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Clinical features and management of non-HIV related lipodystrophy in children: a systematic review

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Lipodystrophy in children

Context: Lipodystrophy syndromes are characterized by generalized or partial absence of adipose tissue, usually associated with insulin resistance-related conditions.

Objective: We conducted a systematic review to synthesize existing data on clinical and metabolic features of lipodystrophy (age at onset < 18 years).

Data Source: Sources included Medline, Embase, Cochrane Library, Scopus and Non-Indexed Citations from inception through January 2016.

Study Selection: Search terms included, but were not limited to ‘lipodystrophy’, and age 0-18 years. Articles that described patients with unambiguous diagnoses of lipodystrophy were included. Since some case series included patients across all ages, some patients > 18 years at reporting, with onset of lipodystrophy at < 18 years were captured. Lipodystrophy secondary to HIV treatment and systemic diseases was excluded.

Data Extraction: Data was extracted in duplicate using a standardized web-based data extraction form.

Data Synthesis: We identified 1,141 patients from 351 studies [mean age at reporting 15.4 ± 14.0 years (range, 0.01-76.5); reporting age < 18 years, n = 744; ≥ 18 years, n = 397]. Onset of fat loss typically occurred during infancy in congenital generalized lipodystrophy (CGL) and later in acquired generalized (AGL), familial partial (FPL) and acquired partial (APL) lipodystrophies. Generalized fat loss involving face, neck, abdomen, thorax, upper and lower limbs was explicitly reported in 65-93% patients with CGL and AGL. As expected from clinical definitions, in FPL, fat loss occurred from upper and lower limbs, with sparing of face and neck. In APL, upper limbs were involved while lower limbs were spared. Other features were prominent musculature, acromegaloïd, acanthosis nigricans and hepatosplenomegaly. Diabetes mellitus was diagnosed in 48% (n=222) of patients with CGL (mean age at onset 5.3 years). Hypertriglyceridemia was observed in CGL, AGL and FPL. Multiple dietary and pharmacological interventions were used with majority of patients being on ≥ 3 interventions and ≥ 18 years of age at time of initiation of intervention. Metreleptin and diet over a mean duration of 29 months lowered serum insulin and triglycerides in CGL.

Conclusions: This is the largest reported pooled database describing lipodystrophy patients with age at onset < 18 years. We have suggested core and supportive clinical features of lipodystrophy and summarized data on available interventions, outcomes and mortality.
Precis: We synthesized clinical and metabolic features of 1,141 patients with lipodystrophy (age at onset < 18 years) and described core and supportive diagnostic features of lipodystrophy.

Introduction

Lipodystrophy is a group of rare congenital or acquired syndromes with an estimated prevalence of < 1 per million (1). Lipodystrophy is characterized by generalized or partial absence of adipose tissue, frequently with a muscular appearance (1-7). It is usually associated with evidence of insulin resistance, (diabetes mellitus, hypertriglyceridemia, and acanthosis nigricans), and may also be associated with transaminitis, pancreatitis, cardiomyopathy, nephropathy and leptin deficiency (8-12).

Lipodystrophies are clinically classified as generalized or partial based on distribution of fat loss, and as congenital or acquired. This yields four major categories: congenital generalized lipodystrophy (CGL; or Berardinelli-Seip syndrome), acquired generalized lipodystrophy (AGL; or Lawrence syndrome), familial partial lipodystrophy (FPL; or Kobberling and Dunnigan syndromes) and acquired partial lipodystrophy (APL; or Barraquer-Simons syndrome) (13). Most of the inherited generalized lipodystrophies are autosomal recessive, whereas the majority of inherited partial lipodystrophies are autosomal dominant (13). Various genetic mutations, including AGPAT2, BSCL2, CAV1, PTRF, PPARG, LMNA, AKT2, PLIN1 and ZMPSTE24 have been identified as causes of lipodystrophy (14-22). However, not all patients with lipodystrophy have a confirmed genetic diagnosis, leading to potential for discovery of novel genes (14,16,23). Multiple other syndromes, including mandibuloacral dysplasia (MAD), Wiedemann Rautenstrauch syndrome, Hutchinson-Gilford progeria syndrome (HGPS) and Donohue syndrome (leprechaunism) have lipodystrophy as a feature of a multisystem disease, and some of these syndromes share common genetic etiologies with the major categories of lipodystrophy described above (19,22,24-26).

Management of lipodystrophy is aimed at correcting associated metabolic abnormalities (27). High dose insulin, well-balanced diet, metformin, oral hypoglycemic agents and lipid-lowering drugs have been used (14,23,28). Metreleptin, recombinant human methionyl leptin, was approved in February 2014 by the U.S. Food and Drug Administration for treatment of generalized lipodystrophy (29), following evidence of significant improvement in metabolic complications of lipodystrophy with metreleptin replacement (7,14,30-34). Metreleptin continues to be an experimental drug for partial lipodystrophy.

Due to rarity of lipodystrophy syndromes, limited evidence exists on their diagnostic criteria and management, particularly in patients less than 18 years of age (35). The Pediatric Endocrinology Society (PES) formed a task force of experts to develop clinical practice guidelines to aid practicing clinicians in the diagnosis and management of patients with lipodystrophy in this age group. Consistent with the National Academy of Medicine standards (36), National Guideline Clearinghouse criteria for inclusion of clinical practice guidelines (37), and Guidelines International Network (38), the PES commissioned the conduct of this systematic review to support the development of key recommendations.

In this systematic review, we synthesized clinical, metabolic and outcomes data of 1,141 patients with lipodystrophy syndromes. These patients had onset of lipodystrophy at less than 18 years of age, however, one-third were reported during adulthood. This is the largest pooled analysis of pediatric-onset lipodystrophy, to date. In this review, core and supportive clinical features of various forms of lipodystrophy are presented. Association of metabolic outcomes with different interventions, including metreleptin, and mortality data of these patients is
discussed. This systematic review, while subject to reporting biases from each manuscript from which the data are derived, nonetheless represents the most comprehensive review to date on lipodystrophy. It has the advantage of not only representing experiences from large centers with expertise in lipodystrophy, but also individual cases from small centers including under-resourced countries.

Materials and Methods

Search methods, eligibility criteria, and the outcomes of interest were specified in advance in a protocol, developed by the study investigators. Outcomes of interest were chosen based on importance to patients and necessity for decision making. Clinical outcomes included distribution of fat, menstrual irregularities, hirsutism, growth, and mortality (39). Metabolic outcomes such as blood glucose, serum insulin, hemoglobin A1C, lipid profile, liver function tests and leptin were included.

Search methods

An expert reference librarian, following the protocol, conducted an electronic search strategy (Supplemental Table 1). Comprehensive search of databases (Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Scopus, Medline In-Process & Other Non-Indexed Citations) was conducted in any language from the inception of each database through August 31st, 2015. We identified additional candidate studies from reference lists of eligible primary studies and reviews, and we queried the content experts. We also obtained de-identified individual patient data from the National Institutes of Health (NIH) lipodystrophy database. Additional searches were done to update the original electronic search up to January 2016.

We used search terms “lipodystrophy”, “congenital generalized lipodystrophy” and “familial partial lipodystrophy”. We limited our search to pediatric age group (age 0-18 years). However, since some of the reports were case series across all age groups, some patients older than 18 years at the time of being reported were captured in our database. Patients older than 18 years were included in our review if they had onset of lipodystrophy at less than 18 years of age.

Eligibility criteria

We included original prospective and retrospective studies that reported data on lipodystrophy. Studies that contained definite description of body fat distribution consistent with that seen in lipodystrophy were selected. Due to rarity of lipodystrophy, most data were extracted from case reports and case series. We reported clinical and metabolic features, interventions and mortality of patients with CGL, AGL, FPL and APL. Rare syndromes including Donohue syndrome, MAD (type A and type B), Wiedemann Rautenstrauch syndrome, HGPS, SHORT syndrome (Short stature, Hyperextensibility, hernia, Ocular depression, Rieger anomaly, and Teething delay), atypical progeroid syndrome, Emery-Dreifuss muscular dystrophy, Brunzell syndrome, CANDLE syndrome (Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature), cephalo-thoraco-brachial lipodystrophy, Cockayne syndrome, facio-troncular lipodystrophy, Lafora disease, Marfan syndrome with neonatal progeroid syndrome-like lipodystrophy, Marfanoid - Progeroid syndrome, neonatal onset lipodystrophy syndrome, Nicolaides Baraitser syndrome, Werner syndrome, and mandibular hypoplasia, deafness and progeroid features (MDP), were also reported.
Exclusion criteria
We excluded lipodystrophy related to HIV treatment, secondary to drug administration (insulin, growth hormone, steroids, antibiotics, and vaccinations), recurrent pressure, lipodystrophia centrifugalis abdominalis infantilis, localized lipodystrophy and juvenile onset dermatomyositis. Lipodystrophy secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections, were excluded. Cases that were described more than once in literature were reported only once in this review. Duplicate reporting of cases was detected by highly meticulous data extraction including year of study, first author’s last name, name and city of institution from where patient was enrolled and coded identifier of each patient, if specified in the article. Adult patients captured in our search were excluded if onset of lipodystrophy occurred after 18 years of age.

Selection of studies
Two reviewers working independently considered the potential eligibility of each abstract and title that resulted from initial search. Eligible studies were reviewed in full-text versions. Two independent reviewers extracted data from each full-text using a standardized form. Disagreements were harmonized by consensus and if not possible through arbitration by a third reviewer.

Data extraction and management
Using a standardized web-based data extraction form, we extracted following descriptive data from each study: demographics (age, sex, ethnicity and form of lipodystrophy), clinical features, interventions they had received, if any (type and duration), measures of outcome (specifically defined as an event or measure and time frame for the ascertainment of this outcome) and mortality data. We extracted outcomes of interest at the longest point of complete follow-up. Due to heterogeneity in patient description, all clinical and metabolic features were not explicitly reported for each patient. We extracted and reported only unambiguously stated data. Data on clinical features were also extracted from patient photographs included in a few articles. Evaluation of publication bias was not feasible because of heterogeneity and because majority of included studies were case reports and case series.

Statistical analysis
Descriptive analyses were used to present patient characteristics. We conducted random-effects meta-analyses based on individual patient data to pool metabolic outcomes before and after interventions. Due to limited number of patients included in each intervention and lack of standardization of assays across the numerous laboratories included in this review, we were not able to statistically compare the changes in metabolic outcomes. Statistical analysis was performed using Stata version 14.1 (StataCorp LLP, College Station, Texas).

Results
Search results and study description
The initial search identified 1,303 articles of which 351 were eligible (Figure 1 and Supplemental Table 2). The original study design in 219 studies was case-report (single patient), 111 were cohorts (number of patients ≥ 2) and 21 studies reported data from the NIH database. Data from the NIH studies were extracted from the individual patient data we received from the NIH and not from published studies. The systematic review included 1,141 patients (case reports: n=219; cohorts: n=811; NIH database: n=111). Within each cohort, only patients that met inclusion criteria were included. Mean age at reporting of all patients was 15.4 ± 14.0
years (range, 0.01-76.5 years). Of the total 1,141 patients in our database, 744 were reported at < 18 years of age and 397 were reported at ≥ 18 years of age. Mean age at onset of lipodystrophy for all patients was 3.1 ± 4.3 years (range, 0.01-17.5 years).

**Congenital generalized lipodystrophy (CGL)**
We identified 519 patients with CGL (Table 1). Majority of patients were white (32%), followed by Asian (24%) and black (17%). Sixty-one percent patients (174 of 286) had a history of parental consanguinity. Mean age at onset of fat loss was 0.3 years (range, 0.0-12 years). Fat loss from face and neck, abdomen, thorax, and upper and lower limbs was explicitly reported in 89-93% patients with CGL (Table 1 and Figure 2a). Sixteen patients were specifically reported to have sparing of palms and soles. Diabetes mellitus (DM) (commonly without ketosis) was diagnosed in 48% (n=222) patients with CGL, with mean age at onset 5.3 years (range, 0.1-34 years).

Other clinical features were prominent musculature (97%), acromegaloïd appearance (76%), protuberant abdomen (80%), prominent veins (86%), acanthosis nigricans (71%), hirsutism (73%), hepatomegaly (84%) and advanced bone age (76%). Majority of patients had normal height velocity (59%, n=119) and normal weight (62%, n=117). Mean percentage body fat was 7.2 % (range, 1.9-17.7), though measurements and reference ranges for percentage body fat could have varied depending on the methodology used. Two-thirds of patients (n=149) reported a family history of similar physical appearance and/or history of fat loss. Polycystic ovaries and menstrual irregularities were present in 9 and 14 female patients, out of 14 and 23 patients respectively, for whom data on menstruation were reported.

Metabolic features of CGL patients were significant for elevated mean serum insulin, hemoglobin A1c, triglycerides and transaminases (Supplemental Table 3). Leptin deficiency was also noted.

**Acquired generalized lipodystrophy (AGL)**
We identified 86 patients with AGL (Table 1). Female predominance (female: male ratio = 2.3) was noted. Majority of patients were white (72%). Mean age at onset of fat loss was 5 years (range, 0.0-15 years). There was progressive loss of fat from face and neck, abdomen, thorax, and upper and lower limbs in 65-74% patients (Table 1 and Figure 2b). Infectious illness preceding the onset of fat loss was present in 17 patients out of 20 for whom this data were reported. Prevalence of DM was 70% (n=46) and mean age at onset of DM was 16.2 years (range, 1.3-62 years).

Similar to CGL, patients with AGL had prominent musculature (94%), acanthosis nigricans (74%), hepatomegaly (80%) and splenomegaly (51%). Data on acromegaloïd features, protuberant abdomen, menstrual irregularities, hirsutism, appetite, growth and bone age were available on too few patients to draw conclusions. Eighteen out of 27 patients (67%) had associated autoimmune diseases.

Hypertriglyceridemia was observed in AGL (Supplemental Table 3). Elevated serum insulin, hemoglobin A1c, total cholesterol and transaminases were reported.

**Familial partial lipodystrophy (FPL)**
We identified 124 patients with FPL (Table 1). White (79%) and female predominance (83%) was noted. Mean age at onset of fat loss was 9.9 years (range, 0.0-16 years). Fat loss was prominent from upper and lower limbs (66% and 73% patients respectively), with sparing of face and neck explicitly reported in 30 of 124 patients (Figure 2c). Prevalence of DM was 53% with mean age at onset 24.2 years (range, 8-57 years).
Other clinical features were prominent musculature (67%), acanthosis nigricans (70%) and positive family history of similar physical appearance and/or history of fat loss (62%). High prevalence of pancreatitis (49%, n= 21) was reported, likely secondary to hypertriglyceridemia (Supplemental Table 3).

**Acquired partial lipodystrophy (APL)**

We identified 124 patients with APL (Table 1). White (73%) and female predominance (83%) was noted. Mean age at onset of fat loss was 8.2 years (range, 0.5-16 years). Most frequent sites of fat loss were face and neck (90%) and upper limbs (82%), followed by thorax (74%) and abdomen (57%) (Figure 2d). Lower limbs were reportedly spared in 28 of 124 patients. Lower prevalence of DM (35%) was noted as compared to AGL (70%). A smaller proportion of patients with APL had acanthosis nigricans (13%), hepatomegaly (29%) and associated autoimmune diseases (31%).

Metabolic abnormalities in APL were less severe compared with other forms of lipodystrophy, except serum BUN which was elevated to 26 mg/dl (range, 0.2-72 mg/dl) (Supplemental Table 3).

**Other lipodystrophy syndromes**

Clinical and metabolic features of other lipodystrophy syndromes are summarized in Supplemental Table 4 and Supplemental Table 5 respectively. Due to a small number of reported patients with even rarer and novel lipodystrophy syndromes, they were combined under ‘Other syndromes’ in these tables.

**Interventions and outcomes**

Interventions described in included studies were metreleptin, diet, omega -3 poly unsaturated fatty acids/fish oil, insulin, metformin, oral hypoglycemic agents, statins, fibrates, nicotinic acid and plasmapheresis. Association of various interventions (single, double and ≥ 3 interventions) with metabolic outcomes is described in Supplemental Table 6. Majority of patients were on ≥ 3 interventions and ≥ 18 years of age at time of initiation of intervention. Due to heterogeneity in dose, route and duration of treatment, as well as small sample size, it was difficult to make statistically significant conclusions regarding management of lipodystrophy in included patients. Diet consisting of ~30% fat, ~20% protein, and ~50% carbohydrates, with limited simple carbohydrates was recommended by most centers. However, the degree to which patients followed recommendation was not captured systematically in reported articles. Broadly, metreleptin and diet over a mean duration of 29 months lowered serum insulin and triglycerides in 7 patients with CGL.

**Mortality data**

Age and cause of mortality for lipodystrophy syndromes is described in Supplemental Table 7. Of the 502 patients with CGL whose mortality status was known at the time of being reported (mean age at reporting 12.6 years), 33 were dead. Mean age at mortality for CGL was 12.5 years (range, 0.4 - 46.0 years) with respiratory infection being the most frequently reported cause of death followed by cardiac failure. Donohue syndrome had a high mortality rate of 50% (21 of 42 patients dead at reporting) and relatively early mean age at mortality (1.2 years, range, 0.03 – 8.3 years), with respiratory infection being the commonest cause.

**Discussion**

We conducted a systematic review to summarize existing data on clinical and metabolic features of non-HIV related lipodystrophy in children. This in-depth review of 1,141 patients with...
lipodystrophy is the largest pooled database, so far reported in literature. Since some of the included reports were case series across all age groups, some patients older than 18 years at the time of being reported (though with onset of lipodystrophy at < 18 years) were captured in our database. We have suggested core and supportive clinical features of four major lipodystrophies (CGL, AGL, FPL and APL) to help clinicians in diagnosis and management decisions (Table 2). Features explicitly reported as present or absent in at least 30-50% patients for each type of lipodystrophy were examined and categorized as core (if present in at least 50% patients) or supportive (if present in at least 25% patients).

Congenital generalized lipodystrophy is a rare autosomal recessive disorder (17). Several CGL mutations have been previously identified in genes including *AGPAT2* (CGL type 1), *BSCL2* (CGL type 2), *CAV1*, and *PTRF* (CGL type 4), with the first two accounting for about 95% of reported patients (18,40-43). These mutations alter gene activation and signaling pathways in differentiation of mesenchymal stem cells into adipocytes (44,45), resulting in loss of subcutaneous adipose tissue. Although the term “congenital” in CGL implies onset in the neonatal period, and in this review generalized fat loss in CGL was usually noted during first 3 years of life, some patients were not identified as having fat loss until early adolescence (15). It is not clear if this relates to use of the term “CGL” to describe genetic causes of generalized loss of fat after the first few years of life, as commonly occurs in familial partial lipodystrophy, or simply represents lack of recognition of fat loss until adolescence. Supportive features for CGL included acromegaloid appearance, hepatomegaly (because of hepatic steatosis) (46), protuberant abdomen (due to organomegaly), and advanced bone age. Onset of DM was during early childhood through adolescence, except in a group of 10 Brazilian CGL patients homozygous for a 1036 bp deletion in the *AGPAT2* gene (*BSCL1* locus), as described by Gomes *et al.* (47) and a single patient in the NIH lipodystrophy database (age at onset of DM 34 years). Gomes *et al.* reported mean age at onset of DM as 25.67 ± 11.25 years in *AGPAT2* group compared to 11.93 ± 8.29 years in *BSCL2* (*669insA Seipin*) group (p=0.007) (47). Diabetes mellitus in CGL was ketosis-resistant, with higher insulin levels and higher insulin resistance reported in *BSCL2* than in *AGPAT2* patients (47).

Acquired generalized lipodystrophy was characterized by female predominance. Patients with AGL had normal fat distribution at birth, however developed generalized loss of subcutaneous adipose tissue during childhood or puberty. Preceding infectious illnesses including *Neisseria meningitidis*, measles, varicella and mumps (3,48,49) were associated with onset of AGL. Histologic analysis of subcutaneous adipose tissue in AGL patients has previously revealed panniculitis (50). In fact, based on a review of 79 patients with AGL, Misra *et al.* (3) proposed subclassification of AGL into 3 varieties, type 1, the panniculitis variety (25%); type 2, the autoimmune variety (25%); and type 3, the idiopathic variety (50%). In our review, autoimmune conditions associated with AGL were vitiligo, autoimmune hepatitis, juvenile rheumatoid arthritis, Sjogren syndrome, Hashimoto’s thyroiditis, Graves’ disease, autoimmune hemolytic disease, nonthrombocytopenic purpura and celiac disease (3,51,52). AGL can also be associated with juvenile dermatomyositis, which was not included in this review (53).

Consistent with prior reviews (3,35), we found that the key distinguishing features between congenital and acquired generalized lipodystrophy were, later age at onset of fat loss, panniculitis, onset of DM during adolescence and somewhat worse dyslipidemia in AGL as compared to CGL. Insulin-resistant DM as well as low percentage body fat were reported in CGL and AGL, which are distinguishing features from type 1 and type 2 diabetes, respectively (35,54,55).
Familial partial lipodystrophy is an autosomal dominant disorder, predominantly affecting females and whites (56). At least 5 subtypes of FPL have been described; FPL type 1 (Kobberling’s syndrome, no causative genes identified), FPL type 2 (Dunnigan’s syndrome) from mutations in nuclear lamin A/C encoded by LMNA gene, FPL type 3 from mutations in PPARγ gene, FPL type 4 from AKT2 gene mutation and FPL type 5 from PLIN1 gene mutation (20,21,56,57). Fat loss in FPL has traditionally been reported to occur around the time of puberty (35), and consistent with that, the mean age of onset of fat loss in this study was 9.9 years. However, we found that some patients were reported to have fat loss in early childhood. Fat loss commonly involved upper and lower limbs. Face and neck were spared, leading to a Cushingoid appearance, primarily in FPL resulting from LMNA mutation (58). Physical appearance and metabolic abnormalities were more pronounced in women and developed at an earlier age compared to men in a Spanish family (59). However, other reports described males in German (60) and French families (61), with metabolic phenotype of FPL and marked hypertriglyceridemia and insulin resistance. Onset of DM in FPL occurred during adulthood and was accompanied by pancreatitis secondary to severe hypertriglyceridemia. The underlying mechanism for dyslipidemia in FPL has not been clearly elucidated.

Acquired partial lipodystrophy was characterized by cephalocaudal pattern of subcutaneous fat loss starting in face and variably including the neck, arms and thorax, with sparing of lower extremities. Onset of fat loss occurred during childhood and rarely during infancy (4). Similar to AGL, preceding infectious illnesses (including measles, varicella and scarlet fever) and associated autoimmune conditions (including autoimmune hepatitis, scleroderma, idiopathic thrombocytopenic purpura, primary hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and vitiligo) were reported (4,62,63). In both FPL and APL, mean percentage body fat was normal, which was reflected in relatively higher leptin levels and less severe phenotypic and metabolic abnormalities, as compared to the generalized variety of lipodystrophy.

Following the GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation) (64), the current direct evidence supporting management of lipodystrophy in children warrants low certainty due to methodological limitations of the available studies (heterogeneity of case reports and case series) and imprecision (i.e. small number of cases). Indirect evidence (that is, evidence derived from other relevant conditions, such as evidence on management of diabetes or dyslipidemia in children without lipodystrophy) warrants higher certainty and can be extrapolated for decision making when appropriate. Metreleptin has been FDA approved for treatment of children with CGL and AGL based on surrogate endpoint data (e.g. triglycerides and hemoglobin A1C) in small numbers of patients; ongoing data collection on pediatric patients treated with metreleptin is needed to determine metreleptin’s effects on morbidity and mortality, as well as long-term safety and efficacy, in this population.

Limitations and strengths
Our findings regarding clinical and metabolic features of four major lipodystrophies are broadly consistent with those of the AACE consensus statement published in 2013 (35). However, in this comprehensive review we provide objective data based on reported patients in the literature. We also described features of other rarer and novel forms of lipodystrophy.

The major weakness of this review results from biased reporting in the literature, with likely underreporting of patients with milder manifestations of lipodystrophy. Overall reporting in included studies was likely biased towards more severe clinical and metabolic features. Features that were more likely to be reported, if present, were history of consanguinity, sites of fat loss,
prominent musculature, presence of preceding infectious illness, reproductive data and intellectual disability. Features less likely to be reported, if absent, were sites of fat sparing, effect on appetite and growth and associated autoimmune conditions. Additionally, inclusion of pediatric age-range in our search strategy might have excluded some cases of lipodystrophy that were reported as adults but had onset of symptoms at less than 18 years of age. Furthermore, because several cases with onset at <18 years were reported after they had reached adulthood, some complications of lipodystrophy, and the management of those complications, occurred in adulthood. On the other hand, because we restricted to patients with age of onset <18 years, the ages at which various features of lipodystrophy occurred in our data set may be systematically biased towards younger ages.

The strength of this review relates to the comprehensive nature of literature search and the measures undertaken to reduce the effect of bias and random error; pre-defined protocol-driven work, duplicate data-extraction and review, and expert contact. This review represents not only the experience from large centers with expertise in lipodystrophy, but also individual cases from smaller centers as well as cases reported in six non-English languages. Additionally, limiting current study to cases with onset < 18 years allowed a focused description of pediatric lipodystrophy.

Implications for practice and research
Diagnosis of lipodystrophy in non-obese patients with metabolic aberrations requires careful history and physical examination, with genetic testing guided by the patient’s specific phenotype. Several genetic mutations have been identified in association with lipodystrophy, each with unique clinical features (Supplemental Table 8). However, some genetic mutations remain to be identified, and thus genetic testing is not 100% sensitive, even in patients with inherited forms of lipodystrophy (1,14,16,23). Patients with generalized lipodystrophy have relative leptin deficiency, however, serum leptin cannot be used as a diagnostic criterion because serum leptin concentrations vary with age, BMI, sex, nutritional status and even emotional state (65-67). Moreover, reference ranges for leptin have not yet been standardized (68,69). Finally, considering the rarity of lipodystrophy syndromes, registry studies might facilitate comprehensive reporting of these patients and avoid publication bias and bias in phenotype description.

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**Figure 1. The process of study selection. Figure Legend:**  
1 We extracted data from studies in Russian, French, Polish, Spanish, Italian and Portuguese; and excluded studies in German, Japanese, Dutch, Hebrew, Hungarian, Korean, Norwegian and Slovakian.  
2 Lipodystrophy related to HIV treatment, secondary to drug administration (insulin, growth hormone, steroids, antibiotics, and vaccinations), secondary to recurrent pressure, lipodystrophia centrifugalis abdominalis infantilis, localized lipodystrophy, juvenile onset dermatomyositis and secondary to systemic diseases such as uncontrolled diabetes mellitus, thyrotoxicosis, anorexia nervosa, malnutrition, malignancy and chronic infections, were excluded.  
3 Age of onset of lipodystrophy < 18 y vs. ≥ 18 y

**Figure 2. Distribution of adipose tissue in four major lipodystrophies (CGL, AGL, FPL, APL). Figure Legend:**  
Fat loss in > 72% patients. Fat loss in 57-72% patients. Fat loss in < 57% patients. Fat sparing. CGL: Congenital Generalized lipodystrophy; AGL: Acquired Generalized lipodystrophy; FPL: Familial. Partial lipodystrophy; APL: Acquired Partial lipodystrophy

*Please refer to Table 1 for exact reported frequencies of sites of fat loss in each of the four major lipodystrophies. For purpose of uniformity in pictorial representation, frequency cut-offs of > 72%, 57-72% and < 57% were used.*
Table 1. Clinical features of four major lipodystrophies (CGL, AGL, FPL, APL)

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>CGL</th>
<th>N (%)</th>
<th>AGL</th>
<th>N (%)</th>
<th>FPL</th>
<th>N (%)</th>
<th>APL</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/Female) (%)</td>
<td>45/55</td>
<td>457</td>
<td>33/77</td>
<td>86</td>
<td>17/83</td>
<td>124</td>
<td>17/83</td>
<td>124</td>
</tr>
<tr>
<td>Ethnicity (W/H/B/A/O) (%)</td>
<td>32/12/17/24/15</td>
<td>231</td>
<td>72/4/10/4/6</td>
<td>69</td>
<td>79/3/5/3/10</td>
<td>67</td>
<td>73/7/0/10/10</td>
<td>41</td>
</tr>
<tr>
<td>History of consanguinity (%)</td>
<td>61</td>
<td>286</td>
<td>47</td>
<td>15</td>
<td>22</td>
<td>9</td>
<td>31</td>
<td>16</td>
</tr>
<tr>
<td>Age at onset of fat loss (y)</td>
<td>0.3 ±1.5 (0.0-12)</td>
<td>340</td>
<td>5.0 ± 3.5 (0.0-15.0)</td>
<td>53</td>
<td>9.9 ± 5.6 (0.0-16.0)</td>
<td>16</td>
<td>8.2 ± 3.9 (0.5-16)</td>
<td>106</td>
</tr>
</tbody>
</table>

**Fat loss [% (n)]**

| Face and neck | 93 (481) | 519 | 74 (64) | 86 | 6 (7) | 124 | 90 (111) | 124 |
| Abdomen       | 90 (469) | 519 | 65 (56) | 86 | 19 (23) | 124 | 57 (70) | 124 |
| Thorax        | 90 (469) | 519 | 65 (56) | 86 | 9 (11) | 124 | 74 (92) | 124 |
| Upper limbs   | 92 (476) | 519 | 73 (63) | 86 | 66 (82) | 124 | 82 (102) | 124 |
| Lower limbs   | 89 (467) | 519 | 73 (63) | 86 | 73 (90) | 124 | 14 (17) | 124 |

**Fat sparing (n)**

| Face and Neck | 0 | * | 3 | * | 30 | * | 2 | * |
| Abdomen       | 0 | * | 3 | * | 6 | * | 11 | * |
| Upper limb    | 0 | * | 2 | * | 0 | * | 1 | * |
| Lower limb    | 0 | * | 2 | * | 0 | * | 28 | * |
| Palms         | 16 | * | 3 | * | 1 | * | 1 | * |
| Soles         | 16 | * | 2 | * | 1 | * | 7 | * |

**Other features**

- Prominent musculature % (n) 97 (284) 294 94 (44) 47 67 (26) 39 65 (15) 23
- Infectious illness preceding onset of fat loss % (n) 31 (15) 49 85 (17) 20 25 (8) 4 67 (16) 24
- Presence of DM % (n) 48 (222) 467 70 (46) 66 53 (50) 95 35 (27) 78
- Age at onset of DM (y) 5.3 ± 5.8 (0.1-34.0) 146 16.2 ± 12.9 (1.3-62.0) 33 24.2 ± 12.7 (8-57) 35 14.8 ± 5.5 (3-22) 8
- Presence of ketosis % (n) 5 (3) 56 13(4) 30 4 (1) 29 0 (0) 15
- Acromegaloitd features % (n) 76 (174) 230 88 (14) 16 33 (1) 3 23 (3) 13
- Proteborant abdomen % (n) 80 (93) 116 88 (14) 16 17 (1) 6 40 (2) 5
- Polycystic ovaries % (n) 64 (9) 14 100 (1) 1 100 (8) 8 30 (3) 10
- Menstrual irregularities % (n) 61 (14) 23 100 (9) 9 86 (6) 7 38 (5) 13
- Prominent veins % (n) 86 (80) 93 88 (22) 25 100 (3) 3 100 (3) 3
- Acanthosis nigricans % (n) 71 (141) 198 74 (34) 46 70 (23) 33 13 (6) 46
- Hirsutism % (n) 73 (121) 165 57 (9) 16 75 (9) 12 42 (8) 19
- Family history of LD % (n) 66 (149) 224 8 (4) 53 62 (51) 82 4 (1) 28
- Hepatomegaly % (n) 84 (231) 299 80 (42) 53 54 (7) 13 29 (17) 58
- Splenomegaly % (n) 64 (78) 121 51 (18) 35 67 (2) 3 7 (1) 14
- Cardiovascular disease % (n) 46 (144) 313 19 (6) 31 6 (3) 50 15 (3) 20
- Pancreatitis % (n) 31 (20) 64 21 (6) 28 49 (21) 43 7 (1) 14
- Percent body fat % 7.2 ± 3.2 (1.9-17.7) 68 9.2 ± 4.5 (0.3-27.0) 28 23.1 ± 6.2 (10.0-44.8) 52 21.6 ± 5.9 (12.5-29.0) 5
- Appetite (I/D/NA) (%) 54/15/31 | 26 | 29/42/29 | 7 | 0/0/100 | 2 | 0/14/86 | 7
- Height velocity (I/D/NA) (%) 32/9/59 | 202 | 47/17/36 | 30 | 0/50/50 | 12 | 7/0/93 | 15
- Weight (I/D/NA) (%) 18/20/62 | 188 | 18/43/39 | 28 | 12/44/44 | 9 | 0/29/71 | 17
- Bone age (A/Dc/NA) (%) 76/10/14 | 103 | 40/13/47 | 15 | 20/40/40 | 5 | 0/0/100 | 3
- Intellectual disability % (n) 47 (108) | 229 | 50 (7) | 14 | 43 (3) | 7 | 8 (1) | 12
- Autoimmune diseases % (n) 6 (4) | 61 | 67 (18) | 27 | 9 (4) | 43 | 31 (19) | 62

CGL: Congenital Generalized lipodystrophy; AGL: Acquired Generalized lipodystrophy; FPL: Familial Partial lipodystrophy; APL: Acquired Partial lipodystrophy; W: White; H: Hispanic; B: Black; A: Asian; O: other; y: years; DM: Diabetes mellitus; I: increased; D: decreased; NA: not affected; LD: lipodystrophy; A: advanced; De: delayed

* total number of patients for whom data were reported in literature; data not explicitly reported in literature were not included in analysis

% of patients for whom data were reported

reported as Mean ± SD (range); measurements and reference ranges may vary depending on the methodology used.

reported as percentage and number of patients for whom this specific site was reported as being involved; loss of fat from palms and soles was explicitly reported in 2-10% patients

reported as number of patients for whom this site was explicitly reported as being spared. This does not imply that the site was not spared in remaining patients
Table 2. Diagnostic features of four major lipodystrophies

<table>
<thead>
<tr>
<th>Congenital Generalized Lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core features:</strong></td>
</tr>
<tr>
<td>1. Generalized lack of subcutaneous fat from entire body (+/- sparing of mechanical fat), resulting in prominence of muscles and veins</td>
</tr>
<tr>
<td>2. Onset of fat loss usually occurs during infancy (mean age 0.3 ± 1.5 years, range 0-12 years)</td>
</tr>
<tr>
<td>3. Evidence of insulin resistance (hyperinsulinemia, diabetes mellitus, acanthosis nigricans, hypertriglyceridemia)</td>
</tr>
<tr>
<td><strong>Supportive features:</strong></td>
</tr>
<tr>
<td>1. Acromegaloïd features</td>
</tr>
<tr>
<td>2. Family history of similar physical appearance and/or history of fat loss in autosomal recessive pattern</td>
</tr>
<tr>
<td>3. Hepatomegaly/NAFLD</td>
</tr>
<tr>
<td>4. Cardiomyopathy</td>
</tr>
<tr>
<td><strong>Common associated genes:</strong> AGPAT2, BSCL2, PTRF, CAV1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired Generalized Lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core features:</strong></td>
</tr>
<tr>
<td>1. Generalized lack of subcutaneous fat from entire body, often without sparing of mechanical fat, resulting in prominence of muscles and veins</td>
</tr>
<tr>
<td>2. Onset of fat loss usually occurs during childhood (mean age 5.0 ± 3.5 years, range 0-15 years)</td>
</tr>
<tr>
<td>3. Evidence of insulin resistance (hyperinsulinemia, diabetes mellitus, acanthosis nigricans, hypertriglyceridemia)</td>
</tr>
<tr>
<td><strong>Supportive features:</strong></td>
</tr>
<tr>
<td>1. Panniculitis or autoimmune disease preceding onset of lipodystrophy</td>
</tr>
<tr>
<td>2. Hepatomegaly/NAFLD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Familial Partial Lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core feature:</strong></td>
</tr>
<tr>
<td>1. Regional lack of subcutaneous fat (legs &gt; arms), resulting in a peripheral muscular appearance, often with fat sparing or fat accumulation in face and neck</td>
</tr>
<tr>
<td>2. Onset of fat loss usually occurs during late childhood through early adolescence (mean 9.9 ± 5.6 years, range 0-16 years)</td>
</tr>
<tr>
<td><strong>Supportive features:</strong></td>
</tr>
<tr>
<td>1. Evidence of insulin resistance (hyperinsulinemia, diabetes mellitus, acanthosis nigricans, hypertriglyceridemia)</td>
</tr>
<tr>
<td>2. Family history of similar physical appearance and/or history of fat loss in autosomal dominant pattern</td>
</tr>
<tr>
<td>3. Pancreatitis</td>
</tr>
<tr>
<td><strong>Common associated genes:</strong> LMNA, PPARG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired Partial Lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Core feature:</strong></td>
</tr>
<tr>
<td>1. Cephalocaudal pattern of subcutaneous fat loss starting in face and variably including the neck, arms and thorax, with sparing of lower extremities</td>
</tr>
<tr>
<td>2. Onset of fat loss usually occurs during late childhood through early adolescence (mean 8.2 ± 3.9 years, range 0.5-16 years)</td>
</tr>
<tr>
<td><strong>Supportive features:</strong></td>
</tr>
<tr>
<td>1. Infectious or autoimmune disease preceding onset of lipodystrophy</td>
</tr>
<tr>
<td>2. Evidence of membranoproliferative glomerulonephritis</td>
</tr>
</tbody>
</table>

NAFLD: Non-alcoholic Fatty Liver Disease; AGPAT2: 1-Acylglycerol-3-Phosphate O-Acyltransferase 2; BSCL2: Berardinelli-Seip Congenital Lipodystrophy Type 2; PTRF: Polymerase I and Transcript Release Factor; CAV1: gene encoding Caveolin 1; LMNA: gene encoding lamin A; PPARG: Peroxisome Proliferator-Activated Receptor Gamma

Ω These features should serve as a useful general framework for clinical diagnosis of lipodystrophy. They do not account for vast heterogeneity of clinical features seen in various lipodystrophy syndromes. Features explicitly reported as present or absent in at least 30-50% patients for each type of lipodystrophy were examined and categorized as core (if present in at least 50% patients) or supportive (if present in at least 25% patients).

"Though CGL and FPL are genetic conditions, family history may be negative
1303 citations obtained by search strategy

713 citations excluded by screening titles/abstracts

590 articles retrieved for full text screening

148 articles excluded
  - Age of onset of symptoms ≥18 y (10)
  - Abstracts only (100)
  - Duplicate articles (11)
  - Foreign language¹ (27)

442 articles met the inclusion criteria

91 articles excluded after data extraction
  - Not intervention of interest (8)
  - Not diagnosis of interest² (56)
  - Mixed population without separate analysis for each type³ (2)
  - Not outcome of interest (25)

351 Studies included in systematic review