/steatosis/NASH, ovarian enlargement, fat redistribution	
LD metabolic features	Hypertriglyceridemia, insulin resistance > diabetes, elevated testosterone	Hypertriglyceridemia, insulin resistance > diabetes	Hypertriglyceridemia

Abbreviations: SQ = subcutaneous.