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review

Current Diagnosis and Treatment, and Clinical Challenges in the Management of Lipodystrophy Syndromes in Children and Youth

Running title: Lipodystrophy in children and youth

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Abstract

Lipodystrophy is a heterogeneous group of disorders characterized by lack of body fat, which can be genetic or acquired. Lipodystrophy is associated with insulin resistance that can develop in childhood and youth, and usually leads to severe metabolic complications. Diabetes mellitus, hypertriglyceridermia, and hepatic steatosis ordinarily develop in these patients, and most girls suffer from menstrual abnormalities. Severe complications develop at a relatively young age, which include episodes of acute pancreatitis,
renal failure, cirrhosis, and complex cardiovascular diseases, and they all are associated with serious morbidity. Treatment of lipodystrophy consists of medical nutrition therapy, exercise, and the use of anti-hyperglycemic and lipid-lowering agents. New treatment modalities such as metreleptin replacement offer a great benefit in the treatment of metabolic abnormalities secondary to lipodystrophy. Current challenges in lipodystrophy management in children and youth include, but not limited to, (1) establishing specialized centers with experience in providing care for lipodystrophy presenting in childhood and adolescence; (2) optimizing algorithms that can provide some guidance for the use of standard and novel therapies to ensure adequate metabolic control and to prevent complications; (3) educating patients and their parents about lipodystrophy management; (4) improving patient adherence to chronic therapies; (5) reducing barriers to access novel treatments; and (5) improving the quality of life of these patients and their families.

**Keywords:** Lipodystrophy; Childhood; Youth, Progeria, Metreleptin.

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**Introduction**
Lipodystrophy is a heterogeneous group of disorders characterized by near total (generalized lipodystrophy, GL) or partial (partial lipodystrophy, PL) lack of the body fat 1. Lipodystrophy can be genetic or acquired. Congenital generalized lipodystrophy (CGL), familial partial lipodystrophy (FPLD), acquired generalized lipodystrophy (AGL), and acquired partial lipodystrophy (APL) consist of four major categories of lipodystrophy in clinical practice, although there are several others such as progeria associated lipodystrophy, auto-inflammatory syndromes, and complex syndromes associated with lipodystrophy (1-5). The current classification schema which is based on clinical presentation may change as our understanding of the disease processes improve. In this paper, we will focus on presentation of various forms of lipodystrophy during childhood and adolescence and then review the general clinical approach for these patients.

**Diagnosis of lipodystrophy in children and youth**

**Genetic lipodystrophy syndromes**

**Congenital generalized lipodystrophy (CGL)**

CGL (Berardinelli-Seip syndrome) is the most common lipodystrophy subtype in infancy and early childhood, while the incidence of FPLD increases close to puberty (3-6). CGL made up almost half (519 of 1141) of pediatric patients with non-HIV lipodystrophy identified by a recent systematic review of a total of 351 studies (6). CGL is an autosomal recessive (AR) rare disorder, in which patients are born with near total lack of the body. These patients have a remarkable phenotype characterized by near total scarcity of adipose tissue, muscular overdevelopment, and prominent subcutaneous veins, which can be noticed either at birth or in the first year of life (7). The prevalence of CGL is uncertain, but it has been previously estimated at approximately 1:10 million (8). A recent study reported an estimated prevalence of 0.23 cases/million for diagnosed GL (9). However, CGL has a higher prevalence in certain parts of the world as a result of consanguineous marriages. We reported an estimated CGL prevalence of 1 in 2 million in Turkey, considerably higher than the previous literature (10) but still quite rare.

There are four major subtypes of CGL based on mechanism:
CGL1 [Online Mendelian Inheritance in Man (OMIM) #608594] is caused by pathogenic variants of the 1 acylglycerol 3-phosphate acyltransferase β2 (AGPAT2) gene (11). The AGPAT2 enzyme converts lysophosphatidic acid into phosphatidic acid, a critical step in triglyceride synthesis (12). Homozygous pathogenic variants that eliminate enzyme activity have been determined in the majority of CGL1 cases. Compound heterozygous or homozygous pathogenic variants with low levels of in vitro enzyme activity have also been reported (7,13). Although patients with CGL1 lack metabolically active adipose tissue, the preservation of residual mechanical adipose tissue in the palms, soles, scalp, orbital and periarticular regions, and the perineum is clinically apparent (14,15).

CGL2 (OMIM #269700) is caused by pathogenic variants of the Berardinelli-Seip congenital lipodystrophy 2 (BSCL2) gene (16), which encodes the transmembrane protein seipin. This protein is involved in the fusion of small lipid droplets in adipocytes, as well as in the differentiation of adipocytes (17). The majority of identified variants have been classified as null pathogenic variants based on functional investigations which lead to severe disruption of the protein. Missense pathogenic variants have also been reported (7,13,18).

Pathogenic variants of the caveolin 1 (CAV1) gene, which encodes caveolin 1 that is a principal component of the caveolae, causes CGL3 (OMIM #612526). A homozygous nonsense pathogenic variant in CAV1 was reported in a patient with CGL from Brazil (19). MRI of the proband confirmed the absence of metabolically active adipose tissue, while bone marrow adipose tissue was preserved (19). Heterozygous CAV1 pathogenic variants have also been associated with PL (20).

CGL4 (OMIM #613327) is caused by homozygous or compound heterozygous pathogenic variants in the polymerase I and transcript release factor (PTRF, or cavin-1) gene (21). PTRF regulates the expression of caveolins 1 and 3. Cavin-1 plays a major role in the formation of caveolae and caveolin stabilization through interaction with the cellular cytoskeleton. Cavin-1 regulates adipocyte differentiation, and it is a determining factor in the capacity of adipose tissue to expand (22). CGL3 and CGL4 have distinct clinical characteristics (23-25) (Table-1).
In addition to these major 4 groups of CGL, patients with GL associated with Lamin A/C ($LMNA$) p.T10I (26), and biallelic peroxisome proliferator activated receptor gamma ($PPARG$) (27) pathogenic variants have been reported. Patients with biallelic loss-of-function pathogenic variants in phosphate cytidylyltransferase 1 alpha ($PCYT1A$) gene were reported to have a severe PL phenotype (28), and potentially can be classified in the CGL category.

Table-1 summarizes subtypes of CGL.

**Familial partial lipodystrophy (FPLD)**

FPLD is a subtype of lipodystrophy with a genetic background which is more common in adults than any other subtype of lipodystrophy (4,8,9,29). FPLD exhibits a typical fat tissue distribution. Phenotypic features are more prominent in females. Loss of adipose tissue is predominantly observed in the upper and lower extremities. Patients may exhibit accumulation of fat in certain areas such as the face and neck and perineal and intra-abdominal depots (2,4,30-32). A Cushingoid- appearance can be observed due to thin limbs, facial fat accumulation, and increased fat in the dorsocervical region resembling a ‘buffalo hump’ (5). The partial loss of fat may be apparent in early life, but typically becomes more pronounced over time in patients with FPLD, and most patients start to lose adipose tissue after puberty (30). For this reason, it is difficult to recognize these patients in childhood, however, a few patients with FPLD were seen in pediatric endocrinology practices (6).

Most FPLD subtypes are inherited in an autosomal dominant (AD) manner. On the other hand, recent evidence suggests that a large group of patients with FPLD1, also known as Koberling-type FPLD (OMIM #608600), follow a polygenic inheritance pattern (33-35). FPLD2, the Dunnigan variety, (OMIM#151660), is caused by AD pathogenic variants in the $LMNA$ gene (36), which encodes nuclear lamins A and C (36,37). $LMNA$ R482W and R482Q are the most common pathogenic variants (38,39). FPLD3 (OMIM#604367) is caused by AD pathogenic variants in the peroxisome proliferator-activated receptor gamma gene ($PPARG$) on chromosome 3p25 (40,41). $PPARG$ plays a major role in the regulation of adiposity differentiation (40). Other subtypes of FPLD are rare, and a recent review of these subtypes can be found in an article by Akinci et al (1). Also, the subtypes of FPLD are presented in Table-2.
Acquired lipodystrophy syndromes

*Acquired generalized lipodystrophy (AGL), Lawrence syndrome*

AGL affects the whole body and causes generalized fat loss. Patients develop typical metabolic complications of lipodystrophy including severe insulin resistance, diabetes, hypertriglyceridemia, and non-alcoholic steatohepatitis (42). The clinical phenotype is very similar to that of CGL. However, patients with AGL are born with normal fat tissue. Loss of adipose tissue typically begins in childhood or adolescence. Marked phenotypic features occur over differing lengths of time, from a few weeks to a year. The cause of the disease is still unknown. The disease coincides with other autoimmune diseases such as juvenile dermatomyositis, type 1 diabetes, autoimmune hepatitis. AGL is associated with panniculitis in some patients. Complement abnormalities may also be present (8,42,43).

*Acquired Partial Lipodystrophy (APL), Barraquer-Simons Syndrome*

APL (OMIM #608709) is characterized by the loss of fat from the face, neck, arms, chest, and abdomen with preservation of lower extremity fat. Clinical onset typically occurs in childhood or adolescence, and females predominate at a ratio of 4:1. Loss of fat first manifests in the face, and gradually progresses to the upper extremities, thorax, and upper abdomen symmetrically in a cephalocaudal fashion. An excessive deposition of fat may be observed in the lower limbs (44). The etiology of APL remains unknown; however, there is a link to autoimmune abnormalities. Coinciding autoimmune conditions can be observed. APL is associated with low complement 3 (C3) levels and membranoproliferative glomerulonephritis (MPGN) in some patients, which may cause end stage renal disease (ESRD) in some patients (44-46). Drusen deposition in macula has also been reported.

*Progeroid disorders and other rare genetic lipodystrophy syndromes*

Lipodystrophy is a part of the clinical picture in many progeroid syndromes (1,47,48). There are also several other complex syndromes associated with lipodystrophy 1. The characteristics of these syndromes are presented in Table-3.

*Other causes of acquired lipodystrophy*
Clinically not receiving enough attention is the possibility of developing lipodystrophy after whole body irradiation (49-54) (as part of bone marrow transplant protocols), cranial irradiation and as a result of hypothalamic tumors (55). When children have aggressive treatments for childhood cancers, they should be followed for development of fat loss and ensuing metabolic abnormalities. In a young child presenting with lipodystrophy, it is very important to consider the possibility of CNS tumors especially when the clinical presentation does not fit with AGL. We are also learning that other forms of cancer therapy such as checkpoint inhibitors may lead to differing extent of fat loss (56,57). These unusual forms of acquired lipodystrophy will be reviewed in a specific review in the near future.

**Clinical Details**

Now that we have reviewed the majority of the lipodystrophy syndromes, we would like to cover clinically important topics in presentation.

**Leptin levels**

GL is characterized by very low or undetectable levels of leptin. On the other hand, leptin concentrations may range from low to normal in PL (58). Also, several studies suggest that baseline serum leptin level may assist physicians to identify PL patients who are more likely to benefit from leptin replacement (59,60). Leptin levels are associated with fat mass, and females have higher leptin levels than men in adulthood (61). However, it is challenging to interpret leptin levels in infancy, childhood, and youthhood. Girls have higher leptin levels after the completion of puberty (62,63). On the other hand, prepubertal levels of leptin are similar in both sexes, although the levels fluctuate during infancy (62,64). Younger infants have higher leptin levels than older infants presumably secondary to an initial increase in breast milk leptin levels from colostrum to mature milk which is followed by a decreasing trend during the first months of lactation and a subsequent increase during the late period of lactation (65-67). Leptin levels correlate with age in prepubertal girls and boys. Leptin levels increase both in boys and girls during early puberty. In boys, this early pubertal peak of leptin is followed by a decrease in leptin levels several years after the rise in serum testosterone levels. On the other hand, girls have
constantly increasing leptin levels during puberty which is in parallel with increasing levels of estrogen. The levels of leptin reach its maximum in mid puberty and remain constant thereafter (62). Thus, clinicians should pay attention to many factors when interpreting leptin levels. Serum leptin measurement may help clinicians with the management of lipodystrophy, but it should not be considered as a reliable tool to diagnose or rule out lipodystrophy. In addition to leptin assay, adiponectin levels are helpful in certain patients. Relatively higher level of adiponectin is a distinguished characteristic of CGL2, although serum leptin is extremely low in all subtypes of CGL (10,68).

**Metabolic abnormalities**

Patients with lipodystrophy may develop metabolic abnormalities associated with insulin resistance before adulthood, which are more severe and have an earlier onset in GL (3,31,43,69). These metabolic abnormalities include, but not limited to, diabetes, hypertriglyceridemia, hepatic steatosis, and non-alcoholic steatohepatitis (NASH) (3). Most females with lipodystrophy suffer from polycystic ovary syndrome (PCOS). Some of the factors determining the severity of metabolic abnormalities are the severity of adipose tissue loss, type of lipodystrophy, age, and sex. However, the severity of metabolic abnormalities may vary even among subjects with the same genetic pathogenic variant (30,32,70,71).

Hyperphagia usually develops due to severe leptin deficiency in early childhood in subjects with CGL (7). Accelerated linear growth, advanced bone age, and signs indicative of acromegaly such as enlargement of the hands, feet, and jaw may be observed (3). Cystic bone lesions are frequently noted in CGL1 patients (10,72,73). Hyperinsulinemia and severe insulin resistance develop in the majority of patients with CGL due to near total adipose tissue loss and leptin deficiency (10,74). Acanthosis nigricans (AN), a clinical marker of insulin resistance, can be observed in body folds such as the axilla and neck during the childhood, with a strong likelihood of a further increase after puberty (3,8). Approximately 45% of patients with CGL develop diabetes mellitus until puberty (7,10). The treatment of diabetes is challenging, and high-doses of insulin (>100 units/day) may be required. Although most patients are poorly controlled, diabetic ketoacidosis rarely develops (however can still be observed) probably as a result of severe hyperinsulinemia and
lack of fat tissue (4). Hypertriglyceridemia usually develops in the childhood. Eruptive xanthomas and recurrent episodes of pancreatitis caused by severe hypertriglyceridemia may emerge after puberty (3). Hepatic disease is more aggressive in patients with CGL2 (10). Hepatomegaly is remarkable at very young ages (3,10). Patients may develop cirrhosis during childhood (10). Polycystic ovary syndrome (PCOS), hyperandrogenism, and menstrual irregularity are common in adolescent girls (75).

Acanthosis nigricans, metabolic abnormalities associated with insulin resistance, and hepatic steatosis may be observed in youth with FPLD (31), albeit milder in presentation compared to CGL. Hypertriglyceridemia is common and can be severe. Acute pancreatitis episodes may be observed. Cardiomyopathy and myopathy (as well as features of muscular dystrophy) may be detected in patients with FPLD2 (8,31,59). In contrast to other forms of lipodystrophy, metabolic complications have rarely been reported in patients with APL (44). However, our previous observations suggested that a subgroup of patients with APL developed metabolic abnormalities associated with insulin resistance, which can also be progressive in some cases. Although the majority of these patients were adults, a few of them developed metabolic abnormalities in their younger years (46).

**Treatment of lipodystrophy in children and youth**

**General guidelines**

Although there is no curative treatment for lipodystrophy syndromes, early diagnosis of these patients may prevent mortality or serious morbidity. The aim of medical treatment is to correct metabolic abnormalities associated with lipodystrophy and prevent end-organ complications. Medical nutrition therapy (MNT) and exercise are important tools in the management of patients with lipodystrophy, although it is not easy for patients and families to follow the instructions. Hyperphagia due to leptin deficiency is enormous in these children. However, weight increase is insufficient. Since overeating exacerbates hepatic steatosis, diabetes, and hyperlipidemia, particularly in babies and children, the fat level should be reduced in the diet, and fat should be predominantly taken in the form of cis-monounsaturated fats and long chain omega 3 fatty acids. Medium chain triglycerides in infant formulas may be helpful to reduce triglyceride levels. The amount of fat in the diet should be severely restricted in patients developing acute
pancreatitis secondary to hypertriglyceridemia. Patients with diabetes also have to balance their intake of carbohydrates (4). Exercise may improve metabolic parameters in patients with lipodystrophy. Sedentary time should be reduced as possible, with focus on minimizing time spent on computer and television. Physical activity can be advised unless contraindicated. A detailed cardiac examination should be performed before advising an exercise plan. Special attention should be paid for patients with CGL4, FPLD2, and progeroid syndromes. CGL patients with lytic bone lesions and also patients with hepatosplenomegaly should avoid contact sports (1,4).

The use of lipid lowering drugs is considered in children and youth with lipodystrophy when diet and exercise fail to control triglyceride levels. Fibrates are commonly used in children with very high triglyceride levels who are at risk for pancreatitis (76). Omega-3 fish oil therapy may also help to reduce triglyceride levels (76,77). Although fibrates, alone and in combination with statins, have been shown to effectively reduce triglyceride levels in adults, data are very sparse in children (6,77). Physicians should pay attention to safety measures while using fibrates for hypertriglyceridemia in children. Liver enzymes should be monitored. The risk of rhabdomyolysis should be kept in mind.

Metformin is the first choice to treat insulin resistant diabetes in children in addition to MNT and lifestyle modification. The FDA approved the use of metformin for pediatric patients 10 years of age or older, referencing that the safety and effectiveness of metformin have been shown in pediatric patients ages 10 to 16 years (78). Lipodystrophy patients with diabetes usually require insulin injections in combination with metformin (6). Insulin doses needed may be very high, and patients may need to use concentrated forms of insulin (4).

Most patients with lipodystrophy desire a better cosmetic appearance. Patients with lipodystrophy may consider having cosmetic surgery, which may help them feel better about their physical appearance and may offer an improved quality of life. Excess unwanted localized fat can be removed from several locations that include the chin, buffalo hump, and vulvar region by liposuction or surgical excision. Lipoatrophic areas may also benefit from autologous adipose tissue transplantation, facial reconstruction, and implants (1).
**Metreleptin therapy**

Recombinant human leptin (metreleptin) therapy can be used to minimize and prevent complications of lipodystrophy (79). Severe hypoleptinemia causes hyperphagia and exacerbates metabolic complications associated with insulin resistance in patients with lipodystrophy 80. Several long-term studies have shown beneficial effects of recombinant human leptin (metreleptin) in generalized lipodystrophies with severe low serum leptin levels (81-84). Metreleptin therapy has been associated with a significant reduction in triglyceride and HbA1c levels, and improvements in appetite control, insulin sensitivity, and hepatic steatosis (82,85-89).

The metabolic effects of metreleptin are quite remarkable in pediatric patients with lipodystrophy. In the largest report of the efficacy of metreleptin in pediatric patients with lipodystrophy so far, Brown et al. (85) showed a reduction of HbA1c from a mean level of 8.3% to 6.5%. Triglyceride levels significantly decreased from 374 mg/dL to 189 mg/dL. The benefit was more prominent in adolescents (from 9.6% to 7.1% for HbA1c, and from 556 mg/dl to 226 mg/dl for triglycerides), presumably because of the presence of a more severe disease at baseline. Insulin sensitivity improved, and half of the patients who were on insulin at baseline were able to discontinue insulin treatment after metreleptin. The levels of liver enzymes decreased, and liver histology improved in a subset of patients who underwent before and after treatment liver biopsies. Metreleptin therapy was also associated with partial normalization of rapid growth in CGL, and improvements in pubertal development. The average dose of metreleptin was 0.082 mg/kg/day (range: 0.04 to 0.19 mg/kg/day; absolute dose: 4.1 mg/day). The dose per kg was nonsignificantly higher in adolescents. Patients with FPLD were treated with higher doses of metreleptin compared to those with GL.

Metreleptin was approved by the Food and Drug Administration (FDA) in 2014 for treatment of adult and pediatric patients with GL to treat metabolic complications of lipodystrophy as an adjunct to diet and lifestyle modifications (90,91). Although metreleptin therapy resulted in heterogeneous improvements in patients with PL, at least a subset of PL, which probably consist of PL patients with low leptin levels, is very likely to benefit from metreleptin (59,60) Although the FDA has yet not approved metreleptin for treatment of PL, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has approved
metreleptin in patients with PL in for whom standard treatments have failed to achieve adequate metabolic control (92). There is no age limit for treatment in the US, and it has been used in infants as young as 6 months of age (85). However, the EMA CHMP’s recent positive opinion includes authorization for metreleptin in children 2 years of age and above with GL, and in children 12 years of age and above with PL (93). In Turkey, metreleptin therapy is currently available only for GL patients for whom standard treatments have failed to control HbA1c and triglyceride levels (94).

Generally recommended starting dose of metreleptin is 5 mg/day in females greater than 40 kg, 2.5 mg/day in males greater than 40 kg, and 0.06 mg/kg/day (0.012 mL/kg) in males and females less than or equal to 40 kg (91). The dose should be kg based in children, and the physicians should keep in mind that most children will require increasing per kg dose, especially as they reach puberty. However, the dose should be adjusted based on clinical response, and tolerability issues such as excessive weight loss in pediatric patients. Metreleptin can be given once daily at any time of day regardless of meals (4,5). The most common side-effects are hypoglycemia and injection site reactions such as erythema and/or urticarial (91). Metreleptin therapy has been shown to have beneficial effects on kidney functions (95). On the other hand, few patients were described with worsening of proteinuria on metreleptin (91). However, this observation needs to be confirmed as the disease progression itself can be responsible for the proteinuria progression.

Two important issues which led to a black box warning in the US need to be specifically discussed: these are neutralizing antibody and T-cell lymphoma development. Metreleptin antibodies were observed to develop in a considerable number of patients with lipodystrophy on metreleptin. However, antibodies with in vivo neutralizing activity have been detected in a small number of patients (96) T-cell lymphoma has been reported in a few patients with AGL treated with metreleptin (97,98). Immune dysfunction is part of the natural history in patients with acquired generalized lipodystrophy (42,44). No lymphoma development has been reported in patients with CGL or FPLD treated with metreleptin so far. Current evidence suggests that lymphoma development in patients with AGL may be associated with the natural history of the disease rather than being a treatment effect associated with metreleptin.
Challenges in the management of lipodystrophy in childhood and youth

The needs of pediatric patients are different from those of adults. There are several challenges specific to children and youth in the management of lipodystrophy. Crying gives the baby a way to call for help when he/she is hungry or uncomfortable. Babies with lipodystrophy feel hungry all the time because of leptin deficiency. Appetite control is almost impossible in generalized lipodystrophy especially during active growth without getting help from metreleptin therapy. Even on metreleptin, patients and parents struggle to decide on the right amount of food to consume. Metreleptin causes weight loss in most patients. It is fearful for parents to see their children lose weight on metreleptin as they look very thin because of lipodystrophy.

Small children may have difficulties with verbalizing symptoms of the disease such as abdominal pain caused by acute pancreatitis, symptoms of high or low glucose levels, muscle symptoms, and infections. It may be also difficult to explain to children and youth why metabolic control is so important in lipodystrophy. The need of different types of therapies, and tasks (such as glucose monitoring, routine blood draws for biochemistry and regular hospital visits, being careful with what type of food they eat and how much food they eat in the presence of a huge appetite caused by leptin deficiency) to achieve this goal would be overwhelming for many of them. Children with lipodystrophy may need multiple injectable treatments such as insulin, and metreleptin. Even though metreleptin therapy allows to discontinue insulin treatment or reduce number of injections, metreleptin is still an injectable agent. The lack of subcutaneous tissue makes the injection technique more challenging in lipodystrophy. It should be also noted that the injection volume would be another issue with metreleptin injections. It may be substantially difficult to get an active child to accept injections, and self-monitoring of blood glucose at home.

The physical appearance is a big problem for adolescents. They may be worried about being with their friends and in new social environments. Anger and temper outbursts are common. They may also have specific fears associated with the subtype of lipodystrophy.
To provide timely diagnosis and improve the delivery and quality of care, specialized centers in lipodystrophy presenting in childhood and youthhood lipodystrophy should be established. Optimizing algorithms for children and youth can provide guidance for the use of standard and novel therapies to ensure adequate metabolic control and to prevent complications of lipodystrophy. These centers may provide efficient education for patients and their parents about lipodystrophy and its management, which would improve patients’ adherence and the quality of life of these patients and their families. Cost of treatment remains the biggest barrier to access to novel treatments such as metreleptin. However, the recent EMA approval of metreleptin therapy is a promising development for lipodystrophy patients in Europe and elsewhere in the world where the recommendations of EMA are adopted by the local authorities. It is important to state that regulatory authority approval does not grantee access, if the health care coverage programs do not include therapies for rare diseases in their formularies. If Metreleptin therapy is not an option in a country, or for a patient’s plan, access to metreleptin can potentially be established through compassionate use programs and other regulatory mechanisms.

Conclusions

Lipodystrophy syndromes are a heterogeneous group of disorders characterized by the lack of adipose tissue which is associated with severe insulin resistance that usually results in metabolic abnormalities leading to serious morbidity and increased mortality. Although there is no definitive cure for lipodystrophy, patients will potentially benefit from an early diagnosis made in childhood which would improve lipodystrophy outcomes by providing care at the earliest stage possible. Effective strategies should be developed to overcome challenges in the management of lipodystrophy in children and youth.

Ethics
Ethics Committee Approval:none
Informed Consent:none

Authorship Contributions
Surgical and Medical Practices: Samim Özen, Baris Akinci, Elif Oral
Concept: Samim Özen, Baris Akinci, Elif Oral
Design: Samim Özen, Baris Akinci, Elif Oral
Data Collection or Processing: Samim Özen, Baris Akinci
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Literature Search: Samim Özen, Baris Akinci, Elif Oral
Writing: Samim Özen, Baris Akinci, Elif Oral

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Diabetes Obes Metab 2017;19:299-301.
Hepatology 2005;41:753-60.


Table 1: Subtypes of CGL, and their genetic and clinical characteristics.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Gene</th>
<th>Molecular basis</th>
<th>Phenotype</th>
</tr>
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<tbody>
<tr>
<td>CGL1</td>
<td>AGPAT2</td>
<td>AGPAT2 plays a major role in the metabolism of lysophosphatidic acid, a powerful</td>
<td>Near total fat loss, preserved mechanical fat, severe insulin resistance,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>signaling molecule responsible for activating a G-protein-linked receptor</td>
<td>metabolic abnormalities, cystic lesions in long bones</td>
</tr>
<tr>
<td>CGL2</td>
<td>BSCL2</td>
<td>Seipin, encoded by BSCL2, plays a key role in the fusion of small lipid droplets</td>
<td>Severe near total fat loss, almost no mechanical fat, severe insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in adipocytes and adipocyte differentiation</td>
<td>resistance, metabolic abnormalities, and occasionally cystic lesions in</td>
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<td></td>
<td></td>
<td></td>
<td>long bones, may be associated with delayed mental development and</td>
</tr>
<tr>
<td>Gene</td>
<td>Mutation</td>
<td>Description</td>
<td>Phenotype</td>
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<tr>
<td>CGL3</td>
<td>CAV1</td>
<td>Caveolin 1 is an integral component of caveolae, which are present on adipocyte membranes. Caveolae translocate fatty acids and other lipids to lipid droplets</td>
<td>Near total fat loss, preserved bone marrow fat, severe insulin resistance, metabolic abnormalities, delayed growth, short stature, hypocalcemia, vitamin D resistance, and osteopenia</td>
</tr>
<tr>
<td>CGL4</td>
<td>PTRF</td>
<td>PTRF is involved in the biogenesis of caveolae and regulates expression of caveolins 1 and 3</td>
<td>Near total fat loss, partially preserved bone marrow fat, myopathy with elevated CK levels, percussion-induced muscle mounding, scoliosis, atlantoaxial instability, pyloric stenosis, gastrointestinal dysmotility, cardiac arrhythmias (catecholaminergic polymorphic ventricular tachycardia, atrial fibrillation, prolonged QT), sudden death</td>
</tr>
<tr>
<td>LMNA</td>
<td>p.T10I</td>
<td>LMNA codes nuclear envelope proteins, lamin A and C. Mutant lamins disrupt the interaction between the nuclear lamina and chromatin and may result in apoptosis, which may be followed by premature adipocyte death</td>
<td>Near total loss of fat developing in early childhood, severe insulin resistance, metabolic abnormalities, and progeroid features</td>
</tr>
<tr>
<td>LMNA (Lamin C-specific)</td>
<td></td>
<td>Mutant lamin C may disrupt its interaction with other cellular proteins, resulting in defective development and maintenance of adipose tissue</td>
<td>Juvenile-onset generalized fat loss, severe insulin resistance, metabolic abnormalities, phenotype highly similar to CGL1</td>
</tr>
<tr>
<td>PPARG (Biallelic)</td>
<td></td>
<td>PPARG is a key regulator of adipocyte differentiation</td>
<td>Generalized fat loss similar to CGL1 or CGL2, severe insulin resistance, metabolic abnormalities</td>
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<table>
<thead>
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<th>Subtype</th>
<th>Gene</th>
<th>Molecular basis</th>
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**Table 2:** Subtypes of FPLD and their genetic and clinical characteristics.
<table>
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<tr>
<th>FPLD1</th>
<th>Unknown</th>
<th>Polygenic etiology?</th>
<th>Fat loss mainly limited to extremities, truncal obesity, palpable “ledge” between lipodystrophic and nonlipodystrophic areas, severe insulin resistance, and metabolic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPLD2</td>
<td>LMNA</td>
<td>LMNA codes nuclear lamina proteins, lamin A and C. Mutant lamins disrupt the interaction between the nuclear lamina and chromatin and may result in apoptosis, which may be followed by premature adipocyte death</td>
<td>Fat loss dominantly affects the limbs, increased musculature, excess fat in the face and neck, labial pseudohypertrophy, increased mon pubis fat, severe insulin resistance, and metabolic abnormalities</td>
</tr>
<tr>
<td>FPLD3</td>
<td>PPARG</td>
<td>PPARG plays a major role in the regulation of adiposity differentiation</td>
<td>Milder fat loss mostly affects the distal limbs, no accumulation of adipose tissue in the face and neck, severe insulin resistance, and metabolic abnormalities</td>
</tr>
<tr>
<td>FPLD4</td>
<td>PLIN1</td>
<td>Perilipin coats lipid droplet and its required for optimal lipid incorporation and release from droplet</td>
<td>Fat loss in the lower limbs and femorogluteal depot, severe insulin resistance, and metabolic abnormalities.</td>
</tr>
<tr>
<td>FPLD5</td>
<td>CIDEC</td>
<td>CIDEC is expressed in the lipid droplets. Pathogenic variants of the CIDEC gene may result in the loss of ability of lipid droplets to store fat and defects in adipocyte differentiation</td>
<td>Partial lipodystrophy, acanthosis nigricans, severe insulin resistance, metabolic abnormalities, and diabetic ketoacidosis</td>
</tr>
</tbody>
</table>

**Lipodystrophy syndromes associated with lipomatosis**

| FPLD6  | LIPE    | LIPE encodes hormone-sensitive lipase, involved in lipolysis regulation | Late-onset partial fat loss affecting the lower limbs, multiple lipomatosis, and progressive distal symmetric myopathy |

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**Notes:**

- **FPLD1 (Koberling type):** Unknown etiology. Fat loss is limited to extremities, truncal obesity, and palpable “ledge” between lipodystrophic and nonlipodystrophic areas. Severe insulin resistance and metabolic abnormalities are also present.

- **FPLD2 (Dunnigan type):** Mutant lamins disrupt the interaction between the nuclear lamina and chromatin. This results in apoptosis and subsequent premature adipocyte death. Fat loss in the limbs is prominent, along with increased musculature, excess fat in the face and neck, and labial pseudohypertrophy.

- **FPLD3:** Mutations in PPARG lead to milder fat loss mainly affecting the distal limbs. No accumulation of adipose tissue in the face and neck occurs.

- **FPLD4:** Pathogenic variants of PLIN1 affect adipocyte differentiation, leading to fat loss in the lower limbs and femorogluteal depot. Severe insulin resistance and metabolic abnormalities are also present.

- **FPLD5:** CIDEC mutations result in the loss of adipocyte differentiation and defects in adipocyte function. Symptoms include partial lipodystrophy, acanthosis nigricans, severe insulin resistance, and metabolic abnormalities.

- **FPLD6:** LIPE encodes hormone-sensitive lipase. Late-onset partial fat loss affecting the lower limbs, multiple lipomatosis, and progressive distal symmetric myopathy are associated with LIPE mutations.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>FPLD Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFN2</td>
<td>MFN2 gene encodes mitofusin 2, a membrane-bound mediator of mitochondrial membrane fusion and inter-organelle communication</td>
<td>Partial lipodystrophy with upper body adipose hyperplasia (lipomatosis without encapsulation), and low leptin levels</td>
</tr>
</tbody>
</table>

**Other FPLD Syndromes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
<th>FPLD Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADRA2A</td>
<td>ADRA2A activation inhibits cAMP production and reduces lipolysis</td>
<td>FPLD phenotype, increased muscularity, needs to be confirmed in further pedigrees</td>
</tr>
<tr>
<td>AKT2</td>
<td>AKT is a serine/threonine protein kinase involved in insulin-stimulated glucose transport</td>
<td>Partial fat loss affecting the limbs, severe insulin resistance, and metabolic abnormalities</td>
</tr>
<tr>
<td>CAV1 (heterozygous)</td>
<td>Caveolin 1 is an integral component of caveolae, which are present on adipocyte membranes. Caveolae translocate fatty acids and other lipids to lipid droplets</td>
<td>Partial fat loss from the upper body with preservation of fat in the lower body, neurodegeneration, cerebellar ataxia, congenital cataracts and neurosensory deafness</td>
</tr>
<tr>
<td>PCYT1A (Biallelic)</td>
<td>Rate-limiting enzyme in the Kennedy pathway of de novo phosphatidylcholine synthesis</td>
<td>Severe lipodystrophy with near total lack of subcutaneous fat in the arms, legs, and buttocks. Preservation of fat in the trunk, in the dorsocervical and submandibular regions, and over the mons pubis. Severe insulin resistance, and metabolic abnormalities, potentially can be classified in the CGL category</td>
</tr>
</tbody>
</table>

Table 3: Progeroid disorders and other rare complex genetic disorders associated with lipodystrophy syndromes.

<table>
<thead>
<tr>
<th>Disorder/Syndrome</th>
<th>Gene</th>
<th>Lipodystrophy pattern</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutchinson-Gilford progeria syndrome</td>
<td>LMNA</td>
<td>Severe partial lipodystrophy which may progress to an almost complete absence of subcutaneous fat</td>
<td>Short stature, low body weight, and progeroid features</td>
</tr>
<tr>
<td>Atypical progeroid syndrome</td>
<td>LMNA</td>
<td>Fat loss more extensive than the typical pattern in FPLD2</td>
<td>Muscular symptoms, skin defects, cardiomyopathy and rhythm abnormalities, and progeroid features</td>
</tr>
<tr>
<td>Mandibulo-acral dysplasia type A (MADA)</td>
<td>LMNA</td>
<td>Partial loss of subcutaneous fat from the extremities along with normal or excessive fat in the face and the neck</td>
<td>Craniofacial, skeletal and cutaneous abnormalities</td>
</tr>
<tr>
<td>Mandibulo-acral dysplasia type B (MADB)</td>
<td>ZMPSTE24</td>
<td>More generalized loss of subcutaneous fat than MADA</td>
<td>Mandibular and clavicular hypoplasia,acroosteolysis, premature renal failure, and progeroid features</td>
</tr>
<tr>
<td>MDP syndrome</td>
<td>POLD1</td>
<td>Progressive loss of fat</td>
<td>Mandibular hypoplasia, deafness, and progeroid features</td>
</tr>
<tr>
<td>JMP syndrome</td>
<td>PSMB8</td>
<td>Panniculitis-induced lipodystrophy</td>
<td>Autoinflammatory syndrome, joint contractures, muscle atrophy, and microcytic anemia</td>
</tr>
<tr>
<td>CANDLE syndrome</td>
<td>PSMB8</td>
<td>Partial loss of adipose tissue from the upper limbs and face</td>
<td>Autoinflammatory syndrome, chronic atypical neutrophilic dermatitis, and recurrent fever</td>
</tr>
<tr>
<td>SHORT syndrome</td>
<td>PIK3R1</td>
<td>Variable loss of subcutaneous fat</td>
<td>Short stature, hyperextensibility, ocular depression, teething delay</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Gene</td>
<td>Description</td>
<td>Associated Features</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------</td>
<td>----------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Néstor-Guillermo progeria syndrome</td>
<td>BANF1</td>
<td>Decreased subcutaneous fat</td>
<td>Progeroid features, growth retardation, thin limbs, and stiff joints</td>
</tr>
<tr>
<td>Neonatal progeroid syndrome</td>
<td>CAV1</td>
<td>Generalized loss of body fat</td>
<td>Progeroid appearance at birth</td>
</tr>
<tr>
<td>Neonatal Marfan progeroid syndrome</td>
<td>FBN1</td>
<td>Generalized loss of fat</td>
<td>Progeroid appearance, Marfanoid habitus, skeletal features, dilated aortic bulb, bilateral subluxation of the lens, myopia, no significant metabolic abnormality associated with insulin resistance</td>
</tr>
<tr>
<td>Keppen-Lubinsky syndrome</td>
<td>KCNJ6</td>
<td>Generalized loss of fat</td>
<td>Severe developmental delay and intellectual disability, microcephaly, large prominent eyes, open mouth, progeroid appearance</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>WRN</td>
<td>Partial lipodystrophy affecting the limbs</td>
<td>Progeroid features</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>BLM</td>
<td>Paucity of adipose tissue and low BMI</td>
<td>Short stature, sun-sensitive, telangiectasia, and risk of cancers</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>ERCC6, ERCC8</td>
<td>Generalized loss of fat</td>
<td>Short stature, mental retardation, chorioretinitis, and progeroid features</td>
</tr>
<tr>
<td>AREDYLD syndrome</td>
<td>Unknown</td>
<td>Generalized loss of fat</td>
<td>Acrorenal field defect, ectodermal dysplasia, and multiple abnormalities</td>
</tr>
<tr>
<td></td>
<td>SPRTN</td>
<td>Lipodystrophy</td>
<td>Progeroid features, hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>OPA3</td>
<td>Lipodystrophy</td>
<td>Optic atrophy, cataracts, and peripheral neuropathy</td>
</tr>
</tbody>
</table>